COMMISSION ON HUMAN MEDICINES (CHM)

COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Tuesday 25th August 2020** at **11:00** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan
Professor N French
Professor D Goldblatt
Professor K Hyrich
Sir M Jacobs
Professor H J Lachmann
Professor P J Lehner
Dr S Misbah
Dr A Riordan
Professor C Robertson
Professor P Shah[1]
Professor T Solomon
Dr R Thorpe
Professor C Weir

Invited Experts

Professor I J Douglas
[redacted]

Secretariat

[redacted]

Professional Staff of MHRA Present

Supporting Specific Items

[redacted]
Dr J Bonnerjea
Dr P Bryan
Dr K Wydenbach

MHRA Observers

[redacted]
Dr S P Lam
[redacted]

[redacted]

29th September 2020

1 – Joined during item 3

1. Introduction and Announcement

1.1 The Chair reminded Members that the papers and proceedings are confidential and should not be disclosed.

1.2 Conflict of Interest Policy (Annex I to the minutes)

The Chair reminded members and participants that, in accordance with the CHM Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members were also reminded to declare any other matter which could reasonably be perceived as affecting their impartiality.

1.3 The following members declared interests and other relevant interests prior to the first meeting:

Professor Sir Munir Pirmohamed - NPNS AstraZeneca - Research grant to UOL to support PhD in drug interactions.

Professor French - Other relevant interest - Provides clinical care when in covering the acute medical wards where patients with COVID-19 are cared. NPNS in GSK - In September 2020 a sub-contract was signed with the Liverpool School of Tropical Medicine to undertake work evaluating the safety and effectiveness of GSK's RTS's malaria vaccine in Malawi. GSK are the primary funders to the LSTM.

Professor Hyrich – NPNS - Professor Hyrich was co-I on an investigator-initiated research grant exploring predictors of outcome in rheumatoid arthritis. NPNS Pfizer- she is a Co-I on a grant exploring adherence to JAK inhibitors in rheumatoid arthritis. NPNS in Abbvie, Professor Hyrich gave some lectures at an education conference on effectiveness of treatment for rheumatoid arthritis.

Sir Michael Jacobs - Other relevant interest - As part of the academic role at the Liverpool School of Tropical Medicine, Sir Michael is a member of the Study Management Team and antiviral drug prioritisation group for the AGILE proof of concept (phase I/II) platform study. Sir Michael is also part of the team that submits new antiviral compounds against SARS-CoV2 for consideration by NIHR for testing on this platform. No commercial or financial interest in the trial or any of the compounds, or any pharmaceutical or biotechnology company.

Professor Lachman – Other relevant interest as a volunteer participant in the Oxford vaccine study and no other involvement in the study.

Dr Misbah - NPNS - Holds honorary Senior Lectureship with University of Oxford & Oxford University Hospitals NHS Foundation Trust.

Dr Riordan - Other relevant interests - Participant in Oxford University's ChAdOx1 nCoV-19 clinical trial –received immunisation 27/8/2020. NPNS - Postgraduate External Examiner for Oxford University (Postgraduate Diploma in Paediatric Infectious Diseases).

[redacted] **-** Other relevant interests – [redacted] provides clinical care for patients with Covid-19; [redacted]

Professor Weir - Other relevant interest arising from link to the Lothian NHS Board. NHS Lothian R&D has partially funded Professor Weir's post at University of Edinburgh, since 2010, so that he could provide methodological advice on health services research studies and clinical trials.

Invited Experts of the Covid-19 Vaccines Benefit Risk Expert Working Group declared the following interests:

Professor Douglas - Personal non-specific in Oxford University, lecturing fees in the last 12 months. Personal interest in GlaxoSmithKline – Shares, current holding Bayer – October 2019 fee for delivering investigator training related to Aflibercept. Non-personal in GlaxoSmithKline - current research grant
At the chair's discretion, Professor Douglas was permitted to remain for the discussion and to answer, but not ask, direct questions from the chair and other members.

[redacted] - Personal Specific interest, [redacted] is a member of a DSMB for clinical trials of a COVID-19 vaccine developed by CUREVAC, Germany - receive DSMB fees for this work.
At the chair's discretion, [redacted] was permitted to remain for the discussion and to answer, but not ask, direct questions from the chair and other members.

[redacted] - personal non-specific interest in AstraZeneca who provide [redacted] department at the London School of Hygiene and Tropical Medicine with an unrestricted research grant 2016-2021. The grant partially contributes to funding [redacted] salary. [redacted] research and employment is not dependent on this funding and Astra Zeneca have no influence on the nature of [redacted] research, or on reporting or dissemination of results.

The register of interests declared by participants had not been deemed to debar any participation. No further interests were declared.

2. Establishment of the Expert Working Group – procedural aspects

2.1 The Expert Working Group (EWG) reviewed the suggested Terms of Reference, the proposed membership and confidentiality requirements. It was noted that the group will advise on the quality, safety and efficacy of Covid-19 vaccines prior to their authorisation, and on emerging evidence on risks and benefits during the course of any Covid-19 immunisation campaign. It was agreed that meeting of the Expert Working Group will be virtual meeting for the foreseeable future. The likely life-time

of the Group was discussed, and it was suggested that the Group will be required for at least 12 months. It was suggested that it may be useful to have a patient representative on the group.

3. Information received from AstraZeneca on their rolling submission

3.1 The EWG heard about the timelines currently planned by Astra Zeneca for their EMA submission:

- End of September: Non-clinical dossier
- Mid-October: CMC dossier
- Beginning of November: Clinical dossier (interim analysis of efficacy - safety)
- Beginning of December: Clinical dossier (primary analysis of efficacy - safety)
- End of December: Formal Marketing Authorisation Application submission

3.2 The EWG heard a summary of the AZD1222 vaccine clinical development plan designed by Oxford University (OU), which includes a Phase I/II study and a Phase II/III study conducted in the UK and two foreign studies initiated in Brazil and South Africa, respectively. Overall, the four studies should enrol approximately 20,000 subjects. Preliminary safety and immunogenicity results of the Phase I/II recently published in The Lancet were presented. Based on these data, OU decided to amend the study protocols to vaccinate a maximum of subjects with a 2-dose regimen.

3.3 The EWG heard about Astra Zeneca's statistical analysis plan for vaccine efficacy, which will be based on a pooled analysis of the four trials and will include an interim and a primary analyses, both triggered by 40 cases of PCR-positive symptomatic COVID-19 disease but in a different population in terms of number of doses received. A statistically significant result would be achieved if the 95% confidence interval (CI) around vaccine efficacy (VE) were > 0%, i.e., the vaccine is demonstrated to be more effective than a placebo.

3.4 The EWG heard that both WHO and FDA guidance recommend as success criteria for vaccine pivotal trials a 95% lower bound of CI that exceeds 30% and a point estimate for VE of at least 50%.

3.5 The EWG expressed significant concerns about approving a vaccine with a 95% CI lower bound between 0 and 30%. It was noted that even though achieving a CI lower bound > 0% was the target for the primary analysis, the trial would not be stopped at this point so there would be continued follow-up and therefore the possibility for further analyses which could generate a higher CI lower bound. Consideration could be given to a vaccine with a 95% CI lower bound > 20% depending on VE point-estimate and robustness of immunogenicity and safety data. A similar approach has been communicated to Astra Zeneca by the EMA Rapporteurs.

3.6 The need to evaluate if the vaccine was 'sterilizing' (i.e., able to prevent any infection, including asymptomatic) was also emphasised; it was confirmed that this was a secondary endpoint.

3.7 The EWG raised issues about the likely heterogeneity of the populations and virus circulation rates across the different countries with potential difficulties in interpreting the pooled analysis results, particularly in the 40 cases planned for the primary efficacy analysis. It seemed possible that all 40 cases could be predominantly clustered in one region or population. The EWG noted that subgroup analyses would be useful to aid understanding of consistency of efficacy and safety in different populations, however it was noted that with only 40 cases to be observed for the primary analysis the possibilities for efficacy sub-group analyses would be limited at that stage.

3.8 [redacted]

3.9 The EWG commented about comparisons between vaccines when several vaccines would be proposed for approval and it was confirmed that each vaccine would be approved on its own based on its quality, safety and efficacy results.

3.10 The EWG also highlighted the possible [redacted] and its potential impact on the immune response, especially with a 2-dose vaccine regimen.

4. Future work / other vaccines

4.1 The EWG had the opportunity to review a paper on some of the potential future vaccines that may be used in clinical trials in the UK or be included in a marketing authorisation application involving the UK. It was clarified that the overview did not include any indication of considerations for each vaccine from the Government Vaccine Taskforce but focused on the scientific aspects for each vaccine. The list of vaccines was not exhaustive and included vaccines at various stages of development, including three which have the potential to deliver phase III data in the next 6 months.

5. Any Other Business

5.1 According to GDPR guidelines, the Group was asked for their permission to share their email address with other members of this group to enable everyone to be included in the 'To' line for all emails and not in the 'BCC' line.

5.2 The members of CHM, Expert Advisory Groups (EAG) and Expert Working Groups (EWG) are usually published on the Government website as well as through summary minutes. The full list of membership may be published externally. The group was asked to inform the ECS secretariat as to whether they had any objections for their name to be published on the website.

5.3 The EWG was informed that with regards to the 'sharing of documentation', there is a secure portal system used by the ECS Secretariat for sharing information. They were informed that the Secretariat will register them onto the portal.

6. Date and time of future meetings

6.1

- **Tuesday 29th September (2.30pm – 5pm)**
- **Wednesday 14th October (10.30am - 1pm)**

- **Wednesday 28th October (1.30pm - 4pm)**
- **Tuesday 10th November (2.30pm - 5pm)**
- **Tuesday 24th November (2.30pm - 5pm)**
- **Monday 7th December (10.30am - 1pm)**
- **Tuesday 22nd December (11.30am - 2pm)**

The Meeting started at 11:04 and ended at 12:56.

Members are reminded that the content of papers and proceeding of the meetings are to be treated as 'Official – sensitive commercial'. Members are also reminded that, in accordance with the Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members must also declare any other matter which could reasonably be perceived as affecting their impartiality. Detailed guidance is set out in the Code of Practice

Annex I

Conflict of Interest Policy for CHM COVID-19 Vaccine Benefit Risk EWG

Chair and Members

- May not hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
- May not currently be or have previously been involved in the development of COVID-19 vaccines

Invited to all meetings, receives all papers and presentations and is permitted full participation in discussion, including drawing up conclusions and recommendations

Invited experts

- May hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
- May currently be or have previously been involved in the development of COVID-19 vaccines

May be invited to all relevant meetings, receives all papers and presentations and is permitted to participate in discussions when invited by the Chair. Does not contribute to conclusions and recommendations

Observers

Are invited to attend all meetings. Will not participate in drawing up conclusions and recommendations.

COMMISSION ON HUMAN MEDICINES (CHM)

COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Tuesday 29th September 2020** at **14:30** via videoconference

Participants Present

Members

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Professor J Breuer
Professor G Dougan
Professor N French
Professor D Goldblatt
Ms S Hunneyball
Professor K Hyrich
Sir M Jacobs
Professor P J Lehner
Dr S Misbah
Dr A Riordan
Professor C Robertson
Professor P Shah
Dr R Thorpe
Mrs M Wang
Professor C Weir

Invited Experts

[redacted]

Apologies

Professor I J Douglas (Invited Expert)
Professor H J Lachmann
Professor T Solomon

Secretariat

[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted] - LD

Supporting Specific Items

[redacted] - LD
[redacted] - LD
Dr P Bryan - VRMM
[redacted] - LD
[redacted] - LD
Dr N Rose - MHRA-NIBSC
Dr C Schneider - MHRA-NIBSC
[redacted] - LD

MHRA Observers

[redacted] - VRMM
Dr S P Lam - LD
[redacted] - LD
Dr M O'Kane - LD
[redacted] - LD
Dr K Wydenbach - LD

[redacted]

15th October 2020

Key

LD = Licensing Division
VRMM = Vigilance & Risk Management of Medicines
NIBSC = National Institute for Biological Standards & Control

1. Introduction and Announcement

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1.3 The following members declared interests and other relevant interests to date:

Professor Sir Munir Pirmohamed - NPNS AstraZeneca - Research grant to UOL to support PhD in drug interactions.

Professor French - Other relevant interest - Provides clinical care when in covering the acute medical wards where patients with COVID-19 are cared. NPNS in GSK - In September 2020 a sub-contract was signed with the Liverpool School of Tropical Medicine to undertake work evaluating the safety and effectiveness of GSK's RTS's malaria vaccine in Malawi. GSK are the primary funders to the LSTM.

Professor Hyrich – NPNS - Professor Hyrich was co-I on an investigator-initiated research grant exploring predictors of outcome in rheumatoid arthritis. NPNS Pfizer- she is a Co-I on a grant exploring adherence to JAK inhibitors in rheumatoid arthritis. NPNS in Abbvie, Professor Hyrich gave some lectures at an education conference on effectiveness of treatment for rheumatoid arthritis.

Sir Michael Jacobs - Other relevant interest - As part of the academic role at the Liverpool School of Tropical Medicine, Sir Michael is a member of the Study Management Team and antiviral drug prioritisation group for the AGILE proof of concept (phase I/II) platform study. Sir Michael is also part of the team that submits new antiviral compounds against SARS-CoV2 for consideration by NIHR for testing on this platform. No commercial or financial interest in the trial or any of the compounds, or any pharmaceutical or biotechnology company.

Dr Misbah - NPNS - Holds honorary Senior Lectureship with University of Oxford & Oxford University Hospitals NHS Foundation Trust

Dr Riordan - Other relevant interests - Participant in Oxford University's ChAdOx1 nCoV-19 clinical trial –received immunisation 27/8/2020
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Professor Weir - Other relevant interest arising from link to the Lothian NHS Board. NHS Lothian R&D has partially funded Professor Weir's post at University of Edinburgh, since 2010, so that he could provide methodological advice on health services research studies and clinical trials.

Invited Experts of the COVID-19 Vaccines Benefit Risk Expert Working Group declared the following interests:

[redacted] - Personal Specific interest, [redacted] is a member of a DSMB for clinical trials of a COVID-19 vaccine developed by CUREVAC, Germany - receive DSMB fees for this work.
At the chair's discretion, [redacted] was permitted to remain for the discussion and to answer direct questions from the chair and other members, but not raise unsolicited comments or questions.

[redacted] - Personal non-specific interest in AstraZeneca who provide [redacted] department at the London School of Hygiene and Tropical Medicine with an unrestricted research grant covering the period 2016-2021. The grant partially contributes to funding [redacted] salary. [redacted] research and employment is not dependent on this funding and AstraZeneca have no influence on the nature of [redacted] research, or on reporting or dissemination of results. Other relevant interest, [redacted] is working on a [redacted] paper and some of the co-authors are statisticians at AstraZeneca in Cambridge. It's an academic paper on [redacted] and is not related to the business side of the company or products.

The register of interests declared by participants had not been deemed to debar any participation in line with the policy. No further interests were declared.

1.4 Apologies have been received from Professor Douglas, Professor Lachmann and Professor Solomon for this meeting.

2. Minutes of the meeting held on Tuesday 25th August 2020

2.1 These minutes were approved as a true and accurate record of the proceedings.

3. Update on Vaccine Manufactures' Submission Plans (verbal update only)

3.1 The Expert Working Group (COVID-19 VBR EWG) were updated on the MHRA's discussion with vaccine manufacturers and their plans for regulatory submissions. For confidentiality reasons code names will be used for the different vaccines in the future except where this is not possible, e.g. where information is received uncoded from third parties. The MHRA also informed the COVID-19 VBR EWG that the MHRA had withdrawn from the government's Vaccine Task Force to avoid any perceived conflict between the MHRA's role in evaluating the quality, safety and efficacy of candidate vaccines and the Task Force's work on the procurement and deployment of vaccines in the UK.

3.2 Initial schedules of the vaccine companies' rolling submissions were presented, emphasizing that these timings could change as the companies further developed

their submissions. The MHRA agreed to update the COVID-19 VBR EWG regularly as further information on the submission timings was obtained.

4. COVID-19 Vaccine Pharmacovigilance and Risk Management Plan standards

4.1 The COVID-19 VBR EWG considered a proposal on the core requirements of a pharmacovigilance system and risk management plans (RMP) for COVID 19 vaccines in the UK.

4.2 It was noted that the legal obligations for pharmacovigilance systems and RMPs are described in Part 11 of The Human Medicines Regulations (2012). This requires, amongst other specific requirements, the recording and reporting of suspected adverse reactions (ADRs), signal detection activities, continuous monitoring of risk-benefit balance based on all data sources, submission of periodic safety update reports (PSURs) and the operation of a risk management system (in accordance with an RMP).

4.3 The COVID-19 VBR EWG heard that the RMP consists of a 'safety specification', a 'pharmacovigilance plan' and a 'risk minimisation plan'. The purpose of the 'safety specification' is to outline what is known about the safety and efficacy of a product at the time of authorisation and any important risks, uncertainties in risk or gaps in knowledge. Based on the specification, the purpose of the 'pharmacovigilance plan' 'risk minimisation plan' is to have in place a scientific strategy to continuously evaluate risk-benefit balance, to address the important risks, uncertainties and gaps in knowledge and to mitigate risks.

4.4 The COVID-19 VBR EWG agreed that there are aspects and specific challenges of the pandemic situation, and the potential mass deployment of a COVID-19 vaccine over a relatively short time period, that require a rigorous approach to pharmacovigilance. It therefore agreed that compliance with the existing scientific standards of pharmacovigilance guidance is required but should also be strengthened and tailored where appropriate.

4.5 The COVID-19 VBR EWG noted and endorsed the proposals outlined in the paper that, in addition to routine pharmacovigilance activities, all applicants should additionally:

- Conduct signal detection activity as close to real-time as possible, and no less than at a weekly interval
- Conduct 'observed vs expected' (as outlined in section P.I.B.4.5 of the EMA's GVP module on vaccines) analysis of suspected ADRs and adverse events of special interest (AESIs) on a routine basis
- Adopt of a list of AESIs (as defined by MHRA) for tailored pharmacovigilance and conduct 'observed vs expected' analyses and targeted follow up of such events.
- Conduct batch-specific surveillance in accordance with the principles outlined in section P.I.B.5 of the GVP vaccines guidance.

- Supplement the existing PSUR requirement with a monthly 'simplified PSUR' approach

Commit to regular (e.g. two-weekly) video-telecon with MHRA to discuss the sPSUR content, ongoing observed vs expected analysis of adverse events of special interest, and any other emerging safety data and signals.

4.6 The COVID-19 VBR EWG agreed that, in addition to these core requirements, there may be additional requirements for individual applicants based on the safety specification and characteristics of individual products, particularly in relation to the need for post-authorisation safety studies (PASS) and post-authorisation efficacy studies (PAES). The COVID-19 VBR EWG heard that, where required, a PASS is intended to further characterise the safety profile, which can include confirmed or potential risks identified from the clinical trials, and important missing information such as safety in groups excluded from pre-authorisation trials. The COVID-19 VBR EWG also heard that PAES could be used to further evaluate important vaccine characteristics, such as long-term protection and the ability of the vaccine to prevent viral acquisition, carriage and transmission.

4.7 The COVID-19 VBR EWG advised that if a well-designed and feasible PASS or PAES study (or other form of proactive surveillance) in a non-UK territory is proposed, then MHRA should consider accepting that in fulfilment of a UK RMP.

4.8 The COVID-19 VBR EWG also agreed that as relevant national public health authorities will be actively co-ordinating all NHS and public-facing communications relating to a COVID-19 vaccine programme, there should not be a default requirement for additional risk minimisation material, and this should be considered on a case by case basis.

5. Efficacy Measures being used in COVID-19 Vaccine pivotal trials

5.1 The COVID-19 VBR EWG reviewed a summary table comparing and contrasting the main efficacy parameters of 4 pivotal trial protocols for 3 COVID-19 vaccines (Oxford/AstraZeneca ChAdOx1 Vector Vaccine, Pfizer BioNTech SARS-COV-2 RNA vaccine and Moderna mRNA-1273 SARS-CoV-2 Vaccine). [redacted] The COVID-19 VBR EWG heard how the COVID-19 vaccines will be determined to be effective. The WHO and FDA guidance on the development of vaccines to prevent COVID-19 was highlighted.

5.2 It was noted that, at the time of the efficacy assessment for the Oxford/AstraZeneca vaccine in the UK, results from the US trial are not anticipated to be included. The assessment will be based on pooled data from 4 trials (UK phase I/II and phase II/III, Brazil phase III and South Africa phase I/II) with approximately 20,000 subjects enrolled. The COVID-19 VBR EWG endorsed this approach.

5.3 It was noted that the method of calculating Vaccine Efficacy (VE) and the approach to statistical analysis differed between all the trials presented. It was agreed that all the methods used are approaches seen previously in vaccine applications and that

they were all acceptable. The results from each of the approaches would be expected to be consistent and the COVID-19 VBR EWG concluded that it would be reasonable to assess each trial based on its pre-specified methodology. For one of the trials a Bayesian analysis was planned so results would be impacted by the choice of prior distribution, however the estimate of VE and associated confidence interval would come from standard frequentist methodology, permitting consistent interpretation with the other trials.

5.4 The differences between the trials with respect to the number of patients targeted for recruitment in different age categories was noted. The COVID-19 VBR EWG noted that this would be an important aspect to consider when assessing the trials.

5.5 The COVID-19 VBR EWG were asked to consider what impact, if any, differences in the clinical definition of symptomatic COVID-19 could have on the primary efficacy endpoint assessment, while all cases would have to be PCR-confirmed. It was noted that sensitivity and specificity of the PCR test is likely to impact on the assessment of the primary endpoint. The COVID-19 VBR EWG considered that case identification and case definition would have an impact, particularly for any comparisons across trials. It was also highlighted that in most of the protocols reviewed, COVID-19 cases were identified by symptoms with subsequent confirmatory PCR testing, rather than also by routine PCR testing.

5.6 The COVID-19 VBR EWG heard that vaccine efficacy with regards to protection against asymptomatic COVID-19 infection, determined by serological testing, was a secondary endpoint in the studies.

5.7 The COVID-19 VBR EWG were concerned that with infrequent serological testing, asymptomatic cases may no longer be seropositive at the time of testing. They highlighted that regular PCR testing would provide additional information about asymptomatic cases. The COVID-19 VBR EWG welcomed the fact that weekly PCR testing was being carried out in a subset of subjects enrolled in the UK Oxford/AstraZeneca phase II/III trial.

5.8 Currently only adult patients have been enrolled into the clinical trials. The COVID-19 VBR EWG recommended that if/when children are included in studies the clinical symptoms of COVID-19 are amended to reflect the disease presentation in this population e.g. diarrhoea and vomiting are common, and sometimes the only, clinical symptoms in children.

5.9 Regarding the success criteria for the primary endpoint in the trials, while there is no strong scientific argument for any particular cut-off, it was considered that the WHO/FDA requirement that the lower bound of the confidence interval for VE should be above 30% with a point estimate of 50% was clinically reasonable. The COVID-19 VBR EWG noted that simply achieving a lower bound above 0% was not sufficient. A lower bound of 20% was discussed and may be acceptable depending on the supporting data and safety information available at the time. A limit for the lower bound of confidence interval of 30% was the preferred option. The COVID-19 VBR EWG also expressed concerns about the success criteria for the primary endpoint, in the context of the importance of public confidence in the vaccines and the scale of vaccination. With this in mind, while study success criteria are defined

in terms of lower bounds of the confidence interval, the COVID-19 VBR EWG recommended the study reports include appropriate emphasis on the point estimate for VE, rather than focussing on the lower bound which represents a worst case.

5.10 The COVID-19 VBR EWG also highlighted that ultimately the decision on whether to license each vaccine will be determined by the overall benefit-risk decision, including the adverse event profile.

6. COVID-19 Vaccine-Specific batch release testing

6.1 The COVID-19 VBR EWG was presented with a paper laying out the Agency's proposal for independent batch release testing of COVID-19 vaccines, both in the scenario of a regular Marketing Authorisation (which is the preferred route), and under a Regulation 174 opinion.

6.2 The MHRA proposed a view that independent batch release should be the default for all vaccines under any scenario; and under Regulation 174, such a requirement would be imposed on the manufacturers. However, this requires that technology transfer of methods to the Official Medicines Control Laboratory (NIBSC) is complete. The Expert Group enquired how a situation would be handled in case such method transfer would not yet be completed at the time of authorisation. The Agency will in such case take a decision based on a multidisciplinary assessment of data on pharmaceutical quality and its robustness, the potency tests involved, review of the manufacturer's data and protocols etc. In such a scenario, batch release may or may not be deferred, which cannot be pre-empted because it will depend on the particular case.

6.3 The Commission for Human Medicines will take these considerations into account when advising on the benefit and risk of a particular vaccine. The COVID-19 VBR EWG was very supportive of the Agency's default position and noted that the Agency's independence from the manufacturers was a key aspect for public confidence and governance. It was noted that not all manufacturers are familiar with vaccine development. It was concluded that the next step will be to put the paper to the CHM for information and endorsement.

7. Paper for information - AZD1222 toxicology

7.1 Members of the COVID-19 VBR EWG noted the paper presented and the potential issue that general and reproductive toxicity studies with AZD1222 are ongoing and may not be completed until after an anticipated licence application, reflecting urgency of vaccine development in this pandemic. The approach of the company to base evaluation of safety of AZD1222 on studies with other vaccines [redacted] but with different [redacted] was noted; however this does not apply to testing in pregnant animals, where no data with other such vaccines are available.

7.2 The COVID-19 VBR EWG discussed that other companies have adopted a similar approach to cross reference studies with other vaccines in order to expedite development. The contribution of a general toxicity study in animals to establishing

safety in the context of several thousand healthy human volunteers dosed was also discussed.

8. Any Other Business

8.1 None.

9. Date and time of next meeting

9.1 The next meeting is scheduled to take place on **Wednesday 14th October 2020** at **10.30am** to **1pm**.

Date and time of future meetings:

- **Wednesday 28th October (1.30pm - 4pm)**
- **Tuesday 10th November (2.30pm - 5pm)**
- **Tuesday 24th November (2.30pm - 5pm)**
- **Monday 7th December (10.30am - 1pm)**
- **Tuesday 22nd December (11.30am - 2pm)**

The Meeting started at 14:30 and ended at 16:39.

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Invited to all meetings, receives all papers and presentations and is permitted full participation in discussion, including drawing up conclusions and recommendations

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Observers

Are invited to attend all meetings. Will not participate in drawing up conclusions and recommendations.

COMMISSION ON HUMAN MEDICINES (CHM)

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Professor H J Lachmann
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Dr S Misbah
Professor C Robertson
Dr R Thorpe
Mrs M Wang
Professor C Weir

Invited Experts

[redacted]

Apologies

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Professor N French
Ms S Hunneyball
Sir M Jacobs
Dr A Riordan
Professor P Shah
Professor T Solomon

Secretariat

[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted] - LD

Supporting Specific Items

[redacted] LD
Dr K Wydenbach - LD

MHRA Observers

[redacted] - LD
Dr S Branch – VRMM
[redacted] - LD
Dr P Bryan - VRMM
[redacted] - LD
[redacted] - LD
Mr K McDonald - LD
[redacted] - LD
Dr C Schneider - MHRA-NIBSC
[redacted] - LD
[redacted] - LD
[redacted] - LD

[redacted]

Key

LD = Licensing Division
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1.2 Conflict of Interest Policy (Annex I to the minutes)

The Chair reminded members and participants that, in accordance with the CHM Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members were also reminded to declare any other matter which could reasonably be perceived as affecting their impartiality.

1.3 The following members declared interests and other relevant interests to date:

Professor Sir Munir Pirmohamed - NPNS AstraZeneca - Research grant to UoL to support PhD in drug interactions. Sir Munir declared the following potential NPNS interests of an IMI project which will not start until 1 November 2020 in Pfizer, Janssen and Sanofi-Aventis

Professor Hyrich – NPNS - Professor Hyrich was co-I on an investigator-initiated research grant exploring predictors of outcome in rheumatoid arthritis. NPNS Pfizer- she is a Co-I on a grant exploring adherence to JAK inhibitors in rheumatoid arthritis. NPNS in Abbvie, Professor Hyrich gave some lectures at an education conference on effectiveness of treatment for rheumatoid arthritis.

Professor Lachman – Other relevant interest as a volunteer participant in the Oxford vaccine study and no other involvement in the study.

Dr Misbah - NPNS - Holds honorary Senior Lectureship with University of Oxford & Oxford University Hospitals NHS Foundation Trust

Professor Weir - Other relevant interest arising from link to the Lothian NHS Board. NHS Lothian R&D has partially funded Professor Weir's post at University of Edinburgh, since 2010, so that he could provide methodological advice on health services research studies and clinical trials.

Invited Experts of the COVID-19 Vaccines Benefit Risk Expert Working Group declared the following interests:

[redacted] - Personal Specific interest, [redacted] is a member of a DSMB for clinical trials of a COVID-19 vaccine developed by CUREVAC, Germany - receive DSMB fees for this work. Personal Specific interest, [redacted] has declared for this meeting that [redacted] is now acting as a temporary consultant for GSK where he receives ad hoc consultant fees.

This conflict of interest (personal specific interest in **GSK**) was discussed prior to the meeting with internal management and government legal team. [redacted]

[redacted] was advised and requested to stand down as an invited expert from this EWG to address any potential perception of bias.
This is based on the overriding principles of the code on conflicts are impartiality and transparency, and the key question in relation to any potential conflict is whether it might give rise to a reasonable perception of bias. [redacted] understood the EWG's position and did not attend the meeting. [redacted] has stood down from this EWG.

[redacted] - Personal non-specific interest in AstraZeneca who provide [redacted] department at the London School of Hygiene and Tropical Medicine with an unrestricted research grant covering the period 2016-2021. The grant partially contributes to funding [redacted] salary. [redacted] research and employment is not dependent on this funding and AstraZeneca have no influence on the nature of [redacted] research, or on reporting or dissemination of results**.** Other relevant interest, [redacted] is working on a statistical methodology paper and some of the co-authors are statisticians at AstraZeneca in Cambridge. It's an academic paper on analysis of subgroups and is not related to the business side of the company or products.

The register of interests declared by participants had not been deemed to debar any other participation in line with the policy. No further interests were declared.

1.4 Apologies have been received from Sir Michael Jacobs, Professors Douglas, French, [redacted] Solomon, Dr Riordan and Ms Hunneyball for this meeting.

2. Minutes of the meeting held on Tuesday 29th September 2020

2.1 The minutes were approved as a true and accurate record of the proceedings, subject to the amendment of item 5.3.

3. Update on Clinical Trials

3.1 AstraZeneca AZD1222

3.1.1 The EWG heard AZD1222 trials in the UK are continuing. The restart approvals had conditions which required further data to be submitted by the Sponsor: all conditions have subsequently been met. Additional information requested was not limited to the primary specific serious cases (SUSARs), but also other less serious suspected ADRs, including a discussion of neurological events related to the vector.

3.1.2 The data provided on the SUSAR / neurological ADR was first reviewed in a blinded manner, and then the review was repeated with case codes assigned. Findings were the same irrespective of blinding status: both concluded that no specific neurological or thrombotic / cardiovascular safety signal had arisen related to vaccine.

3.1.3 The current data demonstrated that adverse events are relatively evenly split between ChAdOx1 vaccinated group and the control group (Meningitis vaccine).

3.1.4 The AZD1222 trial in US remains on hold. in relation to SUSAR 2, MHRA have held no discussions with the FDA to date, but the sponsors have provided the MHRA with an identical full package of ADR data (line listings) as was given to FDA.

3.1.5 Some results for SUSAR 2 are outstanding and the Oxford trial investigators continue to follow this up.

3.1.6 The EWG noted the data on SUSAR 2 of suspected transverse myelitis, indicated a poor antibody response to SARS-CoV-2 spike protein, but it is yet to be clarified if the trial investigators have assessed the data in the context of the immune response to the vector. The EWG requested clinical data on the immune response to the vector (the anti-vector response). The EWG heard that the data is incomplete at present but is being collected in the form of anti-vector response at several time points as a tertiary endpoint. The CTU assessors will continue to follow this up.

3.2 Janssen trial

3.2.1 The EWG heard that Janssen have halted all trials of their adenovirus serotype 26-vector vaccine, noting the UK has not approved any Janssen vaccine trials. MHRA have conducted a rolling review of a phase 3 clinical trial application of their SARS-CoV-2 vaccine and issued grounds for nonacceptance, for which Janssen have confirmed receipt. The company are presently collecting data and further information on the ADR / illness which lead to the approved trials being halted and an update to the MHRA will be provided by Friday 16 October. The EWG heard that there are no UK participants in the trial, the majority of trial participants are recruited in the US, and to a lesser extent in Japan, whilst study centres in EU countries (Spain, The Netherlands) do not appear to be recruiting.

4. Rolling review of AZD1222

4.1.1 The EWG considered the non-clinical rolling review sequence 1 assessment report for the AZD1222 vaccine being developed for use in healthy subjects to prevent COVID-19 disease on exposure to SARS-CoV-2 which was presented to the EWB by the non-clinical assessor.

4.1.2 The EWG agreed the pharmacokinetics posed no concerns, the viral distribution was found to be mainly localised to the vaccination site (apart from some leak to the local lymph node) and viral distribution was not found systemically.

4.1.3 The EWG discussed the immunological responses seen in the four animal models. The EWG noted the monkey animal model is likely to mimic most closely the disease pathology seen in humans, and the physiological responses in the vaccine studies undertaken in this model are reasonably encouraging. The EWG noted that less virus was detectable in bronchoalveolar lavage gathered from vaccinated animals compared to controls, but there was little difference in terms of viral presence on nasal swabs between groups. The EWG considered that vaccinated animals may be protected from developing COVID-19 disease but could still host the virus and be a source of infection. The EWG noted this would likely have implications if the same paradigm occurs in the humans as community infection rates would only be expected

to be lessened in those directly vaccinated, with those vaccinated still able to spread infection.

4.1.4 The EWG noted the data indicating lung damage is reduced is positive and seems to be associated with a vaccine based neutralising antibody response, however a quantifiable degree of immune protection is not available from these animal studies.

4.1.5 There is not enough data available currently to rule out vaccine mediated antibody dependent enhancement of disease (vADE). The EWG noted discussions on the use of hamster models to explore the risk of vADE need to continue. The EWG agreed with the proposal to raise a potential serious risk to public health (PSRPH) to request the company submit a revised overview that considers further the risk of vaccine-associated disease enhancement following AZD1222.

4.1.6 The EWG discussed the evidence seen in the rhesus monkeys of T-cell activation and markers for T-cell exhaustion and whether this could be related to the high viral load given to the animals.

4.1.7 The EWG agreed to add a potential serious risk to public health (PSRPH) with regard to T-cell exhaustion, indicated by PD-1 expression. The company is requested to discuss whether this might cause a loss of vaccine response. The company should present its view as to whether there is a link to this and to the finding that the effect of vaccination, as seen on CT scans at day 5, had become negligible by day 12.

4.1.8 The EWG discussed the assays and whether they are harmonised, i.e. ELISA in humans and ELISA in animals. Inclusion of the macaque sera into the study would be helpful. The EWG also discussed interferon gamma assays and whether they are more specific for SARS-CoV-2 than T-cell proliferation assays. The issue of cross reactivity with seasonal corona viruses was raised in relation to T-cell assays and the following paper (a preprint) was referred to: Ogbe et al. T cell assays differentiate clinical and subclinical SARS-CoV-2 infections from cross-reactive antiviral response. Medrix, posted 29.09.2020.

4.1.9 A key feature of the SARS-Cov-2 virus is that a very high viral load is needed before signs of illness show. A vaccine is unlikely to address this.

4.1.10 The EWG discussed viral shedding and noted that, in humans, viral SAR-CoV-2 RNA including subgenomic RNA, has been detected in the upper respiratory tract in the absence of infectious virus. The EWG noted that it should be determined if the viral RNA detected is inactive residual RNA, or if it is infectious. However, the viral load given in the animal model was severe, via 4 different routes, and does not reflect the clinical nature of the challenge.
The EWG discussed how to interpret in humans, data gained in relation to vaccine constructs with other genes given to animals. There is a concern that may see reaction with an unintended target i.e. that antibody or cellular responses to the novel gene product may cross-react with an unintended target.

4.1.11 The EWG noted that it is very likely that a combination of humoral and cellular responses to the vaccine will be required in order to form appropriate protection from SARS-CoV-2.

4.1.12 The EWG noted that the numbers of animals involved in each study are small and also discussed implications of bias. The EWG agreed to include a point for clarification and to ask the company to comment on how the group sizes in the pharmacological studies in ferrets and rhesus monkeys were determined, including how statistical considerations played a part in these choices. This should include consideration of the magnitude of expected effect seen on challenge with SARS-CoV-2 virus.

4.1.13 The EWG agreed the immune response data is assuring but noted that animal studies do not necessarily give the clinical picture, which can only be derived from clinical studies. ADE is being explored but not concerning at present, based on limited data presently available.

4.1.14 The EWG noted they had previously discussed the approach to the toxicology data. it is not a full package, that is due next spring. The data is based on the ChAdOx1 vector already used in the malaria and MERS vaccines.

5. Any Other Business

5.1 The EWG noted the potential for mutations in the spike protein and the scope for effects on immunity. Additional expert opinions on this theme will be sought by the EWG. The EWG noted that the COG UK mass genome sequencing project is UK based and gives an important mode to investigate and map changes in serum antibody responses, provided the basis for identifying samples of interest is provided to COG UK. The EWG noted that COG UK will be invited to a future Vaccines BR EWG meeting and members of the EWG will be able to put questions to COG UK.

6. Date and time of next meeting

6.1 The next meeting is scheduled to take place on **Wednesday 28th October 2020** at **1.30pm** to **4pm**.

Date and time of future meetings:

- **Tuesday 10th November (2.30pm - 5pm)**
- **Tuesday 24th November (2.30pm - 5pm)**
- **Monday 7th December (10.30am - 1pm)**
- **Tuesday 22nd December (11.30am - 2pm)**

The Meeting started at 10:31 and ended at 11:41.

Members are reminded that the content of papers and proceeding of the meetings are to be treated as 'Official – sensitive commercial'. Members are also reminded that, in accordance with the Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members must also declare any other matter which could reasonably be perceived as affecting their impartiality. Detailed guidance is set out in the Code of Practice

Annex I

Conflict of Interest Policy for CHM COVID-19 Vaccine Benefit Risk EWG

Chair and Members

- May not hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
- May not currently be or have previously been involved in the development of COVID-19 vaccines

Invited to all meetings, receives all papers and presentations and is permitted full participation in discussion, including drawing up conclusions and recommendations

Invited experts

- May hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
- May currently be or have previously been involved in the development of COVID-19 vaccines

May be invited to all relevant meetings, receives all papers and presentations and is permitted to participate in discussions when invited by the Chair. Does not contribute to conclusions and recommendations

Observers

Are invited to attend all meetings. Will not participate in drawing up conclusions and recommendations.

COMMISSION ON HUMAN MEDICINES (CHM)

COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Wednesday 28th October 2020** at **10:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan
Professor N French
Professor D Goldblatt
Ms S Hunneyball
Professor K Hyrich
Professor H J Lachmann[1]
Professor P J Lehner
Dr S Misbah
Dr A Riordan
Professor C Robertson
Dr R Thorpe
Mrs M Wang

Invited Experts

Professor I J Douglas
[redacted]

Apologies

Sir M Jacobs
Professor P Shah
Professor T Solomon
Professor C Weir

Secretariat

[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD

Supporting Specific Items

[redacted] - LD
[redacted] - LD
[redacted] - LD
Dr M O'Kane - LD
[redacted] - LD
[redacted] - LD

MHRA Observers

[redacted] - LD
[redacted] - MHRA-NIBSC
[redacted] - LD
[redacted] - MHRA-NIBSC
[redacted] - MHRA-NIBSC
Dr C Schneider - MHRA-NIBSC
[redacted] - MHRA-NIBSC

[redacted]
19th January 2021

Key

LD = Licensing Division
NIBSC = National Institute for Biological Standards & Control

[1] Joined during item 3

1. Introduction and Announcement

1.1 The Chair reminded Members that the papers and proceedings are confidential and should not be disclosed.

1.2 Conflict of Interest Policy (Annex I to the minutes)

The Chair reminded members and participants that, in accordance with the CHM Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members were also reminded to declare any other matter which could reasonably be perceived as affecting their impartiality.

1.3 The following members declared interests and other relevant interests to date:

Professor Sir Munir Pirmohamed - NPNS AstraZeneca - Research grant to UOL to support PhD in drug interactions. Pfizer, Janssen, Sanofi – Sir Munir is part of an EU-funded IMI consortium on gene therapy, and these companies are partners in the project. The University of Liverpool will get funding from the EU (but not from the partners), this IMI project commences on 3rd November 2020

Professor French - Other relevant interest - Provides clinical care when in covering the acute medical wards where patients with COVID-19 are cared. NPNS in GSK - In September 2020 a sub-contract was signed with the Liverpool School of Tropical Medicine to undertake work evaluating the safety and effectiveness of GSK's RTS's malaria vaccine in Malawi. GSK are the primary funders to the LSTM.

Professor Hyrich – NPNS - Professor Hyrich was co-I on an investigator-initiated research grant exploring predictors of outcome in rheumatoid arthritis. NPNS Pfizer- she is a Co-I on a grant exploring adherence to JAK inhibitors in rheumatoid arthritis. NPNS in Abbvie, Professor Hyrich gave some lectures at an education conference on effectiveness of treatment for rheumatoid arthritis.

Professor Lachman – Other relevant interest as a volunteer participant in the Oxford vaccine study and no other involvement in the study.

Dr Misbah - NPNS - Holds honorary Senior Lectureship with University of Oxford & Oxford University Hospitals NHS Foundation Trust

Dr Riordan - Other relevant interests - Participant in Oxford University's ChAdOx1 nCoV-19 clinical trial –received immunisation 27/8/2020
NPNS - Postgraduate External Examiner for Oxford University (Postgraduate Diploma in Paediatric Infectious Diseases)

Invited Experts of the Covid-19 Vaccines Benefit Risk Expert Working Group declared the following interests:

Professor Douglas - Personal non-specific in Oxford University, lecturing fees in the last 12 months. Personal interest in GlaxoSmithKline – Shares, current holding Bayer – October 2019 fee for delivering investigator training related to Aflibercept. Non-personal in GlaxoSmithKline - current research grant
At the chair's discretion, Professor Douglas was permitted to remain for the discussion and to answer, but not ask, direct questions from the chair and other members.

[redacted] - Personal non-specific interest in AstraZeneca who provide [redacted] department at the London School of Hygiene and Tropical Medicine with an unrestricted research grant 2016-2021. The grant partially contributes to funding [redacted] salary. [redacted] research and employment is not dependent on this funding and Astra Zeneca have no influence on the nature of [redacted] research, or on reporting or dissemination of results**.** Other relevant interest as [redacted] is working on a statistical methodology paper and some of the co-authors are statisticians at Astra Zeneca in Cambridge. It's an academic paper on analysis of subgroups and neither I nor this work have anything to do with their business side (or any drugs at all).

The register of interests declared by participants had not been deemed to debar any other participation in line with the policy. No further interests were declared.

1.4 Apologies have been received from Sir Michael Jacobs, Professor Shah, Professor Solomon and Professor Weir for this meeting.

2. Minutes of the meeting held on Wednesday 14th October 2020

2.1 The minutes were approved as a true and accurate record of the proceedings, subject to the amendment of item 4.1.3.

3. BNT162b2 non-clinical assessment

3.1 The EWG considered the non-clinical Day 14 Assessment Report for the BioNTech Manufacturing GmbH COVID-19 mRNA vaccine BNT162 being developed for use in healthy subjects to prevent COVID-19 disease on exposure to SARS-CoV-2.

3.2 The EWG agreed that the pharmacokinetics posed no particular concerns. The EWG endorsed the points already raised by the assessor and agreed that further points of concern be raised for the company to address.

3.3 The EWG agreed that the company should discuss in detail the potential distribution of the test articles to sites other than the liver, in particular the draining lymph nodes, thymus and spleen, and the potential for binding to cell membranes in particular the neurones, and the potential consequences for safety.

3.4 The EWG agreed the company should either justify the use of a non-validated/non-qualified bioluminescence method to determine the biodistribution of a reporter

luciferase protein instead of detecting the actual BNT162b2 modRNA or provide the validation/qualification data. Any justification should include a discussion on the sensitivity of the method.

3.5 The EWG agreed the company should justify the use of the intravenous route of administration rather than the intramuscular (the clinical) route for the rat PK study and the utility of the study in terms of its clinical relevance should be discussed.

3.6 The EWG considered the pharmacology and agreed that overall, there were no major public health concerns. The EWG endorsed the concerns already raised by the assessor and agreed the company should be asked to answer some further points of concern.

3.7 The EWG agreed that the company should be asked to clarify the source of the antigen used in testing in animal and human assays. The nature of this antigen and if it is known to retain function should be described.

3.8 The EWG discussed study vr-vtr-10671 in rhesus monkeys and the data on IgG responses at day 14 and day 21 presented in figures on page 14 and 15. It was noted there are no similar data from testing at day 0 but results from T-cells at day 0 are presented. The EWG agreed to request company provide the baseline (day 0) data preceding these IgG responses, or if these are not available, to give an explanation for the absence of these data.

3.9 The EWG noted that no characterisation of antibody-dependent cell-mediated cytotoxicity (ADCC) activity of antibodies is presented but this may contribute to the mode of action of antibody induced by vaccination. The EWG agreed to request the company explain whether such testing is planned and if not to give a scientific rationale for the absence of such data.

3.10 The EWG discussed the programmed cell death protein-1 (PD-1) responses described in mice. The EWG agreed the company should be requested to discuss whether this indicates T-cell exhaustion and is evidence of a waning response, or if not, provide an interpretation of this response.

3.11 The EWG endorsed the points of concern raised by the assessor in relation to toxicology.

4. BNT162b2 clinical assessment

4.1 The EWG considered the SARS-Cov-2 vaccine rolling review critical clinical assessment report for the BioNTech Manufacturing GmbH COVID-19 mRNA vaccine BNT162 being developed for use in healthy subjects to prevent COVID-19 disease on exposure to SARS-CoV-2.

4.2 The EWG heard that this is the first cycle of clinical data in the rolling review process for this vaccine consisting of interim phase I immunogenicity and safety data together with data on the bioanalytical assay methods and validation. It was highlighted that the assessment is focused on the BNT162b2 vaccine candidate as it is this version that the company will be taking forward to Phase II & Phase III trials.

The EWG heard that the company anticipate that in the 3rd week November 2020 safety data for 15,000 subjects 2 months post dose 2 will be available, plus safety data on 30,000 subjects 1 month post the 2nd dose. Some 3-month post dose 2 data will also be available from the phase I studies. However, with the exception of a very small amount of 2m post dose 2 data from study BNT162-01, humoral immunogenicity data will only be available for up to 1m post dose 2. Six-month data is not expected until early next year. The EWG was asked to advise if this anticipated duration of humoral immunogenicity data would be sufficient to issue a licence with the condition to provide further data at a later date. The EWG agreed that in these circumstances this could be acceptable.

4.3 The EWG raised concerns about the differences in sensitivity obtained with the N-protein antibody assay in different laboratories (e.g., PHE, Roche and Pfizer) for convalescent samples taken > 14 days post polymerase chain reaction confirmation (albeit different samples) and recommended that efforts should be made to improve the sensitivity of the assay.

4.4 The EWG considered that characterisation of ADCC activity of antibodies may contribute to the understanding of the mode of action of antibody induced by vaccination. The EWG suggested to request the company clarify whether there is any data on ADCC activity available from study BNT162-01 or c4591001 and if not, whether there are any plans to investigate this.

4.5 The EWG discussed antibody binding and the observation that at 7 days post dose 2, subjects dosed with BNT162b2 showed complementary antibody binding (GMC) responses against the SARS-CoV-2 spike (S) protein S1 subunit and receptor binding domain (RBD) consistent with the functional antibody response (GMT). However, it was noted that this is not the case for the data 21 days after the 1st dose, with the binding IgG response much greater than that of the functional antibody. A similar pattern is seen with the interim data from study c4591001. The EWG recommended that the company should comment on this and clarify whether any data is available on the affinity of vaccine induced antibodies towards SARS-CoV-2 S protein S1 subunit and RBD.

4.6 The EWG commented that the strong T-cell response was promising, and that the intracellular cytokine staining data supported a predominantly Th1 response, consistent with the non-clinical data.

The EWG also noted that the immunogenicity responses were promising in the 65 to 85 years of age groups.

The EWG considered the statistical plan and agreed the company should be asked whether, in study c4591001, there are any elements in the study design to ensure that the randomisation is balanced within countries.

4.7 The EWG considered the need for a standard COVID-19 serum and agreed this would aid comparability between assays for different vaccines. The EWG heard that NIBSC timeline to establish such a serum is in December 2020 when there is an extraordinary meeting of the ECBS.

4.8 The EAG endorsed the points of concerns raised by the assessors in relation to the bioanalytical assays, immunogenicity, efficacy and safety.

5. Regulation of challenge agents in the UK – verbal update for information

5.1 The EWG heard an overview of the MHRA involvement in the regulation of human challenge studies in the UK.

5.2 The EWG heard that challenge agents can be administered to examine pathogenesis of a disease or to assess efficacy of a new vaccine or antiviral medicinal product. Such studies require a research ethics committee review and HRA have set up ethics committee just for challenge agents' studies. If the studies involve NHS sites HRA approval is also required and health and safety executive approval would also be required depending on how the agent is made and contained.

5.3 Only studies looking at efficacy of a medicinal product are considered a Clinical Trial Investigational Medicinal Product (CT IMP) which require MHRA approval. In these cases, the medicinal product would be considered a IMP and the challenge agent a non-IMP. In the assessment of the clinical trial both the IMP and non-IMP would be considered in terms of subject safety and would look at dosing, risk mitigations etc in line with standard clinical trial guidance for example first in human clinical trials.

5.4 In terms of public health if a company wanted to run a study which wasn't a clinical trial the MHRA could provide scientific advice as it would form part of a clinical trial at a later date. In this case MHRA would provide advice on the design of the study, safety monitoring, risk mitigations and manufacturing quality of challenge agent itself. The challenge agent would not receive a GMP certificate and the challenge study would not receive an CTA but would receive scientific advice from MHRA and committees.

6. Any Other Business

6.1 None.

7. Date and time of next meeting

7.1 The next meeting is scheduled to take place on **Tuesday 10th November 2020** at **2.30pm** to **5pm**.

Date and time of future meetings:

- **Tuesday 24th November (2.30pm - 5pm)**
- **Monday 7th December (10.30am - 1pm)**
- **Tuesday 22nd December (11.30am - 2pm)**

The Meeting started at 13.32 and ended at 15:17.

Annex I

Conflict of Interest Policy for CHM COVID-19 Vaccine Benefit Risk EWG

Chair and Members

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Invited to all meetings, receives all papers and presentations and is permitted full participation in discussion, including drawing up conclusions and recommendations

Invited experts

- May hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
- May currently be or have previously been involved in the development of COVID-19 vaccines

May be invited to all relevant meetings, receives all papers and presentations and is permitted to participate in discussions when invited by the Chair. Does not contribute to conclusions and recommendations

Observers

Are invited to attend all meetings. Will not participate in drawing up conclusions and recommendations.

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COMMISSION ON HUMAN MEDICINES (CHM)

COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Tuesday 10th November 2020** at **14:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan
Professor N French
Professor D Goldblatt[1]
Ms S Hunneyball
Professor K Hyrich
Sir M Jacobs
Professor H J Lachmann
Dr S Misbah
Dr A Riordan
Professor C Robertson
Professor P Shah
Professor T Solomon
Dr R Thorpe
Mrs M Wang
Professor C Weir

Invited Experts

Professor I J Douglas
[redacted]

Apologies

Professor P J Lehner

Secretariat

[redacted]

[1] Joined during item 3

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted] - LD

Supporting Specific Items

[redacted] - LD
[redacted] - LD
Dr P Bryan - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD

MHRA Observers

Dr S Branch - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
Dr SP Lam - LD
[redacted] - LD
Dr C Schneider - MHRA-NIBSC
[redacted] - LD
[redacted] - LD

Key
LD = Licensing Division
NIBSC = National Institute for Biological Standards & Control
VRMM = Vigilance & Risk Management of Medicines

[redacted]

18th November 2020

1. Introduction and Announcement

1.1 The Chair reminded Members that the papers and proceedings are confidential and should not be disclosed.

1.2 Conflict of Interest Policy (Annex I to the minutes)

The Chair reminded members and participants that, in accordance with the CHM Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members were also reminded to declare any other matter which could reasonably be perceived as affecting their impartiality.

1.3 The following members declared interests and other relevant interests to date:

Professor Sir Munir Pirmohamed - NPNS AstraZeneca - Research grant to UOL to support PhD in drug interactions. Pfizer, Janssen, Sanofi – Sir Munir is part of an EU-funded IMI consortium on gene therapy, and these companies are partners in the project. The University of Liverpool will get funding from the EU (but not from the partners), this IMI project commences on 3rd November 2020

Professor French - Other relevant interest - Provides clinical care when in covering the acute medical wards where patients with COVID-19 are cared. NPNS in GSK - In September 2020 a sub-contract was signed with the Liverpool School of Tropical Medicine to undertake work evaluating the safety and effectiveness of GSK's RTS's malaria vaccine in Malawi. GSK are the primary funders to the LSTM.

Ms Hunneyball - Other relevant interest – writes articles published in the Chemist and Druggist magazine, a trade magazine for pharmacists, but receives no payment for these articles. The information referred to in the articles is in the public domain. Ms Hunneyball makes it clear that these are her personal views and reflections and reference all sources of information used.

Professor Hyrich – NPNS - Professor Hyrich was co-I on an investigator-initiated research grant exploring predictors of outcome in rheumatoid arthritis. NPNS Pfizer- she is a Co-I on a grant exploring adherence to JAK inhibitors in rheumatoid arthritis. NPNS in Abbvie, Professor Hyrich gave some lectures at an education conference on effectiveness of treatment for rheumatoid arthritis.

Sir Michael Jacobs - Other relevant interest - As part of the academic role at the Liverpool School of Tropical Medicine, Sir Michael is a member of the Study Management Team and antiviral drug prioritisation group for the AGILE proof of concept (phase I/II) platform study. Sir Michael is also part of the team that submits new antiviral compounds against SARS-CoV2 for consideration by NIHR for testing on this platform. No commercial or financial interest in the trial or any of the compounds, or any pharmaceutical or biotechnology company.

Professor Lachman – Other relevant interest as a volunteer participant in the Oxford vaccine study and no other involvement in the study.

Dr Misbah - NPNS - Holds honorary Senior Lectureship with University of Oxford & Oxford University Hospitals NHS Foundation Trust

Dr Riordan - Other relevant interests - Participant in Oxford University's ChAdOx1 nCoV-19 clinical trial –received immunisation 27/8/2020
NPNS - Postgraduate External Examiner for Oxford University (Postgraduate Diploma in Paediatric Infectious Diseases)

Professor Solomon - Other relevant interests – Professor Solomon provides clinical care for patients with Covid-19; chaired the MRC/NIHR committee which awarded funding for development of the Oxford Vaccine.

Professor Weir - Other relevant interest arising from link to the Lothian NHS Board. NHS Lothian R&D has partially funded Professor Weir's post at University of Edinburgh, since 2010, so that he could provide methodological advice on health services research studies and clinical trials.

Invited Expert of the Covid-19 Vaccines Benefit Risk Expert Working Group declared the following interests:

Professor Douglas - Personal non-specific in Oxford University, lecturing fees in the last 12 months. Personal interest in GlaxoSmithKline – Shares, current holding Bayer – October 2019 fee for delivering investigator training related to Aflibercept. Non-personal in GlaxoSmithKline - current research grant
At the chair's discretion, Professor Douglas was permitted to remain for the discussion and to answer, but not ask, direct questions from the chair and other members.

[redacted] - Personal non-specific interest in AstraZeneca who provide [redacted] department at the London School of Hygiene and Tropical Medicine with an unrestricted research grant 2016-2021. The grant partially contributes to funding [redacted] salary. [redacted] research and employment is not dependent on this funding and Astra Zeneca have no influence on the nature of [redacted] research, or on reporting or dissemination of results**.** Other relevant interest as [redacted] is working on a statistical methodology paper and some of the co-authors are statisticians at Astra Zeneca in Cambridge. It's an academic paper on analysis of subgroups and neither I nor this work have anything to do with their business side (or any drugs at all).

The register of interests declared by participants had not been deemed to debar any other participation in line with the policy. No further interests were declared.

1.4 Apologies have been received from Professor Lehner for this meeting.

2. Minutes of the meeting held on Wednesday 28th October 2020

2.1 The minutes were approved as a true and accurate record of the proceedings, subject to the amendment of less abbreviations to specific paragraphs.

3. Plans for Vaccine Assessment for Nov/Dec – Verbal Update

3.1 The EWG heard a high-level summary update (via presentation) of the rolling assessments of the Pfizer/BioNTech mRNA vaccine (BNT162b2) and the AstraZeneca vaccine (AZD1222).

3.2 BNT162b2

3.2.1 The EWG heard that DHSC are working on a large communications piece and MHRA will contribute to that. MHRA informed if the vaccine is authorised, a Q & A will be prepared along with a public assessment report, and that MHRA would contribute to DHSC comms on 'myth busting'. The EWG agreed it would be useful for MHRA comms colleagues to be invited to the EWG to provide an overview of the communications plan.

3.2.2 The EWG heard that a separate CHM Expert Working Group has been in place since May to advise MHRA on its pharmacovigilance strategy. There are four strands to this: enhanced passive surveillance (yellow cards), targeted active surveillance (app-based), rapid cycle analysis and ecological analysis (based on electronic healthcare records) and epidemiological studies where required.

3.2.3 The EWG heard Dr Phil Bryan will give a short summary on these safety assessments at the next meeting.

3.2.4 The EWG heard that the MHRA have flagged to NHSEI that automated collection of vaccination records into electronic healthcare records is a key requirement for proactive surveillance.

3.2.5 The EWG discussed the issues surrounding the storage requirements of BNT162b2. The EWG heard the MHRA will be examining the stability data for the vaccine to see if it can support supply to the primary care sector.

3.2.6 The EWG heard the vaccine will have a median of 2 months safety data which is in line with FDA requirements regarding the safety exposure for an Emergency Use Authorisation of COVID-19 vaccines.

3.2.7 The EWG noted that the timings of the Pfizer interim analyses had been changed. It is expected that these changes were made when still blinded to the data to avoid bias and that the efficacy will be stated as 'unadjusted observed rate' and not 'adjusted observed rate'. This can be confirmed once the data has been received.

3.2.8 The EWG discussed the issues around releasing investigational medicinal product (IMP) for a mass vaccination programme. The company have referred to clinical trial

product, emergency use product and commercial product. It will not be clear which product is intended for the UK until MHRA receives the data.

3.2.9 The EWG heard that the company is seeking emergency authorisation in US. If MHRA can confirm that the product intended for the UK is the same as that for the US, this may provide some assurance.

3.2.10 The EWG heard a decision on the use of clinical trial product will likely be necessary in December.

3.2.11 The EWG discussed whether current placebo (saline) recipients will receive the trial product if it is known to be effective. The EWG heard that the company have not yet informed MHRA of their intentions however it was noted that FDA and WHO guidance recommends continuation with placebo control. The EWG discussed how in low income countries this could be their only opportunity to receive the vaccine.

3.2.12 The EWG discussed whether the safety of the lipid nanoparticles should be examined separately as the placebo is saline only. The EWG heard MHRA has already raised a non-clinical question on this and is awaiting a response from the company.

3.2.13 The EWG heard that if the double-blind trial is stopped this will mean only 2-3 months efficacy is available ahead of mass vaccination.

3.1.14 The EWG heard that WHO draft guidance on the minimum clinical criteria for [redacted] states a median of [redacted] months follow-up clinical data to be acceptable. It is noted that any real risks are usually observed within 6 weeks of the vaccination. Overall, the duration of follow-up for the trial is 2 years.

3.2.15 The EWG noted the independence of the MHRA in the decision-making process for the potential approval of the vaccine. It was also noted that the independence of the decision of the Vaccine Benefit Risk EWG and Commission of Human Medicines (CHM) is key. The EWG heard that MHRA has separated themselves from the vaccine taskforce in order to avoid any potential conflicts.

3.3 AZD1222

3.3.1 The EWG heard that recruitment to the AstraZeneca trial was near completion in the most recent communication a few weeks ago. The total number of participants will be lower than the BNT vaccine (around 20,000).

3.3.2 The EWG heard that AstraZeneca had planned interim analyses, but the statistical plan has undergone several revisions and MHRA have not seen the last version. The EWG heard that no clinical data has been provided to the MHRA yet. Quality (3 sequences) and non-clinical (1 sequence) data is under assessment.

4. <u>Any Other Business</u>

4.1 None.

5. Date and time of next meeting

The next meeting is scheduled to take place on **Tuesday 24th November 2020** at **2.30pm**.

Date and time of future meetings:

- **Monday 7th December (10.30am - 1pm)**
- **Tuesday 22nd December (11.30am - 2pm)**

The Meeting started at 14:31 and ended at 15:54.

Members are reminded that the content of papers and proceeding of the meetings are to be treated as 'Official – sensitive commercial'. Members are also reminded that, in accordance with the Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members must also declare any other matter which could reasonably be perceived as affecting their impartiality. Detailed guidance is set out in the Code of Practice

Annex I

Conflict of Interest Policy for CHM COVID-19 Vaccine Benefit Risk EWG

Chair and Members

- May not hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
- May not currently be or have previously been involved in the development of COVID-19 vaccines

Invited to all meetings, receives all papers and presentations and is permitted full participation in discussion, including drawing up conclusions and recommendations

Invited experts

- May hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
- May currently be or have previously been involved in the development of COVID-19 vaccines

May be invited to all relevant meetings, receives all papers and presentations and is permitted to participate in discussions when invited by the Chair. Does not contribute to conclusions and recommendations

Observers

Are invited to attend all meetings. Will not participate in drawing up conclusions and recommendations.

COMMISSION ON HUMAN MEDICINES (CHM)

COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Wednesday 18th November 2020** at **15:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan
Professor N French
Professor D Goldblatt
Ms S Hunneyball
Professor K Hyrich
Sir M Jacobs
Professor H J Lachmann
Professor P J Lehner
Dr S Misbah
Professor S Price
Dr A Riordan
Professor C Robertson
Professor T Solomon
Dr R Thorpe
Mrs M Wang
Professor C Weir

Members of the CTBV Expert Advisory Group

Professor B K Park
Professor M Turner

Members of the CPS Expert Advisory Group

Mr VI G Fenton-May
Mr R Lowe
Professor Y Perrie
Professor K M G Taylor (Chair of CTBV)
Dr S Walsh

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
Dr P Bryan - VRMM
[redacted] - LD

Supporting Specific Items

[redacted] - PHE
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD

MHRA Observers

[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
Dr S Branch - VRMM
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - VRMM
Dr S P Lam - LD
[redacted] - VRMM
[redacted] - LD
Mr K McDonald - LD

Observer

Professor S Ralston (Chair of CHM)

Apologies

Professor P Shah

Secretariat

[redacted]

[redacted]

[redacted]

Minute Taker

[redacted] - LD

[redacted] - LD

Dr N Rose - MHRA-NIBSC

[redacted] - LD

[redacted] - LD

Mr P Tregunno - VRMM

[redacted] - LD

[redacted] - LD

Dr K Wydenbach - LD

Key

LD = Licensing Division
NIBSC = National Institute for Biological Standards & Control
VRMM = Vigilance & Risk Management of Medicines
CHM = Commission on Human Medicines
CTBV = Clinical Trials, Biologicals & Vaccines EAG
CPS = Chemistry, Pharmacy & Standards EAG
PHE = Public Health England

[redacted]

18th January 2021

1. Introduction and Announcement

1.1 The Chair reminded Members that the content of papers and proceeding of the meeting are strictly confidential and should be treated as 'Official – sensitive commercial' and should not be disclosed. There is no consent for members / participants to record the meeting, take screenshots or photographs of presentations.

1.2 Conflict of Interest Policy (Annex I to the minutes)

The Chair reminded members and participants that, in accordance with the CHM Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members were also reminded to declare any other matter which could reasonably be perceived as affecting their impartiality.

1.3 The following members declared interests and other relevant interests to date:

C19VBR EWG

Professor Sir Munir Pirmohamed - NPNS AstraZeneca - Research grant to UOL to support PhD in drug interactions.
Other relevant interests in Pfizer, Janssen, Sanofi – Sir Munir is part of an EU-funded IMI consortium on gene therapy, and these companies are partners in the project. The University of Liverpool will get funding from the EU (but not from the partners), this IMI project commences on 3rd November 2020.
AGILE – this is a Liverpool early phase trial platform (between University of Liverpool and Liverpool School of Tropical Medicine). It is funded by the Wellcome Trust and UKRI/DHSC/NIHR. It is NOT evaluating vaccines, but only drugs to treat COVID-19. Sir Munir is not on the trial management group, and he is not directly involved in choosing the compounds for the study. Sir Munir has no involvement with any of the developers of the compounds to be studied (academic or industrial).
Sir Munir is a member of the UK COVID Therapeutics Advisory Panel (UK-CTAP), which is advising the CMO on which compounds need to be prioritised for the RECOVERY+ trial (RECOVERY is funded via NIHR/DHSC).

Professor French - Other relevant interest **-**. Provides clinical care when in covering the acute medical wards where patients with COVID-19 are cared.
NPNS in GSK- In September 2020 a sub-contract was signed with the Liverpool School of Tropical Medicine to undertake work evaluating the safety and effectiveness of GSK's RTS's malaria vaccine in Malawi. GSK are the primary funders to the LSTM.

Ms Hunneyball - Other relevant interest – writes articles published in the Chemist and Druggist magazine, a trade magazine for pharmacists but receives no payment for these articles. The information referred to in the articles is in the public domain. Ms Hunneyball makes it clear that these are her personal views and reflections and reference all sources of information used.

Professor Hyrich - NPNS - Professor Hyrich was co-I on an investigator-initiated research grant exploring predictors of outcome in rheumatoid arthritis. NPNS Pfizer- she is a Co-I on a grant exploring adherence to JAK inhibitors in rheumatoid arthritis. NPNS in Abbvie Professor Hyrich gave some lectures at an education conference on effectiveness of treatment for rheumatoid arthritis.

Sir Michael Jacobs - Other relevant interest - As part of the academic role at the Liverpool School of Tropical Medicine, Sir Michael is a member of the Study Management Team and antiviral drug prioritisation group for the AGILE proof of concept (phase I/II) platform study. Sir Michael is also part of the team that submits new antiviral compounds against SARS-CoV2 for consideration by NIHR for testing on this platform. No commercial or financial interest in the trial or any of the compounds, or any pharmaceutical or biotechnology company.

Professor Lachman – Other relevant interest as a volunteer participant in the Oxford vaccine study and no other involvement in the study.

Professor Lehner - Other relevant interest – Professor Lehner previously held a DPAC (Discovery Partnership with Academia) agreement with GSK, but this has been completed.

Dr Misbah - NPNS - Holds honorary Senior Lectureship with University of Oxford & Oxford University Hospitals NHS Foundation Trust.

Dr Riordan - Other relevant interests - Participant in Oxford University's ChAdOx1 nCoV-19 clinical trial –received immunisation 27/8/2020
NPNS - Postgraduate External Examiner for Oxford University (Postgraduate Diploma in Paediatric Infectious Diseases)

Professor Solomon - Other relevant interests – Professor Solomon provides clinical care for patients with Covid-19; chaired the MRC/NIHR committee which awarded funding for development of the Oxford Vaccine.

Professor Weir - Other relevant interest arising from link to the Lothian NHS Board. NHS Lothian R&D has partially funded Professor Weir's post at University of Edinburgh, since 2010, so that he could provide methodological advice on health services research studies and clinical trials.

CTBV EAG

Professor Park - NPNS in GSK Research & Development Ltd. and in Janssen as I received a research grant in the past two years. The grant has been handed over to a colleague in 2020 and the grant is due to finish in 2020. Professor Park received no direct payment. In addition, Professor Park have two active IMI grants for Transbioline and Quantitatve Systems Toxicology, he is the PI on the TransBioline grant for the University of Liverpool. Both grants are paid directly to the University of Liverpool.

Professor Turner – Other relevant interest. Professor Turner is a Non Executive Director (non-remunerated) on the Board of the Cell and Gene Therapy Catapult (CGT).
CGT have been tasked by UK Government with re-purposing a factory in Braintree to manufacture either a vaccine or a therapeutic mAb. No decision has been made as to whether or what product CGT Braintree may be asked to manufacture and that decision will be made by UK Government. Professor Turner does not believe that CGT Board will have any material input into the decision as to what product may be manufactured.

CPS EAG

Mr V'lain Fenton-May – None

Mr Robert Lowe – None

Professor Perrie - NPNS in Pfizer & AstraZeneca arising from a contract for a grant (March 2018), which includes contributions from these companies to the University of Strathclyde, Janssen in writing a grant for a PhD (now funded), GSK – arising from an EU grant to University of Strathclyde (Jan 2019-Dec 2019)

Professor Kevin Taylor – None

Dr Susannah Walsh – None

CHM (Observer)

Professor Ralston – NPNS – Sanofi, Pfizer, Janssen, AstraZeneca & Other relevant interests in NHS Lothian and Oxford University. Professor Ralston has an honorary consultant contract with NHS Lothian but has not been involved in any trials relating to COVID-19. He also has agreed to be an external examiner for Oxford University clinical trials MSc; however, this has not yet started.

The register of interests declared by participants had not been deemed to debar any other participation in line with the policy. No further interests were declared.

1.4 Apologies have been received from Professor Shah for this meeting.

1.5 The Chair welcomed the following:

Members of the Clinical Trials, Biologicals and Vaccines Expert Advisory Group (CTBVEAG)

- **Professor B Kevin Park**
- **Professor Marc Turner**

Members of the Chemistry, Pharmacy & Standards Expert Advisory Group (CPSEAG).

- **Professor Kevin Taylor**
- **Mr V'lain Fenton-May**
- **Mr Robert Lowe**
- **Professor Yvonne Perrie**
- **Dr Susannah Walsh**

Professor Ralston, Chair of CHM who joined as an observer.

[redacted] Consultant Epidemiologist, Public Health England, Immunisation and Countermeasures Division, who participated for item 7 to give an update on PHE Surveillance activities.

1.6 The Chair informed the Group that Members and Invited Experts who had declared personal interests (or potentially perceived interest) were not invited to this meeting and will not be participating in the future meetings.

2. Minutes of the meeting held on Tuesday 10th November 2020

2.1 The minutes were approved as a true and accurate record of the proceedings.

3. Current status of rolling assessment of Pfizer/BioNTech mRNA vaccine (BNT162b2)

3.1 The EWG heard a high-level summary update of the rolling assessment of the Pfizer/BioNTech mRNA vaccine (BNT162b2). The EWG also heard high-level summary given by NIBSC on the planned controls for vaccine batch release.

3.2 The EWG heard that the planned controls for vaccine batch release centre on four parameters: product appearance, identity (encapsulation, RNA integrity), potency, and protocol review. Due to time constraints, it is unlikely that all of these controls will be in place at the time of first batch release; however, a risk mitigation based approach has been pre-defined to discern the various configurations of control measures which would be considered sufficient to ensure batch consistency.

3.3 The EWG heard MHRA are expecting to clarify if the first batches of the vaccine will be of the same specification as those used in the clinical trial. The EWG heard there would be a lower degree of risk associated with the 'clinical trial product' due to the availability of safety data from the trial. The EWG heard that data to aid with the qualification of the batches intended for the UK market has been requested.

3.4 The EWG noted that a data sharing approach between competent authorities could facilitate the rapid acquisition of batch data for instances where batches are divided between nations. The EWG heard that in this regard, MHRA are defining an approach to sharing data with the FDA and further options are being explored.

3.5 The EWG noted the sparse data and information on: flow, batch testing, protocols, and full details of the roll-out.

3.6 The EWG asked if the company are required to respond to the 36 questions posed by the MHRA. The MHRA confirmed that whilst there is no formal obligation to reply, key issues such as sufficient data / detail on: product stability, batch qualification and adventitious agents, e.g. TSE status, will be required prior to any form of authorisation being awarded.

3.7 The EWG asked about the EMA's rolling review of BNT162b2 and how it differs from the MHRA's review process for regulation 174 (temporary authorisation of the supply of an unlicensed vaccine). The EWG heard that the outcome of the EMA's assessment, if positive, is grant of a Marketing Authorisation (MA), either conditional or full MA. The MHRA's current review of BNT162b2 in line with regulation 174 is a risk-based evaluation in the context of emergency use and does not result in a MA for the product but a separate form of authorisation to supply. The emergency use review process seeks to confirm the absence of major issues or gaps in the data that could represent safety concerns, prior to the vaccine's deployment.

3.8 The EWG asked about the dimensions of the final presentation for the vaccine, in relation to the storage space needed and the feasibility of ensuring adequate control of the cold chain. The EWG heard the design of the presentation was envisaged for use in a mass vaccination programme, hence the pack size of 195 multi-dose vials. The EWG heard that the plans place reliance on networks of PCNs hiring larger venues such as community halls. The EWG heard representatives from NHS England and DHSC will be invited to a subsequent meeting of the EWG to outline the operational model. The EWG noted vaccination of care home residents will need to be considered within deployment operations and that further stability data are required to underpin the deployment model.

3.9 The EWG heard that based on currently available stability data, once the vials are removed from ultra-low temperature storage the shelf-life at 2-8^{o}C is 120 hours and once diluted with saline the shelf life is 6 hours; this is in line with WHO recommendations for unpreserved vaccines intended for use in mass vaccination campaigns. The EWG heard supply will include distribution via third party wholesalers, necessitating pack splitting, as such labelling will require precise guidance on storage and storage precautions.

3.10 The EWG noted it was summer in South America during the phase II/III trial. The EWG asked if data from the South American cohort could be used for comparative analysis with other trial regions to inform on the robustness of the cold chain. The EWG noted that the vaccine usage protocol should assure applicability to real-world scenarios including maintaining the safety profile of returning of vials to cold storage and acceptable in-use duration between isolating first dose and last dose from the vial. The EWG noted that assurance of sterility and the availability of sterilisation method data should also be assessed in detail. The EWG heard the multidose vial does not contain any preservatives.

3.11 The EWG asked if the lipid nanoparticle element of the vaccine possesses any adjuvant properties, aside from innate adjuvant activity. The EWG noted a separate evaluation of quality would likely be required if the nanoparticles have been included in the formulation to act as an adjuvant, in addition to their main role of delivering mRNA through the lipid bilayer. The MHRA confirmed that presently no specific data have been submitted on the nanoparticles as an adjuvant.

3.12 The EWG heard vaccine efficacy (VE) was evaluated versus placebo 2 weeks after vaccine dose 2: VE 95.5%, 90 cases of COVID-19 in placebo and 4 cases of COVID-19 in the treatment group (C.I 88.8 – 98.4).The EWG heard that the WHO state the point estimate of efficacy for a COVID-19 vaccine should be at least 50% (reduction in COVID-19 disease cases) and the lower bound of the 95% confidence interval (adjusted) should be >30%. The EWG noted that ~84% of the trial participants were Caucasian.

3.13 The EWG noted the current data are limited to establish efficacy of the vaccine in preventing severe COVID-19 illness with 7 severe cases, all in the placebo group; 5 cases were reported between Dose 1 and Dose 2 and 2 cases were reported at least 7 days after Dose 2. The EWG noted lack of data in those excluded from the phase II/III trial (pregnant women, people with worsening health, those immunocompromised). The EWG noted further data on VE versus placebo in subgroups at greater risk would be valuable.

3.14 The EWG heard 43% of trial participants were over the age of 55 years. The EWG noted that the exposure data are reassuring in over 65s, but there are limited data in those aged 85 and over. The EWG noted if a full breakdown of participants by age was available, calculations could help to understand VE versus placebo in the upper age brackets. The EWG noted that as a minimum, individual listing data on antibody response in the older age should be provided. The EWG also noted that data from subjects close to the threshold of obesity could be useful to assess VE versus placebo in overweight subjects.

3.15 The EWG heard the data cover a median duration of follow-up after the second dose of less than 2 months. The EWG expressed concern that the minimum median duration of efficacy and safety follow-up requirements specified by WHO (median 3 months follow-up) and FDA (median 2 months follow-up) to assess benefit-risk, may not be met in time for the decision on the Regulation 174 authorisation. The EWG also noted that the duration of follow-up data currently available could be insufficient to capture the development of adverse events. The EWG noted that the currently available interim data may not have sufficient duration of follow-up as protection through innate immunity or immediate post vax neutralization titres

of short duration may be incorrectly identified as secondary immune response (antibody mediated response) to the vaccine.

3.16 The EWG noted the preparations for roll-out for the NHS is the 30 November 2020.

3.17 The EWG heard that VE in seronegative + seropositive participants is the second co-primary end-point in the trial. The data on this end-point are expected to be included in the final analysis, however, the data may not be available at time of decision on authorisation within terms of regulation 174.

3.18 The EWG noted the absence of data on VE against transmission, and the importance of this for understanding the potential to reach herd immunity. The EWG heard the trial design was not configured to measure the vaccine's efficacy against disease transmission.

3.19 The EWG noted that the data indicate a highly reactogenic vaccine with levels of reactogenicity similar to those observed with the typhoid vaccine. The EWG heard the extent of data to support the reactogenicity profile is in line with WHO requirements. The EWG noted product information and communications will need to inform recipients of what to expect from the vaccine. The EWG heard that systemic reactions are more frequent and more severe after dose 2, and in younger recipients.

3.20 The EWG noted regarding vaccine associated enhancement of disease (VAED), T helper 1 (Th1) versus T helper 2 (Th2) cellular and humoral immunity data are reassuring. However, VAED may not be apparent until VE starts to wane.

3.21 The EWG asked about the death in the vaccine group. The EWG heard the subject was a 60-year-old male, obese, and taking two concomitant medicines for depression. The EWG heard that specific cardiovascular events are usually recorded as a cause of death rather than arteriosclerosis. However, this reflects the content of narrative provided.

3.22 The EWG noted that in the phase I trial, lymphopenia was reported in the vaccine group. The EWG heard the company confirmed the vaccine's mechanism of action is expected to induce lymphopenia, and all events of lymphopenia in phase I were transient and resolved completely. Testing for lymphopenia was not conducted in phase II/III of the trial.

3.23 The EWG noted the potential signal of lymphadenopathy from the clinical trial data, 44 events in the vaccine arm related to upper limb lymph nodes compared to 4 in the placebo group. The EWG noted a potential linkage to the 6 cases of appendicitis in the vaccine arm compared to one case in the placebo group should be explored further and monitored. The EWG heard that the MHRA are currently conducting a detailed evaluation these events. The EWG noted that a signal of lymphadenopathy was also observed in the non-clinical data, lymphadenopathy was reversible, and the literature suggest the signal was expected for vaccines. The EWG noted that non-clinical data on reproductive toxicity would be beneficial in particular, data on use in pregnancy, but it was appreciated that the non-clinical data are still being generated.

3.24 The EWG heard that historical incidence data suggests that Guillain-Barré Syndrome when associated with vaccine administration, usually occurs within 6 weeks of dosing, and highest risk is 2-3 weeks post-dose (Polakowski et al, 2013; American Journal of Epidemiology, Babazadeh et al, 2019; Journal of Translational Internal Med.). The EWG noted that gastrointestinal (G.I) AEs such as intussusception and G.I perforation should be carefully assessed.

3.25 The EWG noted that antipyretics given at the time of some other vaccines have been postulated to interfere with immune response. The EWG heard antipyretics were not recommended to be given as a prophylaxis in the clinical trial protocol. The EWG heard clinical trial data is available on dosing and administration of antipyretics and this will likely inform the phrasing of the SmPC i.e. to suggest use only for pain and fever experienced from Day 2 post-vaccination.

3.26 The EWG noted the Pfizer's press release from today stated that the trial limit of 170 evaluable cases of COVID-19 has been reached and VE is confirmed in both those with or without previous COVID-19 infection. The EWG heard that these data are expected to be submitted to the MHRA in due course. The EWG heard in this package data on 15,000 subjects covering a median follow-up above 2 months post dose 2 is likely to be included.

3.27 The EWG heard the number of trial subjects given the vaccine in Germany, Turkey and South Africa was limited as recruitment to these sites was only beginning when the required number of COVID-19 clinical cases had been reached in the US, Argentina and Brazil.

3.28 The EWG noted the potential importance of vaccine failure data from the 8 participants that were vaccinated but still contracted COVID-19. Data should include the clinical features of their disease including symptomatic status, viral load, pathogenesis and immunogenicity. The EWG noted that the data should be requested. The EWG heard in the package of interim data, the case narratives of the subjects that experienced vaccine failures have been provided and none of these cases were severe.

3.29 The EWG noted the importance of stratified data on symptomatic seropositive trial participants to help inform expectations when vaccinating exposed individuals in the community. The EWG heard that the primary analysis only includes seronegative subjects and that the information in seropositive patients is not yet available. The EWG heard that there is no excess of COVID-19 cases in the active arm vs the placebo arm in those cases not included in the primary analysis, which would include cases in seropositive subjects.

3.30 The EWG also enquired about cases occurring before the second dose of the vaccine. The EWG heard that there appears to be protection even after only the first dose is received, with preliminary analyses by the assessors based on the case narratives showing fewer cases before dose 2 is received in the active arm compared to placebo.

3.31 The EWG heard case studies outside of the period of interim review indicate fewer COVID-19 infections in the vaccine arm prior to the second dose (32 vaccine versus 75 placebo group) suggestive of protective effect of the vaccine after first dose. The EWG noted an extreme imbalance would be worth investigating, but lesser imbalances should be protected by the processes of blinding and randomisation, and there is presently nothing to suggest a lapse in blinding or inadequate randomisation.

3.32 The EWG noted the background attack rate data in table 16 shapes the subgroup analysis. Approximately a third of COVID-19 cases in the placebo group were in Argentina, which is half of the number of COVID-19 cases reported in the US subjects; however, the majority of subjects were in the US (12,500 versus 2500). It was asked whether adjustments have been made for this in the analysis. It was confirmed that the analysis was not stratified by country. The EWG noted the relatively higher number of COVID cases in US subjects was most likely to be due to the differences in COVID-19 incidence rates in the US compared to Argentina. The EWG heard the MHRA will explore this data further.

3.33 The EWG requested future access via the portal to the presentation slides and the statistical analysis plan. The EWG commented that the read-only functionality of the assessment

report documentation, prevents the ability to highlight relevant data and make comments electronically. The EWG heard this step was taken to enhance data security.

3.34 The MHRA acknowledged the potential safety concerns over the limited duration of follow-up, and that information to draw robust conclusions on safety was currently insufficient. The EWG heard a specific date for receiving additional data is not yet available, but assessment will continue on any incoming data, and details of further data / assessment will be presented to EWG and/or CHM as appropriate.

4. Pharmacovigilance / Update on PHE Surveillance activities

4.1 The EWG received a summary of MHRA vaccine pharmacovigilance and the progress towards implementation. The EWG subsequently received a summary of PHE plans for post marketing vaccine surveillance.

4.2 The EWG noted that the MHRA and PHE must endeavour to ensure that pharmacovigilance data is rapidly shared between all nations of the United Kingdom.

4.3 The EWG noted that traceability needs to be established in terms of vaccine failures in order to conduct root cause analyses. The EWG heard vaccine failure data will be obtainable as part of base line and convalescent (recovered patients) enhanced surveillance, but gathering this information is not currently possible through surveillance of data from blood banks. The EWG noted that the power calculation for vaccine failures should be re-visited to ensure the sample size is sufficient.

5. Any Other Business

5.1 The MHRA secretariat proposed an extraordinary EWG meeting on Saturday 21 November 2020 at approximately 2pm, for an explanatory session of the Pfizer vaccine assessment report.

6. Date and time of next meeting

The next meeting is scheduled to take place on **Friday 20th November 2020** at **2.30pm**.

Date and time of future meetings:

- **Tuesday 24th November 2020** at **2.30pm**.
- **Monday 7th December (10.30am - 1pm)**
- **Tuesday 22nd December (11.30am - 2pm)**

The Meeting started at 15:30 and ended at 18:20.

Members are reminded that the content of papers and proceeding of the meetings are to be treated as 'Official – sensitive commercial'. Members are also reminded that, in accordance with the Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members must also declare any other matter which could reasonably be perceived as affecting their impartiality. Detailed guidance is set out in the Code of Practice

Annex I

Conflict of Interest Policy for CHM COVID-19 Vaccine Benefit Risk EWG

Chair and Members

- May not hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
- May not currently be or have previously been involved in the development of COVID-19 vaccines

Invited to all meetings, receives all papers and presentations and is permitted full participation in discussion, including drawing up conclusions and recommendations

Invited experts

- May hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
- May currently be or have previously been involved in the development of COVID-19 vaccines

May be invited to all relevant meetings, receives all papers and presentations and is permitted to participate in discussions when invited by the Chair. Does not contribute to conclusions and recommendations

Observers

Are invited to attend all meetings. Will not participate in drawing up conclusions and recommendations.

COMMISSION ON HUMAN MEDICINES (CHM)

COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Friday 20th November 2020** at **14:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan
Professor N French
Professor D Goldblatt
Ms S Hunneyball
Professor K Hyrich
Sir M Jacobs
Professor H J Lachmann
Professor P J Lehner
Dr S Misbah
Professor S Price
Dr A Riordan
Professor C Robertson
Professor P Shah
Professor T Solomon
Dr R Thorpe
Mrs M Wang
Professor C Weir

Members of the CTBV Expert Advisory Group

Professor B K Park
Professor M Turner

Members of the CPS Expert Advisory Group

Mr VI G Fenton-May
Mr R Lowe
Professor Y Perrie
Professor K M G Taylor (Chair of CPS)
Dr S Walsh

Observer

Professor S Ralston (Chair of CHM)

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted] - LD

MHRA Observers

[redacted] - VRMM
[redacted] - LD
[redacted] - MHRA-NIBSC
[redacted] - LD
[redacted] - LD
Dr S Branch - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - MHRA-NIBSC
[redacted] - VRMM
Mr K McDonald - LD
[redacted] - LD
[redacted] - LD
Dr N Rose - MHRA-NIBSC
Dr C Schneider - MHRA-NIBSC
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD

Presentations

COG-UK

[redacted]

Pfizer/BioNTech

[redacted]

Moderna

[redacted]

Secretariat

[redacted]

Key

LD = Licensing Division
NIBSC = National Institute for Biological Standards & Control
VRMM = Vigilance & Risk Management of Medicines
CTBV = Clinical Trials, Biologicals & Vaccines EAG
CPS = Chemistry, Pharmacy & Standards EAG
PHE = Public Health England
CHM = Commission on Human Medicines

[redacted]

7th December 2020

1. Introduction and Announcement

1.1 The Chair reminded Members that the content of papers and proceeding of the meeting are strictly confidential and should be treated as 'Official – sensitive commercial' and should not be disclosed. There is no consent for members / participants to record the meeting, take screenshots or photographs of presentations.

1.2 The Chair informed members and participants that this is a call for evidence meeting.

The Chair welcomed the presenters at today's meeting.

2. The EWG heard presentations from COG-UK, [redacted], Research Associate at the University of Cambridge now coordinating all the activities of the mutational analysis and tracking working group for the COG-UK consortium.

3. The EWG also heard presentations from Pfizer/BioNTech, [redacted] and [redacted] and from Moderna, [redacted].

4. Any Other Business

4.1 Members have been asked to review Information Security Briefing on Covid-19 Vaccine Data and confirm that they understand and agree to adhere to the protocols.

The Meeting started at 14:32 and ended at 16:10.

Members are reminded that the content of papers and proceeding of the meetings are to be treated as 'Official – sensitive commercial'. Members are also reminded that, in accordance with the Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members must also declare any other matter which could reasonably be perceived as affecting their impartiality. Detailed guidance is set out in the Code of Practice

COMMISSION ON HUMAN MEDICINES (CHM)

COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Saturday 21st November 2020** at **14:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan
Professor N French
Professor D Goldblatt
Ms S Hunneyball
Professor K Hyrich
Sir M Jacobs
Professor H J Lachmann
Professor P J Lehner
Dr S Misbah
Professor S Price
Dr A Riordan
Professor C Robertson
Professor T Solomon
Dr R Thorpe
Mrs M Wang
Professor C Weir

Members of the CTBV Expert Advisory Group

Professor B K Park
Professor M Turner

Members of the CPS Expert Advisory Group

Mr VI G Fenton-May
Professor Y Perrie
Professor K M G Taylor (Chair of CPS)
Dr S Walsh

Observer

Professor S Ralston (Chair of CHM)

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted] - LD

MHRA Supporting specific items

[redacted] - LD
[redacted] - LD
Dr N Rose - MHRA-NIBSC
[redacted] - LD
[redacted] - LD

MHRA Observers

[redacted] - Government Legal Team
Dr S Atkinson - Dir
Dr M Bailey - MHRA-NIBSC
[redacted] - LD
[redacted] - LD
[redacted] - LD
Dr S Branch - VRMM
[redacted] - Accenture IT Support
[redacted] - LD
Dr P Bryan - VRMM
[redacted] - MHRA-NIBSC
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
Dr SP Lam - LD
[redacted] - VRMM
[redacted] - LD
Mr K McDonald - LD
Ms T Moore - IE&S

Apologies

Professor P Shah

Mr R Lowe (Member of CPS)

NHS / PHE presenters for item 2

[redacted] – NHS Wales

[redacted] – NHS Northern Ireland

[redacted] – NHS England

[redacted] – NHS Wales

[redacted] – NHS England

[redacted] – NHS England

[redacted] – NHS England

[redacted] – NHS Scotland

[redacted] – PHE

[redacted] – NHS England

[redacted] - IE&S

Dr J Raine - MHRA CEO

[redacted] - LD

Dr C Schneider - MHRA-NIBSC

[redacted] - IE&S

[redacted] - LD

[redacted] - LD

Secretariat

[redacted]

[redacted]

[redacted]

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NHS = National Health Service
PHE = Public Health England
IE&S = Inspection, Enforcement & Standards
Dir = Director of Operational Transformation
MHRA CEO = Chief Executive

[redacted]

7th December 2020

1. Introduction and Announcement

1.1 The Chair reminded Members that the content of papers and proceeding of the meeting are strictly confidential and should be treated as 'Official – sensitive commercial' and should not be disclosed. There is no consent for members / participants to record the meeting, take screenshots or photographs of presentations.

1.2 Conflict of Interest Policy (Annex I to the minutes)

The Chair reminded members and participants that, in accordance with the CHM Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members were also reminded to declare any other matter which could reasonably be perceived as affecting their impartiality.

1.2 The following members declared non-personal interests and other relevant interests to date:

C19VBR EWG

Professor Sir Munir Pirmohamed - NPNS AstraZeneca - Research grant to UOL to support PhD in drug interactions.
Other relevant interests in Pfizer, Janssen, Sanofi – Sir Munir is part of an EU-funded IMI consortium on gene therapy, and these companies are partners in the project. The University of Liverpool will get funding from the EU (but not from the partners), this IMI project commences on 3rd November 2020.
AGILE – this is a Liverpool early phase trial platform (between University of Liverpool and Liverpool School of Tropical Medicine). It is funded by the Wellcome Trust and UKRI/DHSC/NIHR. It is NOT evaluating vaccines, but only drugs to treat COVID-19. Sir Munir is not on the trial management group, and he is not directly involved in choosing the compounds for the study. Sir Munir has no involvement with any of the developers of the compounds to be studied (academic or industrial).
Sir Munir is a member of the UK COVID Therapeutics Advisory Panel (UK-CTAP), which is advising the CMO on which compounds need to be prioritised for the RECOVERY+ trial (RECOVERY is funded via NIHR/DHSC).

Professor French - Other relevant interest **-** Provides clinical care when in covering the acute medical wards where patients with COVID-19 are cared. NPNS in GSK - In September 2020 a sub-contract was signed with the Liverpool School of Tropical Medicine to undertake work evaluating the safety and effectiveness of GSK's RTS's malaria vaccine in Malawi. GSK are the primary funders to the LSTM.

Ms Hunneyball - Other relevant interest – writes articles published in the Chemist and Druggist magazine, a trade magazine for pharmacists, but receives no payment for these articles. The information referred to in the articles is in the public domain. Ms Hunneyball makes it clear that these are her personal views and reflections and reference all sources of information used.

Professor Hyrich – NPNS - Professor Hyrich was co-I on an investigator-initiated research grant exploring predictors of outcome in rheumatoid arthritis. NPNS Pfizer- she is a Co-I on a grant exploring adherence to JAK inhibitors in rheumatoid arthritis. NPNS in Abbvie, Professor Hyrich gave some lectures at an education conference on effectiveness of treatment for rheumatoid arthritis.

Sir Michael Jacobs - Other relevant interest - As part of the academic role at the Liverpool School of Tropical Medicine, Sir Michael is a member of the Study Management Team and antiviral drug prioritisation group for the AGILE proof of concept (phase I/II) platform study. Sir Michael is also part of the team that submits new antiviral compounds against SARS-CoV2 for consideration by NIHR for testing on this platform. No commercial or financial interest in the trial or any of the compounds, or any pharmaceutical or biotechnology company.

Professor Lachmann – Other relevant interest as a volunteer participant in the Oxford vaccine study and no other involvement in the study.

Dr Misbah - NPNS - Holds honorary Senior Lectureship with University of Oxford & Oxford University Hospitals NHS Foundation Trust.

Professor Price - NPNS in GSK and AstraZeneca – which relates to donations provided by both companies to the British Toxicology Society (BTS) to support their Annual Congress and Education and Training of which Professor Price is currently President of the Society (2020-2022).

Dr Riordan - Other relevant interests - Participant in Oxford University's ChAdOx1 nCoV-19 clinical trial –received immunisation 27/8/2020. NPNS - Postgraduate External Examiner for Oxford University (Postgraduate Diploma in Paediatric Infectious Diseases).

Professor Solomon - Other relevant interests – Professor Solomon provides clinical care for patients with Covid-19; chaired the MRC/NIHR committee which awarded funding for development of the Oxford Vaccine.

Professor Weir - Other relevant interest arising from link to the Lothian NHS Board. NHS Lothian R&D has partially funded Professor Weir's post at University of Edinburgh, since 2010, so that he could provide methodological advice on health services research studies and clinical trials.

CTBV EAG

Professor Park - NPNS in GSK Research & Development Ltd. and in Janssen as I received a research grant in the past two years. The grant has been handed over to a colleague in 2020 and the grant is due to finish in 2020. Professor Park received no direct payment. In addition, Professor Park have two active IMI grants for Transbioline and Quantitatve Systems Toxicology, he is the PI on the TransBioline grant for the University of Liverpool. Both grants are paid directly to the University of Liverpool.

Professor Turner – NPNS interest. Professor Turner is a Non Executive Director (non-remunerated) on the Board of the Cell and Gene Therapy Catapult (CGT).
CGT have been tasked by UK Government with re-purposing a factory in Braintree to manufacture either a vaccine or a therapeutic mAb. No decision has been made as to whether or what product CGT Braintree may be asked to manufacture and that decision will be made by UK Government. Certainly I don't believe that CGT Board will have any material input into the decision as to what product may be manufactured.

CPS EAG

Mr V'lain Fenton-May – None

Professor Yvonne Perrie - NPNS in Pfizer & AstraZeneca arising from a contract for a grant (March 2018), which includes contributions from these companies to the University of Strathclyde, Janssen in writing a grant for a PhD (now funded), GSK – arising from an EU grant to University of Strathclyde (Jan 2019-Dec 2019)

Professor Kevin Taylor – None

Dr Susannah Walsh – None

CHM (Observer)

Professor Ralston – NPNS – Sanofi, Pfizer, Janssen, AstraZeneca & Other relevant interests in NHS Lothian and Oxford University. Professor Ralston has an honorary consultant contract with NHS Lothian but has not been involved in any trials relating to COVID-19. He also has agreed to be an external examiner for Oxford University clinical trials MSc; however, this has not yet started.

The register of interests declared by participants had not been deemed to debar any other participation in line with the policy. No further interests were declared.

The Chair welcomed

Members of the Clinical Trials, Biologicals and Vaccines Expert Advisory Group (CTBVEAG)

Chair and Members of the Chemistry, Pharmacy & Standards Expert Advisory Group (CPSEAG).

Chair of CHM – **Professor Ralston** who joined as an observer

NHS:

- [redacted] –Medical Director, NHS England

Public Health England (PHE)

- [redacted] – Deputy Director at PHE

NHS Deployment Team

- PHE **–** [redacted] (Paper – 201030 PHE Operating Model – central storage and UK distribution covid vaccine & products. Slides - Courageous UK supply chain)
- NHSE **–** [redacted] and [redacted] with [redacted] to assist.
- NHS Wales **–** [redacted] and [redacted]
- NHS Northern Ireland **–** [redacted]
- NHS Scotland **–** [redacted] **(**Paper – NHS Scotland CHM Covid-19VBR deployment)

2. The Expert Working Group (EWG) heard presentations on deployment from PHE, NHS England, NHS Wales, NHS NI and NHS Scotland

2.1 The EWG discussed whether whole populations should be vaccinated in rural areas due to difficulties in separating out vulnerable populations.

2.2 The EWG heard that packing down was noted as an option in order to reduce waste but seems to be problematic for all nations apart from Scotland.

2.3 The EWG heard from NHSE that wastage was estimated to be 15-20%. NHSW will adopt a zero-tolerance approach towards wastage but accepts due to the characteristics of the vaccine it will occur.

2.4 The EWG heard that information on the impact of shaking and movement of the vaccine during transit has been informally provided to NHS from Pfizer. The data needs to be submitted to MHRA first for review.

2.5 The EWG discussed the labelling of the diluent and questioned whether, as the diluent looks like the usual saline vial, the diluent for the vaccine will be colour coded to ensure the right diluent is used.

2.6 The EWG agreed that a series of SOPs are required from one end of the chain to the next in terms of processes and pharmaceutical oversight. Staff need to be adequately trained. Experienced vaccinators only may be used.

2.7 The EWG heard NHS confirm that a PPE distribution will be arranged to match the vaccination plan. Specific PPE is required at distribution sites to defrost the vaccine and has been set up.

2.8 The EWG heard 175 PILs are to be provided per pack. The PILs are currently in English language only but company are working to put them in different languages. It is not yet clear whether the patient will receive a PIL beforehand or at point of vaccination. The PIL will also be made available online.

2.9 The EWG noted the discussion around the possibility of distribution of the vaccine between end users in order to reduce wastage. The pack size limits flexibility and the characteristics of this vaccine may also be prohibitive to movement. Each site must commit to use an entire pack in the right time frame. Moving vaccine from one end-user would likely be acceptable only in extreme circumstances and in line with Regulation 174 to address lack of supply and its surplus.

2.10 The EWG agreed the cold chain will need to be validated in terms of temperature management and vaccine stability.

2.11 The EWG heard that it is usual practice to deliver to GPs in cold storage. GPs are requested to have the appropriate storage facilities (fridges) in order to qualify for vaccination and PHE are procuring fridges for GPs if they do not have adequate ones.

2.12 The EWG emphasised that collection of patient data in a timely manner is extremely important to gain knowledge on the safety of the vaccine as soon as possible during the mass vaccination campaign.

3. The EWG heard a presentation on the non-clinical assessment of BNT162b2

3.1 The EWG heard that responses to the 13 non-clinical questions posed to the company in October 2020 are awaited.

3.2 The EWG noted the lack of data on reproductive toxicity and histopathology and agreed the experts would review and discuss the available data with the non-clinical assessors. The EWG agreed to discuss it again at the next Vaccine BR EWG Tuesday 24th November 2020.

4. The EWG heard a presentation on the quality assessment of BNT162b2

4.1 The EWG heard there were no major quality objections. The EWG discussed the wide drug product specifications and heard that they are to be expected for the vaccine at this stage. Any results observed that seem out of line will be addressed.

4.2 The EWG noted the importance of measuring immunogenicity in patients in controlled trials once they have been vaccinated. Studies to validate the cold chain will also be important. If requested NIBSC could be involved in examining vaccine potency as it enters and leaves cold chain.

4.3 EWG heard that stability data are expected and that the company have been asked to provide information about shipment and impact of transporting defrosted product in the network and how the product is impacted by shear forces.

5. The EWG heard a presentation on the clinical assessment of BNT

5.1 The EWG discussed whether a limit should be imposed on the age of the population to receive the vaccine as the benefit risk balance is less clear in younger patients. However, it was noted that the setting may also be relevant to the benefit risk balance, i.e. healthcare practitioners. The safety data appears to be comparable between different age groups. The EWG heard that the company are yet to provide a breakdown of the numbers in each age group, but it is expected to be a good spread across. The EWG noted that the company proposed vaccination of subjects aged 16 and over.

5.2 The EWG discussed the vaccination of younger female healthcare practitioners of child-bearing age and whether it would be feasible for such women to undertake a pregnancy test with the roll out of vaccine. It may be the case that it is not necessary to withhold the vaccine from pregnant women but at this stage it is not clear due to the lack of clinical and non-clinical data.

5.3 The EWG noted that recommendations will be required regarding concomitant flu vaccination.

5.4 The EWG agreed that a decision will need to be made with some gaps in the data and it will be important this is communicated to the population at large.

6. <u>Date and time of next meeting</u>

Tuesday 24th November 2020 at 2.30pm

The Meeting started at 14:00 and ended at 17:06.

Members are reminded that the content of papers and proceeding of the meetings are to be treated as 'Official – sensitive commercial'. Members are also reminded that, in accordance with the Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members must also declare any other matter which could reasonably be perceived as affecting their impartiality. Detailed guidance is set out in the Code of Practice

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Invited experts

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Observers

Are invited to attend all meetings. Will not participate in drawing up conclusions and recommendations.

COMMISSION ON HUMAN MEDICINES (CHM)

COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Tuesday 24th November 2020** at **14:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan
Professor N French
Professor D Goldblatt
Ms S Hunneyball
Professor K Hyrich
Professor H J Lachmann
Professor P J Lehner
Dr S Misbah
Professor S Price
Dr A Riordan
Professor C Robertson
Professor T Solomon[1]
Dr R Thorpe
Mrs M Wang
Professor C Weir

Apologies

Sir M Jacobs
Professor P Shah

Members of the CTBV Expert Advisory Group

Professor B K Park
Professor M Turner

Members of the CPS Expert Advisory Group

Mr VI G Fenton-May
Mr R Lowe
Professor Y Perrie
Professor K M G Taylor (Chair of CPS)
Dr S Walsh

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted] - LD

Supporting specific items

[redacted] - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - LD
[redacted] - Government Legal Team
Professor Van-Tam - DMO[2]
[redacted] - LD

MHRA Observers

[redacted] - Government Legal Team
Ms R Arrundale - Policy
Dr M Bailey - MHRA-NIBSC
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
Dr S Branch - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - MHRA-NIBSC
[redacted] - LD
[redacted] - LD
[redacted] - Policy
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - LD
Dr SP Lam - LD
[redacted] – Government Legal Team

Observers - CHM

Professor S Ralston (Chair of CHM)
Ms S Bradford
Dr J Fraser
Professor J Friedland
Professor R Gilson
Professor M Macleod
Dr R Mann
Professor S Meredith
Dr M Wilson
Mrs H Ward (Invited Expert of CHM)

Secretariat

[redacted]
[redacted]
[redacted]

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Mr K McDonald - LD
[redacted] - IE&S
Dr M O'Kane - LD
[redacted] - LD
Dr J Raine - MHRA-CEO
Dr N Rose - MHRA-NIBSC
Dr C Schneider - MHRA-NIBSC
[redacted] - LD
[redacted] - IE&S
[redacted] - LD
Mr P Tregunno - VRMM
[redacted] - LD
[redacted] - Government Legal Team
[redacted] - LD
Dr K Wydenbach - LD

Minute Takers

[redacted] - LD
[redacted] - LD

[redacted]
18th January 2021

[1] Left during item 4 & returned during item 5

[2] Left after the presentation of his item 2

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1.3 The following members invited experts and observers declared interests and other relevant interests for this meeting:

C19VBR

Professor Sir Munir Pirmohamed - NPNS AstraZeneca - Research grant to UOL to support PhD in drug interactions.
Other relevant interests in Pfizer, Janssen, Sanofi – Sir Munir is part of an EU-funded IMI consortium on gene therapy, and these companies are partners in the project. The University of Liverpool will get funding from the EU (but not from the partners), this IMI project commences on 3rd November 2020.
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Professor Lachmann – Other relevant interest as a volunteer participant in the Oxford vaccine study and no other involvement in the study.

Dr Misbah - NPNS - Holds honorary Senior Lectureship with University of Oxford & Oxford University Hospitals NHS Foundation Trust

Professor Price - NPNS in GSK and AstraZeneca – which relates to donations provided by both companies to the British Toxicology Society (BTS) to support their Annual Congress and Education and Training of which Professor Price is currently President of the Society (2020-2022)

Dr Riordan - Other relevant interests - Participant in Oxford University's ChAdOx1 nCoV-19 clinical trial –received immunisation 27/8/2020. NPNS - Postgraduate External Examiner for Oxford University (Postgraduate Diploma in Paediatric Infectious Diseases)

Professor Solomon - Other relevant interests – Professor Solomon provides clinical care for patients with Covid-19; chaired the MRC/NIHR committee which awarded funding for development of the Oxford Vaccine.

Professor Weir - Other relevant interest arising from link to the Lothian NHS Board. NHS Lothian R&D has partially funded Professor Weir's post at University of Edinburgh, since 2010, so that he could provide methodological advice on health services research studies and clinical trials.

CTBV

Professor Park - NPNS in GSK Research & Development Ltd. and in Janssen as I received a research grant in the past two years. The grant has been handed over to a colleague in 2020 and the grant is due to finish in 2020. Professor Park received no direct payment. In addition, Professor Park have two active IMI grants for Transbioline and Quantitatve Systems Toxicology, he is the PI on the TransBioline grant for the University of Liverpool. Both grants are paid directly to the University of Liverpool.

Professor Turner – Other relevant interest. Professor Turner is a Non Executive Director (non-remunerated) on the Board of the Cell and Gene Therapy Catapult (CGT).
CGT have been tasked by UK Government with re-purposing a factory in Braintree to manufacture either a vaccine or a therapeutic mAb. No decision has been made as to whether or what product CGT Braintree may be asked to manufacture and that decision will be made by UK Government. Certainly I don't believe that CGT Board will have any material input into the decision as to what product may be manufactured.

CPS

Mr V'lain Fenton-May – None

Mr Robert Lowe – None

Professor Yvonne Perrie - NPNS in Pfizer & AstraZeneca arising from a contract for a grant (March 2018), which includes contributions from these companies to the University of Strathclyde, Janssen in writing a grant for a PhD (now funded), GSK – arising from an EU grant to University of Strathclyde (Jan 2019-Dec 2019)

Professor Kevin Taylor – None

Dr Susannah Walsh – None

CHM

Professor Ralston – NPNS – Sanofi, Pfizer, Janssen, AstraZeneca & Other relevant interests in NHS Lothian and Oxford University. Professor Ralston has an honorary consultant contract with NHS Lothian but has not been involved in any trials relating to COVID-19. He also has agreed to be an external examiner for Oxford University clinical trials MSc; however, this has not yet started.

Professor Friedland – NPNS - GlaxoSmithKline, Sanofi, Pfizer

Professor Gilson – NPNS - Pfizer, GlaxoSmithKline, Novavax, Janssen, Oxford University

Professor Macleod – NPNS - Sanofi, Pfizer, Janssen

Dr Mann – NPNS - Sanofi

Professor Meredith – NPNS - Janssen, GlaxoSmithKline, Pfizer, AstraZeneca, Sanofi The Unit in which Professor Meredith works at University College London is coordinating the Imperial Covid Vaccine trials, however Professor Meredith is not involved.

Professor Patel – NPNS - Pfizer & NPNS – University of Nottingham have a scientific collaboration with Astra Zeneca who are providing free compound (a p38- small molecule inhibitor for the University to use in a dendritic cell caner trial the University is working on. AZ have also agreed to a donation to the University's scientific team for covering cost of reagents for the immune assays in the trial.

1.4 Apologies have been received from Sir Michael Jacobs and Professor Shah for this meeting.

1.5 The Chair welcomed:

Professor Van-Tam, Deputy Chief Medical Officer to present Epidemiological Data.

Chair and Members of the Commission on Human Medicines (CHM)

Members of the Clinical Trials, Biologicals and Vaccines Expert Advisory Group (CTBVEAG)

Chair and Members of the Chemistry, Pharmacy & Standards Expert Advisory Group (CPSEAG).

The following members of the Government legal team: [redacted], [redacted] and [redacted].

2. Professor Van-Tam, Deputy Medical Officer to present Epidemiological Data

2.1 The EWG heard a presentation from Professor Van-Tam. Professor Van-Tam agreed to follow up with a letter to the Chair to detail data on age-related COVID-19 mortality. The EWG noted that there were very few deaths in under 16s in England due to COVID in the first wave.

2.2 The EWG noted that some seasonality of coronavirus has been observed but was not as pronounced as seen with influenza virus and RSV. A stable signal cannot be observed for COVID-19 due to isolation measures and pharmaceutical intervention.

2.3 The EWG heard that the priorities for vaccination are residents in care homes for older adults and their carers and then all those 80 years of age and over, and frontline health and social care workers. With regard to pregnancy and women of childbearing age, information is currently being prepared for the JCVI PHE green book. It is not yet known that vaccines are unsafe for pregnant women. However, there are also no data to show that they are safe. The initial position in the green book is do not administer the vaccine to pregnant women but, there could be individual cases where there is extreme clinical vulnerability in a pregnant woman and decision would be made on a case-by-case basis with the respective clinician.

2.4 The EWG considered whether HCPs require vaccination in order to protect themselves or to protect the patient / elderly public. The EWG heard that vaccination of frontline health and social care workers is recommended as they are at increased personal risk of exposure to infection with COVID-19, and also of transmitting that infection to susceptible and vulnerable patients in health and social care settings. Apart from the risk of severe disease in HCW (albeit low in the younger age groups), there is a risk of long-COVID, the precise prevalence of which is unclear. Vaccination of HCPs will also help to maintain resilience in the NHS and for health and social care providers. There is evidence that infection rates are higher in residential care home staff than in those providing domiciliary care or in healthcare workers. Care home workers are therefore considered a very high priority for vaccination.

3. The EWG heard a summary on the legal aspects of Regulation 174

3.1 The EWG heard of other examples where Regulation 174 had been employed such as Flublok Quadrivalent vaccine.

3.2 The EWG heard that the timeline during which authorisation for distribution of a vaccine under Regulation 174 can be used is context specific. The EWG can implement any timeline that it considers appropriate, for example, temporary approval for an undisclosed time, limit approval to the season where coronavirus is expected to be prevalent, or until coverage is reached in a particular sub-set of the population.

4. The EWG heard an update on the non-clinical aspects of the assessment of the COVID-19 vaccine BNT162b2

4.1 The EWG heard that responses to non-clinical questions due from the company have not yet been received. It was also noted that the non-clinical pharmacokinetics were not performed in a conventional way. There is no information provided whether the vaccine, or elements thereof, cross the placenta, enter nodes of lactating mammals, crosses blood/brain barrier, or whether lipid nanoparticles bind to cell membranes, or travel to thymus or spleen. It is not clear whether the company will perform these studies.

4.2 The EWG discussed the lack of developmental and reproductive toxicity and histopathology data. Data to validate the choice of animal model is also awaited.

4.3 The EWG heard that in terms of the data observed so far there are no toxicological findings that would prevent the use of the vaccine. However, it was agreed that clear exclusions and exceptions for pregnant women, women of childbearing age and lactating women will need to be defined. Information is also required regarding the 23 incidental pregnancies that occurred in the clinical study in the pre-and post-vaccination window. The duration of this window also needs clarification.

4.4 The EWG noted the clinical trial exclusion criteria is expected to be followed during deployment, unless the non-clinical data become available and support expanding use to pregnant women and women of childbearing potential not taking dual birth control measures.

4.5 The EWG discussed inclusion of a contraindication in pregnant women in the SmPC and agreed if there is evidence of harm, a contraindication may be appropriate. However, at present the animal study is not complete and information is lacking. Women of childbearing potential could be included in the vaccination programme, provided effective contraceptive measures are being used for an appropriate period before and maintained for a period after vaccination, in addition to a negative pregnancy test result before vaccination. Information provided to women of childbearing age needs to be as informed and explicit as possible for facilitate informed decision. The EWG noted the most recent version of product information states the vaccine should not be used in people who are breastfeeding. The EWG requested a review of the data of RNA absorption through the infant gastrointestinal tract, and any evidence the company have used to support excluding women who are breastfeeding. The EWG noted the broad impacts and disadvantages to many women & children.

4.6 The EWG discussed whether the novel lipid nanoparticles distribute to a foetus and whether they are teratogenic. This information is required and the lack of it is a concern when considering the vaccination of younger healthcare and social care workers.

4.7 The EWG agreed it is not known whether mRNA would have unexpected negative consequence to an embryo or foetus, and it may be the case that a pregnancy test is integrated into the health system as part of the vaccination.

4.8 The EWG agreed that lung histopathology has not been provided but may be available; this information will be requested from the company as a high priority.

4.9 The EWG noted that data on carcinogenicity is not a requirement for the antigenic component of a vaccine due to the short exposure of the vaccine. Likewise, genotoxicity data have not been provided which is in line with the regulatory framework for a vaccine. The EWG discussed the potential risks associated with a mRNA vaccine, for example, modulation of gene expression and the potential for off-target mutations, in addition to the risk of potential toxicity of the novel lipid nanoparticles. The EWG agreed these risks need to be balanced against the degree of risk associated with COVID-19 disease across age-ranges and groups.

5. The EWG heard a presentation on the quality assessment of BNT162b2

5.1 The EWG heard there were no major quality objections. The issues remaining relate to the lack of experience with the novel format of the vaccine and the wide specifications set for batches, in particular the drug product. The EWG heard that some responses from the company had been received shortly before this meeting but some issues remain outstanding. It remains to be seen whether the responses raise any more issues.

5.2 The EWG heard that the labelling is complete now and cannot be amended. Any further information required would have to be made available via the information for use and other product information that will be provided to those people to be vaccinated.

5.3 The EWG heard that of the 2 specific batches that had been identified for supply in the UK; one has been used in a study from which the risk benefit profile was established. However, this batch was only used in 5 US centres and the doses used are not known. Despite this, that batch may fulfil criteria to be clinically qualified which addresses some of the uncertainties.

5.4 The EWG heard that batch CTM12 consists of 67665 vials and batch CTM consists of 67470 vials.

5.5 The EWG discussed mRNA degradation, the low limits set and the lack of explanation from the manufacturer. Given the good immune response observed with the vaccine, a question on the criticality of mRNA integrity was discussed by the EWG.

5.6 The EWG also noted that the limits for in vitro cell expression were also wide being set at 30% or above. This could lead to large differences across batches.

5.7 The EWG noted the difficulties in estimating potency of a vaccine where the antigen production is driven by mRNA. The effect of the cold chain was also discussed. A mechanism may be required (in a small population in each devolved area) to test the vaccine as it is administered to patients in order to provide early serological information. Data could also be returned to NIBSC for potency validation and cell transfection to see if antigens are being generated.

5.8 The EWG heard that NIBSC will be releasing the product in line with the specification in place and will not be adopting an in-house specification. It was noted that particle size, although a critical attribute, is not being evaluated by NIBSC. The current timeframe prevents this step being available.

5.9 MHRA informed the EWG that there is a stipulation for batches to be released that are in conformity with the limits specified in the clinical studies.

5.10 The EWG discussed how to monitor the timeline of 2 hours for mixing of the vaccine at room temperature when this is performed in the community. The stability of the vaccine should be maintained. It was noted that it might be better for the vaccine to be administered via mass vaccination and therefore the vaccine will not need to go in and out of the fridge repeatedly. Ideally the vaccinee should be identified beforehand and vaccinated together.

5.11 The EWG noted that in general, the stability of the product seems acceptable although there is some concern remaining with regard to the vaccine being thawed and then transported.

6. The EWG heard a presentation on the clinical assessment of BNT162b2

6.1 The EWG heard that MHRA has now received everything they can reasonably expect for an application under Regulation 174.

6.2 The EWG discussed the need for information on the use of analgesia and whether it would interfere with the immune response, comorbidities in older patients and the number of patients aged 70/80 years in the trial. MHRA agreed to check the patient listings. The EWG discussed fatigue as a symptom of vaccination and agreed that any mention of it in the SmPC will require quantification with regard to the onset and duration.

6.3 The EWG discussed the exclusion of immunosuppressed patients in the trial. MHRA agreed to check the protocol for the definition of immunosuppressed, and to gain full breakdown of the data on immunomodulators and immunosuppressants to gain insight for label.

6.4 The EWG discussed the number of protocol deviations that were excluded from the primary efficacy endpoint but included in 'all efficacy' endpoint. However, it was noted that these exclusions did not affect the efficacy which was reassuring.

6.5 The EWG discussed whether the vaccine could be recommended in those with a history of symptomatic Covid-19 illness.

6.6 The EWG noted there was no indication of enhanced disease in the clinical trial. It was noted that data on seropositive patients were included in terms of efficacy but not available in terms of safety. However, this may be available in the latest submission.

6.7 The EWG considered the age group the vaccine should be indicated for and noted that the manufacturer is currently proposing to include 16-17 year olds. The EWG agreed that the most clear benefit is observed in the >50 years age group. However, it was noted that limiting the age group for vaccination would have to be based on data. Efficacy data is available in all age groups and is equivalent in the different age groups identified in the data supplied.

6.8 The EWG raised concerns with the lack of longer-term safety data. Any potential rare side effects will become apparent as the numbers vaccinated increase. Post-authorisation safety data will be collected and will inform on any potential safety issues.

6.9 The EWG discussed whether it would be possible to defer a decision on vaccinating the younger population until more data is received.

6.10 The EWG heard that the full line listings were received the night before the meeting and the assessment team requires time to review these and report back to EWG.

7. The EWG heard a presentation on the RMP assessment of BNT162b2

7.1 The MHRAs core RMP for COVID-19 vaccines has been shared and discussed with the company previously. It was noted that it would be the company's responsibility to fulfil the conditions and content set out in the agreed RMP.

7.2 The EWG heard about the clinical studies included in the applicant's pharmacovigilance plan. The applicant is planning to conduct these studies. Geographically these are in Europe and the US, but the UK could be specified. The EWG heard that in the MHRAs core RMP, it has been highlighted that MHRA would accept studies performed outside of the UK if they contain a relevant population.

7.3 The EWG discussed the importance of brand and batch recording and their impact on traceability. The MHRA informed there is much discussion around this issue. PHE is intending to record batch data with linkage to patient records where possible. Where the vaccine is given outside of primary care it can be captured in the new NHS system; however, it will not automatically flow into CPRD data sets. MHRA informed that this is being addressed with the NHS. There is a push to record patient data and it is being worked on.

7.4 The EWG queried whether vaccine failures and a deeper dive (immunological, host genomic, viral genomic) into these will be included in post-authorisation studies. MHRA informed that PHE plan to carry out post-authorisation effectiveness studies and this would be a valuable source of information.

8. The EWG discussed product information for the vaccine

8.1 The EWG heard that the PIL and SmPC are being reviewed and the company will be made aware of comments on a rolling basis.

9. Future Steps / Any Other Business

9.1 The EWG was unable to review data received today. The next meeting of the EWG is to be arranged.

The Meeting started at 14:33 and ended at 18:15.

Members are reminded that the content of papers and proceeding of the meetings are to be treated as 'Official – sensitive commercial'. Members are also reminded that, in accordance with the Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members must also declare any other matter which could reasonably be perceived as affecting their impartiality. Detailed guidance is set out in the Code of Practice

Annex I

Conflict of Interest Policy for CHM COVID-19 Vaccine Benefit Risk EWG

Chair and Members

- May not hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
- May not currently be or have previously been involved in the development of COVID-19 vaccines

Invited to all meetings, receives all papers and presentations and is permitted full participation in discussion, including drawing up conclusions and recommendations

Invited experts

- May hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
- May currently be or have previously been involved in the development of COVID-19 vaccines

May be invited to all relevant meetings, receives all papers and presentations and is permitted to participate in discussions when invited by the Chair. Does not contribute to conclusions and recommendations

Observers

Are invited to attend all meetings. Will not participate in drawing up conclusions and recommendations.

COMMISSION ON HUMAN MEDICINES (CHM)

COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Friday 27th November 2020** at **14:45** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan
Professor N French[1]
Professor D Goldblatt
Ms S Hunneyball
Professor K Hyrich
Sir M Jacobs
Professor H J Lachmann
Professor P J Lehner
Dr S Misbah
Professor S Price
Dr A Riordan
Professor C Robertson
Professor T Solomon
Dr R Thorpe
Mrs M Wang
Professor C Weir

Apologies

Professor P Shah

Members of the CTBV Expert Advisory Group

Professor B K Park
Professor M Turner

Members of the CPS Expert Advisory Group

Mr VI G Fenton-May
Mr R Lowe
Professor Y Perrie
Professor K M G Taylor (Chair of CPS)
Dr S Walsh

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted] - LD

Supporting specific items

[redacted] LD
[redacted] - LD
[redacted] - LD
Dr N Rose - MHRA-NIBSC
[redacted] - LD

MHRA Observers

[redacted] - Government Legal Team
Ms R Arrundale - Policy
[redacted] - Dir
Dr M Bailey - MHRA-NIBSC
[redacted] - LD
[redacted] - MHRA-NIBSC
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - VRMM
[redacted] - LD
Dr P Bryan - VRMM
[redacted] - MHRA-NIBSC
[redacted] - VRMM
[redacted] - LD
[redacted] LD
[redacted] - Policy
[redacted] - LD
[redacted] - LD
[redacted] - VRMM
[redacted] - LD
Dr SP Lam - LD

Observers - CHM

Professor S Ralston (Chair of CHM)
Dr J Fraser
Professor J Friedland
Professor R Gilson
Professor M Macleod
Professor S Meredith
Dr M Wilson
Mrs H Ward (Invited Expert of CHM)

[redacted] - VRMM
[redacted] – Government Legal Team
Mr K McDonald - LD
[redacted] - IE&S
[redacted] - LD
[redacted] - Government Legal Team
[redacted] - LD
Dr C Schneider - MHRA-NIBSC
[redacted] - LD
[redacted] - IE&S
[redacted] - LD

Secretariat

[redacted]
[redacted]
[redacted]

Mr P Tregunno - VRMM
[redacted] - LD
[redacted] - LD

Key
LD = Licensing Division
NIBSC = National Institute for Biological Standards & Control
VRMM = Vigilance & Risk Management of Medicines
CTBV = Clinical Trials, Biologicals & Vaccines EAG
CPS = Chemistry, Pharmacy & Standards EAG
PHE = Public Health England
CHM = Commission on Human Medicines
DMO = Deputy Medical Officer
IE&S = Inspection, Enforcement & Standards
Dir = Director of Operational Transformation

[1] Joined at item 2

[redacted]
18th January 2021

1. Introduction and Announcement

1.1 The Chair reminded Members that the content of papers and proceeding of the meeting are strictly confidential and should be treated as 'Official – sensitive commercial' and should not be disclosed. There is no consent for members / participants to record the meeting, take screenshots or photographs of presentations. The meeting was recorded by the MHRA Secretariat for minute taking purposes only. The Chair & Members including all participants gave full consent to the recording prior to the start of the meeting.

1.2 Conflict of Interest Policy (Annex I to the minutes)

The Chair reminded members and participants that, in accordance with the CHM Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members were also reminded to declare any other matter which could reasonably be perceived as affecting their impartiality.

1.3 The following members invited experts and observers declared interests and other relevant interests for this meeting:

C19VBR

Professor Sir Munir Pirmohamed - NPNS AstraZeneca - Research grant to UOL to support PhD in drug interactions.
Other relevant interests in Pfizer, Janssen, Sanofi – Sir Munir is part of an EU-funded IMI consortium on gene therapy, and these companies are partners in the project. The University of Liverpool will get funding from the EU (but not from the partners), this IMI project commences on 3rd November 2020.
AGILE – this is a Liverpool early phase trial platform (between University of Liverpool and Liverpool School of Tropical Medicine). It is funded by the Wellcome Trust and UKRI/DHSC/NIHR. It is NOT evaluating vaccines, but only drugs to treat COVID-19. Sir Munir is not on the trial management group, and he is not directly involved in choosing the compounds for the study. Sir Munir has no involvement with any of the developers of the compounds to be studied (academic or industrial).
Sir Munir is a member of the UK COVID Therapeutics Advisory Panel (UK-CTAP), which is advising the CMO on which compounds need to be prioritised for the RECOVERY+ trial (RECOVERY is funded via NIHR/DHSC).

Professor French - Other relevant interest **-** Provides clinical care when in covering the acute medical wards where patients with COVID-19 are cared. NPNS in GSK - In September 2020 a sub-contract was signed with the Liverpool School of Tropical Medicine to undertake work evaluating the safety and effectiveness of GSK's RTS's malaria vaccine in Malawi. GSK are the primary funders to the LSTM.

Ms Hunneyball - Other relevant interest – writes articles published in the Chemist and Druggist magazine, a trade magazine for pharmacists, but receives no payment for these articles. The information referred to in the articles is in the public domain. Ms Hunneyball makes it clear that these are her personal views and reflections and reference all sources of information used.

Professor Hyrich – NPNS - Professor Hyrich was co-I on an investigator-initiated research grant exploring predictors of outcome in rheumatoid arthritis. NPNS Pfizer- she is a Co-I on a grant exploring adherence to JAK inhibitors in rheumatoid arthritis. NPNS

in Abbvie, Professor Hyrich gave some lectures at an education conference on effectiveness of treatment for rheumatoid arthritis.

Sir Michael Jacobs - Other relevant interest - As part of the academic role at the Liverpool School of Tropical Medicine, Sir Michael is a member of the Study Management Team and antiviral drug prioritisation group for the AGILE proof of concept (phase I/II) platform study. Sir Michael is also part of the team that submits new antiviral compounds against SARS-CoV2 for consideration by NIHR for testing on this platform. No commercial or financial interest in the trial or any of the compounds, or any pharmaceutical or biotechnology company.

Professor Lachmann – Other relevant interest as a volunteer participant in the Oxford vaccine study and no other involvement in the study.

Dr Misbah - NPNS - Holds honorary Senior Lectureship with University of Oxford & Oxford University Hospitals NHS Foundation Trust.

Dr Riordan - Other relevant interests - Participant in Oxford University's ChAdOx1 nCoV-19 clinical trial –received immunisation 27/8/2020. NPNS - Postgraduate External Examiner for Oxford University (Postgraduate Diploma in Paediatric Infectious Diseases)

Professor Solomon - Other relevant interests – Professor Solomon provides clinical care for patients with Covid-19; chaired the MRC/NIHR committee which awarded funding for development of the Oxford Vaccine.

Professor Weir - Other relevant interest - arising from link to the Lothian NHS Board. NHS Lothian R&D has partially funded Professor Weir's post at University of Edinburgh, since 2010, so that he could provide methodological advice on health services research studies and clinical trials.

CTBV

Professor Park - NPNS in GSK Research & Development Ltd. and in Janssen as I received a research grant in the past two years. The grant has been handed over to a colleague in 2020 and the grant is due to finish in 2020. Professor Park received no direct payment. In addition, Professor Park have two active IMI grants for Transbioline and Quantitatve Systems Toxicology, he is the PI on the TransBioline grant for the University of Liverpool. Both grants are paid directly to the University of Liverpool.

Professor Turner – Other relevant interest. Professor Turner is a Non Executive Director (non-remunerated) on the Board of the Cell and Gene Therapy Catapult (CGT).
CGT have been tasked by UK Government with re-purposing a factory in Braintree to manufacture either a vaccine or a therapeutic mAb. No decision has been made as to whether or what product CGT Braintree may be asked to manufacture and that decision will be made by UK Government. Certainly I don't believe that CGT Board will have any material input into the decision as to what product may be manufactured.

CPS

Mr V'lain Fenton-May – None
Mr Robert Lowe – None

Professor Yvonne Perrie - NPNS in Pfizer & AstraZeneca arising from a contract for a grant (March 2018), which includes contributions from these companies to the University of Strathclyde, Janssen in writing a grant for a PhD (now funded), GSK – arising from an EU grant to University of Strathclyde (Jan 2019-Dec 2019).
Professor Kevin Taylor – None
Dr Susannah Walsh – None

CHM

Professor Ralston – NPNS – Sanofi, Pfizer, Janssen, AstraZeneca & Other relevant interests in NHS Lothian and Oxford University. Professor Ralston has an honorary consultant contract with NHS Lothian but has not been involved in any trials relating to COVID-19. He also has agreed to be an external examiner for Oxford University clinical trials MSc; however, this has not yet started.

Professor Friedland – NPNS - GlaxoSmithKline, Sanofi, Pfizer

Professor Gilson – NPNS - Pfizer, GlaxoSmithKline, Novavax, Janssen, Oxford University

Professor Macleod – NPNS - Sanofi, Pfizer, Janssen

Professor Meredith – NPNS - Janssen, GlaxoSmithKline, Pfizer, AstraZeneca, Sanofi The Unit in which Professor Meredith works at University College London is coordinating the Imperial Covid Vaccine trials, however Professor Meredith is not involved.

1.4 Apologies have been received from Professor Shah for this meeting.

1.5 The Chair welcomed:

Chair and Members of the Commission on Human Medicines (CHM)

Members of the Clinical Trials, Biologicals and Vaccines Expert Advisory Group (CTBVEAG)

Chair and Members of the Chemistry, Pharmacy & Standards Expert Advisory Group (CPSEAG).

2. The EWG heard a presentation on the non-clinical aspects of BNT162b2

2.1 The EWG heard that the company have not provided any reproductive toxicity information. There is nothing to suggest that the product is teratogenic but without data to support this, it cannot be known for certain.

2.2 The EWG considered that in the absence of all the necessary data a path forward may be to apply the same approach as that taken in the clinical trials. Physicians will require clear advice on what do if a pregnant patient requests vaccination.

2.3 The EWG agreed the proposed wording for Section 4.6 of the Information for UK healthcare Professionals document.

2.4 The EWG noted that a communications strategy will be required to ensure patients are informed around the advice for women of childbearing age, pregnant and lactating women before they present for vaccination.

2.5 The EWG discussed whether it may be necessary for women of childbearing age to do a pregnancy test before vaccination as per the clinical trial population.

3. Clinical aspects of BNT162b2

3.1 The EWG heard that the clinical assessment team have now received sufficient data to reach a position on the authorisation of use of the vaccine under a Regulation 174.

3.2 The EWG noted that the prioritisation with regard to vaccination would be in accordance with the guidance from JCVI. The EWG agreed that the prioritisation is supported by the clinical trial data.

3.3 The age range for vaccination was discussed taking account of the pivotal clinical trial. The EWG noted that the benefits of the vaccine were apparently lower for the younger age groups. In view of this and given the short period of time that the vaccine has been studied, the question was raised if use in subjects less than 50 years of age was justified; one member of the EWG considered that it was not. The EWG discussed and concluded that the risk / benefit of COVID-19 mRNA Vaccine BNT162b2 is considered to be positive in all subjects aged 16 years and over.

3.4 The EWG discussed the need for inclusion of additional wording in Section 4.4 of the Information for UK healthcare Professionals in relation to the use of BNT162b2 in subjects who had already received partial or full vaccination with another COVID-19 vaccine. It was agreed that additional wording should be included and considered wording around 'not to recommend' and 'no evidence'.

3.5 The EWG considered use of the vaccine in people with a clinical history of COVID-19 or in people with no history of clinical illness but serological findings of COVID-19 antibodies or antigens at least in one assay. While the percentage of subjects in the clinical trials who were seropositive or PCR positive at baseline was relatively small, the efficacy and safety data in these patients was comparable to that in seronegative subjects. The EWG did not consider past infection to be a risk for vaccination based on experience from other vaccines and therefore considered that the vaccine could be administered in these subgroups. The group recommended that the company be requested to evaluate these subgroups further in a post-authorisation effectiveness study. The sizeable population of HCPs who have previously had COVID-19 could contribute to such a study.

3.6 The EWG agreed that Section 4.5 of the 'Information for UK healthcare Professionals document' should contain information on concomitant vaccination. Participants in the pivotal study were excluded from the receiving the flu vaccination 14 days prior or 14 days after vaccination with BNT162b2.

3.7 The EWG noted the sequencing of paragraphs 1 and 2 in Section 4.8 of the 'Information for UK healthcare Professionals document' could be reversed.

3.8 The EWG agreed that in Section 5.1 of the 'Information for UK healthcare Professionals document', the disease severity (mild), should be stated for cases of COVID-19 disease in both the vaccinated and placebo groups.

3.9 The EWG discussed whether the vaccine could be administered via subcutaneous administration (SC) for certain populations (those with bleeding disorders or those receiving anticoagulants) and noted the absence of data to support SC use. The EWG agreed administration should be intramuscular (IM) as per the clinical trial population. In general practice, it is routine to administer other vaccines e.g. flu vaccine via the IM route to patients

taking anti-coagulants but care is taken to apply pressure to the injection site for an adequate length of time. It was agreed this information and other relevant information, should be part of a training package for healthcare professionals. The EWG recommended that this information should be disseminated to the public. The EWG also noted existing guidance which advocates a risk-based approach but permits patients on oral anticoagulants to receive IM injections (Medicines Q and As, 'Can small volume intramuscular injections be given to patients taking oral anticoagulants?' 2018; NHS, SPS).

3.10 The EWG discussed the information presented in Sections 6.2 and 6.4 of the 'Information for UK healthcare Professionals document' with regard to the stability of the vaccine. The in-use shelf-life details are considered to be unclear, and it needs to be established whether the text implies that the vaccine is stable for 6 hours or 8 hours. The EWG noted this will be discussed further in the quality discussion.

3.11 The EWG considered information in the 'Information for UK healthcare Professionals document' with regard to immunocompromised patients and agreed a statement should be added that no data are available for use in immunocompromised and immunosuppressed groups. The EWG stressed the importance of the company designing robust post-authorisation studies to assess vaccine efficacy in immunocompromised and immunosuppressed patients.

3.12 The EWG agreed that all common adverse events are adequately reflected in the 'Information for UK Patients' document. The EWG heard the most frequent adverse events were usually mild or moderate and resolved within a few days post vaccination. The EWG heard the clinical assessment team are updating the 'Information for UK healthcare Professionals document' and 'Information for UK Patients' document in liaison with the company.

4. The EWG heard a summary on the quality aspects of BNT162b2

4.1 The EWG heard that the batches relevant for the UK for a potential Regulation 174 approval are developmental batches which are subject to change and two batches have been evaluated by MHRA. The company has offered three other developmental batches to be considered for use through Regulation 174. However, their suitability is uncertain at this point in time; one is manufactured at a facility MHRA is not familiar with, one contains lipid-associated particles which were partially characterised and an unidentified late migrating band was observed on capillary gel electrophoresis of the third batch which requires further investigation.

4.2 The EWG agreed that, making decisions on approval under Regulation 174 in a batch specific manner is the safest route available. However, this position may be adjusted to allow approval for multiple batches under Regulation 174 in the future, if adequate data are provided.

4.3 The EWG heard that concerns remain with the two original batches the MHRA are evaluating as the specifications for the drug substance and the drug product are too broad with regard to the upper and lower limits and therefore it is not currently feasible to compare these two batches to those given to subjects in clinical studies. Particular points of concern are mRNA integrity and particle size.

4.4 The EWG heard that the company proposed a 6-month shelf-life. For the two batches in question, only 2-week stability data (at both 2-8°C and -80°C ±10°C) for one batch were made available and issues such as mRNA degradation are emerging. In view of the limited stability data available, the designation of a shelf-life for the finished product would have to

be a judgement based on the stability data received by the MHRA and comparability to the clinical trial batch data.

4.5 The EWG noted it was important to have data on particular quality aspects such as length of RNA, 5'-capping of RNA, and success of lipid particle encapsulation to ensure efficacy is maintained.

4.6 The EWG noted the issue of public confidence if authorisation via Regulation 174 is permitted given the lack of qualification of the two batches under review. The EWG expressed the need to be aware of the potential cumulative effects, of multiple small risks / gaps in the data. The EWG noted that it is possible to perform immunological testing of some vaccinees to confirm surrogate measures of efficacy at the point of vaccine administration, and to request samples are provided to NIBSC for testing.

4.7 The EWG heard that data on shear stress have been requested but not yet received. The EWG noted MHRA are receiving data from the company on a daily basis.

4.8 The EWG enquired whether the MHRA are receiving the same data as provided by the company to the FDA. The EWG noted that it may be the case that the batches the FDA are evaluating are further along the development lifecycle than those allocated for the UK.

4.9 Discussions and conclusions

The Chair summarised the discussion and noted that the EWG considered the non-clinical aspects of the assessment could be favourable with mitigations in place in relation to women of childbearing age, pregnant women and lactating women. Similarly, the EWG considered the clinical aspects of the assessment could be favourable with the inclusion of the proposed changes to product information and post-authorisation commitments. However, the EWG considered critical issues remain in the quality aspects of the assessment and further consideration of the data are required.

4.10 The EWG agreed that a quality subgroup would convene with the MHRA assessment team on Saturday 28th November 10am to review the quality data further and to refer any quality conclusions to the Commission for consideration at the CHM meeting Monday 30th November.

5. <u>Future Steps / Any Other Business</u>

5.1 None.

6. <u>Date and time of next meeting</u>

To be confirmed

The Meeting started at 14:50 and ended at 17:05.

Members are reminded that the content of papers and proceeding of the meetings are to be treated as 'Official – sensitive commercial'. Members are also reminded that, in accordance with the Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members must also declare any other matter which could reasonably be perceived as affecting their impartiality. Detailed guidance is set out in the Code of Practice

Annex I

Conflict of Interest Policy for CHM COVID-19 Vaccine Benefit Risk EWG

Chair and Members

- May not hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
- May not currently be or have previously been involved in the development of COVID-19 vaccines

Invited to all meetings, receives all papers and presentations and is permitted full participation in discussion, including drawing up conclusions and recommendations

Invited experts

- May hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
- May currently be or have previously been involved in the development of COVID-19 vaccines

May be invited to all relevant meetings, receives all papers and presentations and is permitted to participate in discussions when invited by the Chair. Does not contribute to conclusions and recommendations

Observers

Are invited to attend all meetings. Will not participate in drawing up conclusions and recommendations.

COMMISSION ON HUMAN MEDICINES (CHM)

COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP - Quality ad hoc Group

Minutes of the meeting held on **Saturday 28th November 2020** at **10:00** via videoconference

Participants Present

Members

Professor K M G Taylor (Chair)
Mr VI G Fenton-May
Mr R Lowe
Professor Y Perrie
Dr R Thorpe
Dr S Walsh[1]

Observer - CHM

Professor S Ralston (Chair of CHM)

BioNTech/Pfizer Representatives

[redacted] - BioNTech
[redacted] - Pfizer
[redacted] - BioNTech
[redacted] - Pfizer
[redacted] - Pfizer
[redacted] - Pfizer
[redacted] - Pfizer
[redacted]
[redacted] – BioNTech
[redacted] - Pfizer
[redacted]

Secretariat

[redacted]
[redacted]

[1] Joined during item 3

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD

Supporting specific items

[redacted] - LD

MHRA Observers

Dr S Atkinson - Dir
Dr M Bailey - MHRA-NIBSC
[redacted] - MHRA-NIBSC
[redacted] - LD
[redacted] - LD
[redacted] - LD
Dr SP Lam - LD
Mr K McDonald - LD
[redacted] - IE&S
[redacted] - Government Legal Team
Dr J Raine - MHRA-CEO
Dr N Rose - MHRA-NIBSC
[redacted] – IE&S
Dr C Schneider - MHRA-NIBSC
[redacted] - LD
[redacted] - IE&S
[redacted] - LD

[redacted]

18th January 2021

Key
LD = Licensing Division
NIBSC = National Institute for Biological Standards & Control
VRMM = Vigilance & Risk Management of Medicines
CTBV = Clinical Trials, Biologicals & Vaccines EAG
CPS = Chemistry, Pharmacy & Standards EAG
PHE = Public Health England
CHM = Commission on Human Medicines
DMO = Deputy Medical Officer
Dir = Director of Operational Transformation
MHRA CEO = Chief Executive
IE&S = Inspection, Enforcement & Standards

1. Introduction and Announcement

1.1 The Chair reminded Members that the content of papers and proceeding of the meeting are strictly confidential and should be treated as 'Official – sensitive commercial' and should not be disclosed. There is no consent for members / participants to record the meeting, take screenshots or photographs of presentations. The meeting was recorded by the MHRA Secretariat for minute taking purposes only. The Chair & Members including all participants gave full consent to the recording prior to the start of the meeting.

1.2 Conflict of Interest Policy (Annex I to the minutes)

The Chair reminded members and participants that, in accordance with the CHM Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members were also reminded to declare any other matter which could reasonably be perceived as affecting their impartiality.

1.3 The following members, invited experts and observers declared the following interests and other relevant interests for this meeting:

Professor Yvonne Perrie - NPNS in Pfizer & AstraZeneca arising from a contract for a grant (March 2018), which includes contributions from these companies to the University of Strathclyde, Janssen in writing a grant for a PhD (now funded), GSK – arising from an EU grant to University of Strathclyde (Jan 2019-Dec 2019).

Professor Ralston (Observer) – NPNS – Sanofi, Pfizer, Janssen, AstraZeneca & Other relevant interests in NHS Lothian and Oxford University. Professor Ralston has an honorary consultant contract with NHS Lothian but has not been involved in any trials relating to COVID-19. He also has agreed to be an external examiner for Oxford University clinical trials MSc; however, this has not yet started.

1.4 The Chair welcomed:

Company representative from BioNTech / Pfizer at 11am.

Observer, Professor Ralston, Chair of the Commission on Human Medicines (CHM)

2. Quality Assessment Report

2.1 The EWG quality sub-group heard that there had been a last-minute change to the batches relevant for the UK for a potential Regulation 174 opinion as of the evening of Friday 27th November. The immediate concerns of comparability as associated with the original two batches under review were no longer a priority whereas a discussion of the particulate 'defect' became more urgent as this impacted on the batch being considered as of this date. The EWG quality sub-group also heard that two further batches are also identified as being the next two batches intended for UK supply. One of these batches was associated with an investigation of a late migrating RNA species by capillary electrophoresis which was also characterised as a priority concern.

2.2 The preliminary assessment report on EJ0553, EJ0724 and EJ1688 was sent to the EWG quality sub-group members during the discussion. This report was based on the submission received the day before (27.11.2020). An accompanying paper highlighted the comparability

between the drug substance (RNA), as well as the drug product (manufacturing process) used in clinical trials, emergency and commercial use.

2.3 The company joined the meeting to address questions on the concerned batches, which prioritised the following issues: i) particulate matter found in EJ0553; ii) "late migrating species" in Batch EJ1688); iii) RNA integrity in early Process 2 batches; iv) stability data available for the proposed deployment model (e.g. -90 °C vs -60 °C).

2.4 The EWG quality sub-group discussed the particulate matter found in the batch of immediate interest (EJ0553). It was highlighted that vials containing particulates were removed from the batch based on 100% visual inspection. With regards to the visual inspection, it was highlighted that this particular batch failed to meet its own AQL for major defects on inspection. Discussions considered the nature of these particles, and when they are formed in the process, and that < 1.5% of the total batch was removed due to the appearance of white-coloured particulate matter. On examination the company explained that these "lipid-associated particles" are around 500-600 µm in length and not spherical. Initially, the company commented that these particles only consisted of lipids, but later indicated that these particles also contain RNA. However, no studies have been performed to determine the ratio of lipids or RNA in these particles. The particles were described as "flaky" in appearance. The company said that the particles were process filling line-associated (after sterile filtration) and not a stability-indicating phenomenon. It was also not the first time that this particular filling line was used for the manufacture of this product. A higher occurrence of subvisible particles was also seen when peristaltic pumps were used for the manufacture of LNPs, which is not currently used for the upscale batches. The company also confirmed that there does not appear to be a correlation between subvisible and visible particulate matter. The appearance of these lipid-associated particles increases at the end of the filling line. However, the company also acknowledged that no IPCs or visual inspection is performed during manufacturing process until after filling.

2.5 The company further explained that these particles did not alter the concentration of the drug product and they did not think this would have an impact on safety and efficacy of the product. However, as these were rejected vials, they did not perform a potency test on these rejected vials. It was confirmed by the company that this was an occurrence in more than one batch, including a clinical trial batch. However, no other batches were reported by the company at the meeting to have failed the AQL for major defects on inspection. The occurrence is said to be dependent on the batch size manufactured, which implied that the process could be optimised to ensure freedom from particles.

2.6 The company also indicated these particles 'disappear' after the product is diluted with normal saline and they do not recommend shaking the vials. The company said that it is recommended that the administrator should inspect the vial before administration for all parenteral products, not just for this product. However, the assessment team commented that pulling out vials from a batch that were deemed defective is not considered good practice and the reliance on HCPs to decide if there were particles present in the vials following dilution is also not ideal. The information for HCPs indicates that diluted vaccine should be discarded if particulates are present.

2.7 Since the product is sterilised by filtration through a 0.2 µm pore filter, and that these particles are generally found after filtration, during the filling stage, the EWG quality sub-group did not consider that these are aggregating particles, although no micrographs have been presented to confirm this. The reflections of the EWG quality sub-group were that the particulate matter for this batch was an OOS (out of specification) observation; the particles were described as intrinsic in nature; whilst not typically expected were not understood to be associated with a change in concentration of RNA containing LNPs, all of which provided some reassurance

that efficacy is not adversely impacted. An evaluation had been conducted and these were requested as supplementary information to be sent following this meeting. The company is also working on improving the number of rejects due to particulate matter.

2.8 Additional documentation is anticipated to help address residual safety concerns. It was thought that information on the batch generated by NIBSC may provide additional interpretation of these particles.

2.9 With regard to the potency assay, a discussion on its reliability and specification was also made and it was confirmed that assay utilising 150 µg does show a more comparable and acceptable read out than the assay utilising 100 µg. It was also confirmed with the company that 150 µg was to be used for future studies.

2.10 The EWG quality sub-group considered the late migrating RNA species (LMS) found in a drug product batch and not found in drug substance. The EWG quality sub-group were satisfied that the use of orthogonal methods to characterise this species as (likely) conformationally folded or reversibly aggregated RNA that is not denatured in the sample preparation of the CGE method supports the claim that this is actually an artefact of sample handling required to perform the RNA integrity test which requires extraction and denaturing of the RNA from the LNP before being assayed. This is not required for drug substance analysis where this species is not observed.

2.11 The comparability of the drug substance source used for the proposed batch (EJ0553) and the tested clinical batches was discussed at length, particularly considering the critical parameters such as particle size, RNA integrity, and 5' capped RNA. It was reassuring that the RNA integrity for the newer batches are relatively higher than the previously assigned batches (EE) for release in the UK. The EWG quality sub-group considered that the drug product is deemed comparable as the potency assay is variable which makes interpretation of the available data difficult, while other key parameters such as particle size, polydispersity, and RNA integrity can be compared, as long as the potency does not drop below 50 %. A concern was raised that if the product has less than 50 % RNA integrity, it may suggest that half of the product is not what it was laid out to be. Nevertheless, it seems more reassuring to the EWG quality sub-group that the later developmental batches have a higher level of RNA integrity that is more comparable with the earlier clinical batches. It was important to determine where the uncertainty in the RNA integrity came from.

2.12 The EWG was informed about difficult to interpret results regarding the length of the polyA tail found in the CoA for batch EJ0553. They considered this concern mitigated by the potency results for this batch, which appeared to be within the clinically qualified ranges.

2.13 The EWG sub-group considered that whilst the new batch under consideration was considered more acceptably comparable to previous clinical trial batches whereas the original two batches had not been, this was only through comparison with this single batch.

2.14 A concern about the continuity of supply of the vaccine was raised. It was considered important for deployment of the product in mass vaccination programme.

2.15 The EWG quality sub-group considered stability of the drug product in relation to the deployment model as it is understood. It was confirmed that there are no stability data available for the batch concerned and there was in fact no interpretable stability data from any so-called emergency use batches manufactured through process 2. It was confirmed to the sub-group that all stability statements were based on reliance of extrapolating stability data found on process 1 small scale clinical trial batches. Where total reliance was difficult to accept for the original batches under consideration this seemed more feasible to the sub-

group for the batch under consideration since this was, for release testing results, more closely comparable in terms of physicochemical aspects to clinical trial batches than the originally proposed batches had been. The EWG sub-group considered that a comparison of stability profiles is normally a contributory analysis when establishing comparability. In this instance reliance has to be made on comparability at Time 0, without confirmation from measured stability data. It was confirmed that two independent transport episodes of 6 hours each in a truck at refrigerated temperatures had been validated on an unconfirmed single batch. It is thought that this is not likely to be sufficient to support long primary care network distribution pathways. The company do not intend to submit any further stability data that would qualify additional transportation nodes in the deployment of vaccine. Stability data confirming temporary excursions to -90°C. The Tg (glass transition temperature) of higher than -60°C was reassuring.

2.16 The company agreed to provide further data on rubber stopper fragmentation studies qualifying multiple punctures of the rubber stopper after exposure to ultra low temperatures.

2.17 Overall, the EWG quality sub-group was positive in their opinion on the quality of the drug product batch under consideration but felt that the issue of intrinsic particle formation will need to be addressed further by the company. QP release certification and investigation of particles documentation should be required of the company.

3. Future Steps / Any Other Business

3.1 None.

4. Date and time of next meeting

N/A

The Meeting started at 10:05 and ended at 15:21.

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Conflict of Interest Policy for CHM COVID-19 Vaccine Benefit Risk EWG

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Invited experts

- May hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
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Observers

Are invited to attend all meetings. Will not participate in drawing up conclusions and recommendations.

COMMISSION ON HUMAN MEDICINES (CHM)

COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP - Quality ad hoc Group

Minutes of the meeting held on **Monday 7th December 2020** at **10:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan
Professor N French
Professor D Goldblatt
Ms S Hunneyball
Professor K Hyrich
Sir M Jacobs
Professor H J Lachmann
Professor P J Lehner
Dr S Misbah
Professor S Price
Dr A Riordan
Professor C Robertson
Professor T Solomon
Dr R Thorpe
Mrs M Wang
Professor C Weir

Apologies

Professor P Shah

Members of the CTBV Expert Advisory Group

Professor B K Park
Professor M Turner

Members of the CPS Expert Advisory Group

Mr VI G Fenton-May
Professor Y Perrie
Professor K M G Taylor (Chair of CPS)
Dr S Walsh

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted] - LD

Supporting specific items

[redacted] - LD
[redacted] - LD
[redacted] - LD
Ms R Bosworth - COMMS
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - MHRA-NIBSC
[redacted] - LD
[redacted] - MHRA-NIBSC

MHRA Observers

Ms R Arrundale - Policy
[redacted] - VRMM
Dr S Branch - VRMM
[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
Dr SP Lam - LD
Mr K McDonald - LD
[redacted] - LD
Dr N Rose - MHRA-NIBSC
Dr C Schneider - MHRA-NIBSC

[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD

Observer
Professor S Ralston (Chair of CHM)

Secretariat
Dr K Wydenbach - LD

[redacted]

[redacted]

18th January 2021

Key
LD = Licensing Division
NIBSC = National Institute for Biological Standards & Control
VRMM = Vigilance & Risk Management of Medicines
CTBV = Clinical Trials, Biologicals & Vaccines EAG
CPS = Chemistry, Pharmacy & Standards EAG
CHM = Commission on Human Medicines
COMMS = MHRA Communication Team

1. Introduction and Announcement

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1.3 The following members, invited experts and observers declared interests and other relevant interests for this meeting:

C19VBR

Professor Sir Munir Pirmohamed - NPNS AstraZeneca - Research grant to UOL to support PhD in drug interactions.
Other relevant interests in Pfizer, Janssen, Sanofi – Sir Munir is part of an EU-funded IMI consortium on gene therapy, and these companies are partners in the project. The University of Liverpool will get funding from the EU (but not from the partners), this IMI project commences on 3rd November 2020.
AGILE – this is a Liverpool early phase trial platform (between University of Liverpool and Liverpool School of Tropical Medicine). It is funded by the Wellcome Trust and UKRI/DHSC/NIHR. It is NOT evaluating vaccines, but only drugs to treat COVID-19. Sir Munir is not on the trial management group, and he is not directly involved in choosing the compounds for the study. Sir Munir has no involvement with any of the developers of the compounds to be studied (academic or industrial).
Sir Munir is a member of the UK COVID Therapeutics Advisory Panel (UK-CTAP), which is advising the CMO on which compounds need to be prioritised for the RECOVERY+ trial (RECOVERY is funded via NIHR/DHSC).

Professor Breuer – NPNS – Professor Breuer is joining the data safety monitoring committee, DSMB, a study looking at combining vaccines being run by Matthew Snape in Oxford. There does not appear to be any involvement of the vaccine manufacturers and is for already licensed vaccines. The study is funded by the NIHR (Dec 2020).

Professor French - Other relevant interest **-** Provides clinical care when in covering the acute medical wards where patients with COVID-19 are cared. NPNS in GSK - In September 2020 a sub-contract was signed with the Liverpool School of Tropical Medicine to undertake work evaluating the safety and effectiveness of GSK's RTS's malaria vaccine in Malawi. GSK are the primary funders to the LSTM.

Ms Hunneyball - Other relevant interest – writes articles published in the Chemist and Druggist magazine, a trade magazine for pharmacists, but receives no payment for these articles. The information referred to in the articles is in the public domain. Ms Hunneyball

makes it clear that these are her personal views and reflections and reference all sources of information used.

Professor Hyrich – NPNS - Professor Hyrich was co-I on an investigator-initiated research grant exploring predictors of outcome in rheumatoid arthritis. NPNS Pfizer- she is a Co-I on a grant exploring adherence to JAK inhibitors in rheumatoid arthritis. NPNS in Abbvie, Professor Hyrich gave some lectures at an education conference on effectiveness of treatment for rheumatoid arthritis.

Sir Michael Jacobs - Other relevant interest - As part of the academic role at the Liverpool School of Tropical Medicine, Sir Michael is a member of the Study Management Team and antiviral drug prioritisation group for the AGILE proof of concept (phase I/II) platform study. Sir Michael is also part of the team that submits new antiviral compounds against SARS-CoV2 for consideration by NIHR for testing on this platform. No commercial or financial interest in the trial or any of the compounds, or any pharmaceutical or biotechnology company.

Professor Lachmann – Other relevant interest as a volunteer participant in the Oxford vaccine study and no other involvement in the study.

Professor Lehner - Other relevant interest – Professor Lehner previously held a DPAC (Discovery Partnership with Academia) agreement with GSK, but this has been completed. Professor Lehner's participation in his local hospital D and T governance committee deliberations would form the normal activity and professional responsibility in his post and does not interfere with the EWG considerations (Sept 2020).

Dr Misbah - NPNS - Holds honorary Senior Lectureship with University of Oxford & Oxford University Hospitals NHS Foundation Trust.

Professor Price - NPNS in GSK and AstraZeneca – which relates to donations provided by both companies to the British Toxicology Society (BTS) to support their Annual Congress and Education and Training of which Professor Price is currently President of the Society (2020-2022).

Dr Riordan - Other relevant interests - Participant in Oxford University's ChAdOx1 nCoV-19 clinical trial –received immunisation 27/8/2020. NPNS - Postgraduate External Examiner for Oxford University (Postgraduate Diploma in Paediatric Infectious Diseases).

Professor Solomon - Other relevant interests – Professor Solomon provides clinical care for patients with Covid-19; chaired the MRC/NIHR committee which awarded funding for development of the Oxford Vaccine.

Professor Weir - Other relevant interest arising from link to the Lothian NHS Board. NHS Lothian R&D has partially funded Professor Weir's post at University of Edinburgh, since 2010, so that he could provide methodological advice on health services research studies and clinical trials.

CTBV

Professor Park - NPNS in GSK Research & Development Ltd. and in Janssen as I received a research grant in the past two years. The grant has been handed over to a colleague in 2020 and the grant is due to finish in 2020. Professor Park received no direct payment. In addition, Professor Park have two active IMI grants for Transbioline

and Quantitative Systems Toxicology, he is the PI on the TransBioline grant for the University of Liverpool. Both grants are paid directly to the University of Liverpool.

Professor Turner – NPNS interest. Professor Turner is a Non Executive Director (non-remunerated) on the Board of the Cell and Gene Therapy Catapult (CGT).
CGT have been tasked by UK Government with re-purposing a factory in Braintree to manufacture either a vaccine or a therapeutic mAb. No decision has been made as to whether or what product CGT Braintree may be asked to manufacture and that decision will be made by UK Government. Professor Turner does not believe that CGT Board will have any material input into the decision as to what product may be manufactured.

CPS

Mr V'lain Fenton-May – None

Professor Yvonne Perrie - NPNS in Pfizer & AstraZeneca arising from a contract for a grant (March 2018), which includes contributions from these companies to the University of Strathclyde, Janssen in writing a grant for a PhD (now funded), GSK – arising from an EU grant to University of Strathclyde (Jan 2019-Dec 2019)

Professor Kevin Taylor – None

Dr Susannah Walsh – None

Observer – Chair of CHM

Professor Ralston – NPNS – Sanofi, Pfizer, Janssen, AstraZeneca & Other relevant interests in NHS Lothian and Oxford University. Professor Ralston has an honorary consultant contract with NHS Lothian but has not been involved in any trials relating to COVID-19. He also has agreed to be an external examiner for Oxford University clinical trials MSc; however, this has not yet started.

1.4 The Chair welcomed:

Invited Experts of the CTBV and CPS Expert Advisory Groups, and Observer, Professor Ralston, Chair of the Commission on Human Medicines (CHM)

2. Minutes of the Covid-19 VBR EWG meetings

2.1 COVID19VBR EWG Wednesday 18 November 2020 Draft Minutes

2.1.1 These minutes will be revisited after further amendments have been made.

2.2 COVID19VBR EWG Friday 20 November 2020 Draft Minutes

2.2.1 These minutes were approved as an accurate and true record of the proceedings.

2.3 COVID19VBR EWG Saturday 21 November 2020 Draft Minutes

2.3.1 These minutes were approved as an accurate and true record of the proceedings.

2.4 COVID19VBR EWG Tuesday 24 November 2020 Draft Minutes

2.4.1 These minutes will be revisited after further amendments have been made.

3. Update on Pfizer/BioNtech

3.1 The EWG heard an update on the Pfizer/BioNtech vaccine BNT 162b2. The EWG heard that 8 or 9 batches have been allocated to the UK.

The EWG discussed how variations in batches may possibly affect immunogenicity in patients. The EWG agreed batches should be checked to make sure they are immunogenetic. The EWG heard PHE are looking at serology of individuals that have been vaccinated. The EWG agreed it would be useful to compare serology between individuals who have received vaccine from different batches.

The EWG noted that the data from NIBSC was consistent and met the defined criteria but it was agreed that the specifications provided by the company were not adequate and they should provide proper lower and upper limits. If the specifications are not adequate it is difficult to reject bad batches. In particular, the [redacted] requires adequate upper and lower limits for the specification.

The EWG agreed that the definition of RNA integrity requires improvement and more detail on how it relates to immunogenicity. The EWG also noted that the cold chain has not been validated.

3.2 The EWG heard that each individual receiving vaccine will be given a little card with the brand and the batch number on it.

The EWG discussed the public perception on the release of emergency use batches. The EWG heard that batches can be rejected if they are not satisfactory and then it will fall to the company to provide replacement batches, but it would not be known when replacement batches would be provided. The EWG agreed that the release of further batches is at the discretion of MHRA and does not need EWG or CHM approval.

3.3 The EWG heard that dose response studies have been performed with the vaccine and some response was observed between the 10 and 30 microgram dose (18-55 years age group) but the response was flat between the 20 and 30 micrograms dose (18-55 years age group). A stronger response was seen between the 20 and 30 micrograms dose in the 65 – 85 years age group. This suggests batch variability is likely to have less of an effect.

3.4 The EWG heard that some of the instructions for use are causing issues and MHRA staff are meeting with Chief Pharmacists to resolve these. The EWG heard that in terms of deployment the stability data the MHRA has seen has not changed and no further qualification has been provided by the company. The shelf-life remains 120 hours at [redacted] once removed from the freezer (undiluted), and no further information has been provided on the diluted vaccine. The breakdown of the packs is performed at [redacted] and the countdown with regard to shelf-life begins as soon as the vaccine comes out of the freezer. The stability data allows for two transportations by refrigerated lorry in two 6-hour transports (undiluted) in refrigerated conditions. Once major distribution has been achieved, the more distant deployment, for example to care homes and rural homes, is more difficult. Transport of vaccine via boat or plane has not been qualified. When the vaccine reaches a temperature above [redacted] the 'clock starts to tick' and all vaccine administration needs to be done within 120 hours. The EWG agreed deployment is not within the remit of MHRA.

The EWG agreed that MHRA can release the three batches of BNT162b2.

4. Update from Communications team

4.1 The EWG heard a summary on the communications plan. The EWG heard that any requests for interviews received by any member of the EWG should be refused and these requests forwarded onto the news centre at MHRA. The EWG discussed the comments made by the ex-Vice President of Pfizer. The EWG heard that the communications team will contact Pfizer with regard to this. The EWG heard that MHRA will be considering members of the EWG making comments on this vaccine and the process of authorisation in the future but at present the communications are being very closely managed.

5. AZD1222 update

5.1 The EWG heard an update on the assessment of the AZD1222 vaccine candidate. Three batches have been allocated to the UK.

5.2 The EWG agreed it is unlikely that any more data with regard to T-cell exhaustion can be gained unless any clinical signals are observed. The EWG noted it would be interesting to see if any hepatic toxicity signals are seen in the clinical trial data. The EWG agreed that information with regard to reproductive studies should be consistent with that for the Pfizer vaccine.

The EWG noted that the nonclinical package of data is all at one dose so there is no dose response data. The EWG agreed that any signals seen in the clinical data should be tracked back to the nonclinical data.

The EWG heard a summary of the assays from NIBSC.

The EWG heard the [redacted] evaluates [redacted] and [redacted] in cases of infection after vaccination, and the [redacted] method for the detection of antibodies (against COV-2 S, COV-2 N protein and COV-2 RBD) evaluates an immunogenicity response in convalescent sera. The EWG noted that a different package should be used for evaluating the immunogenicity response. The sample should not be from convalescence sera, it should be validated against the relevant characteristics of the population receiving the vaccine. The EWG agreed that the company should share how they validated the [redacted] that was used.

The EWG agreed the [redacted] is suitable for use to evaluate cases of infection after vaccination.

5.3 The EWG heard that only symptomatic patients were included in the primary analysis. A secondary endpoint is the incidence of asymptomatic cases as determined by weekly PCR tests on nose/throat swabs (in the UK COV002 study only)

The EWG discussed the low dose (LD)/high dose (SD) regimen used in the AZ/Oxford trials and whether this was intentional or not. The applicant is applying for a SD/SD dosing regimen (not the LD). Reports from Oxford state the LD was planned and AZ report it was a mistake. The EWG heard this does not affect how the results are interpreted.

The EWG heard that use of the LD was not intended. Depending on the product manufacturer the concentration of virus particles was measured using a different method, which explains the difference in the dose after the manufacturer was changed. This will be addressed in the next meeting.

The clinical studies COV001 and COV002 have been inspected by MHRA Inspectorate. No critical findings were found for the first study, and the second inspection is ongoing.

The EWG heard that the LD was not planned from the beginning of the study, but when the sponsor became aware the trial was still unblinded, they reacted, and a protocol amendment was included to introduce the LD.

The EWG heard the primary efficacy population analysis was young (median 40 years, 60% female, 450 subjects ≥ 70 years), a much younger population than for the Pfizer vaccine. For the LDSD group, patients were 18-55 years of age with a median of 40 years age.
The EWG heard that the applicant has planned efficacy analysis by BMI and comorbidity, this data is expected.

The EWG discussed how priming with a small dose followed by a large dose can achieve a better response, may be due to immune memory which can give a stronger booster effect. It is also possible that it may be due to a lower neutralising antibody response to the ChAdOx1 vector itself, which may allow for a better anti-Spike response to the booster dose. The EWG agreed it would be useful to have immunological responses to the ChAdOx1 vector itself.

The EWG heard that data have been published in the last Lancet paper which reported the anti-ChAdOx1 response is lower with the lower dose which may be part of the reasoning.

5.4 The EWG heard the applicant has not provided an explanation of why a saline placebo was used for the South African study and a meningococcal vaccine for the other 3 studies.

6. Moderna update

6.1 The EWG heard an outline of the quality, non-clinical and clinical data submitted so far. The EWG also heard about the expected timing and content of future submissions.

The EWG heard that a Regulation 174 letter may be received this year; a national marketing authorisation is not legally possible before 01 January 2021. A Regulation 174 approval before 01 January 2021 could be feasible if the Company submits the data according to the plan shared with the MHRA, and no major issues arise on assessment. The EWG considered whether a less urgent approach would be more appropriate as the UK is unlikely to receive product before Spring 2021.

The EWG heard that following an urgent meeting with the company 3 days ago, MHRA was informed that a batch may be available for the UK before the end of this year.

The EWG heard that NIBSC has not yet seen any material for this vaccine yet and therefore if a Regulation 174 letter is received NIBSC would only be able to present a very sparse study plan for this vaccine.

The EWG heard that MHRA will provide an update of submission and assessment timelines in the near future.

6.2 The EWG heard that the applicant will provide MHRA with any questions/responses they have received/submitted to the EMA. The EWG heard that the applicant has performed a general toxicity study that is non-GLP and that this was agreed by the EMA. The EWG noted that the nonclinical AR will be shared with the committee in the near future.

7. Future Steps / Any Other Business

7.1 Members were reminded that:

The content of papers and proceeding of the meeting are strictly confidential and should not be disclosed.

All enquiries, approaches, interview requests and requests for comments made directly to the members from the media or stakeholders, verbal or written, should be declined and referred to the agency's news centre in the first instance.

7.2 The Secretariat informed the Group that we may be moving over to a new platform 'Microsoft Teams' for future meetings of the EWG.

8. Date and time of next meeting

Thursday 10th December 2020 at 14:30

The Meeting started at 10:36 and ended at 13:36.

Members are reminded that the content of papers and proceeding of the meetings are to be treated as 'Official – sensitive commercial'. Members are also reminded that, in accordance with the Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members must also declare any other matter which could reasonably be perceived as affecting their impartiality. Detailed guidance is set out in the Code of Practice

Annex I

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Invited to all meetings, receives all papers and presentations and is permitted full participation in discussion, including drawing up conclusions and recommendations

Invited experts

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Observers

Are invited to attend all meetings. Will not participate in drawing up conclusions and recommendations.

COMMISSION ON HUMAN MEDICINES (CHM)

COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP - Quality ad hoc Group

Minutes of the meeting held on **Thursday 10th December 2020** at **14:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan
Professor N French
Professor D Goldblatt
Ms S Hunneyball
Professor K Hyrich
Sir M Jacobs
Professor H J Lachmann
Professor P J Lehner
Dr S Misbah
Professor S Price
Dr A Riordan
Professor C Robertson
Professor T Solomon
Dr R Thorpe
Mrs M Wang[1]
Professor C Weir[2]

Apologies

Professor P Shah

Members of the CTBV Expert Advisory Group

Professor B K Park
Professor M Turner

Members of the CPS Expert Advisory Group

Mr VI G Fenton-May
Mr R Lowe
Professor Y Perrie
Professor K M G Taylor (Chair of CPS)
Dr S Walsh

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted] - LD

Supporting specific items

[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - VRMM
Dr N Rose - MHRA-NIBSC
[redacted] - LD

MHRA Observers

Ms R Arrundale - Policy
[redacted] - VRMM
Dr S Branch - VRMM
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] (Accenture IT)
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD

[redacted]

18th January 2021

Observer

Professor S Ralston (Chair of CHM)

Secretariat

[redacted]

[redacted]

[redacted]

[1] Joined during item 2

[2] Left during item 2

Key

LD = Licensing Division
NIBSC = National Institute for Biological Standards & Control
VRMM = Vigilance & Risk Management of Medicines
CTBV = Clinical Trials, Biologicals & Vaccines EAG
CPS = Chemistry, Pharmacy & Standards EAG
CHM = Commission on Human Medicines

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Other relevant interests in Pfizer, Janssen, Sanofi – Sir Munir is part of an EU-funded IMI consortium on gene therapy, and these companies are partners in the project. The University of Liverpool will get funding from the EU (but not from the partners), this IMI project commences on 3rd November 2020.
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Sir Munir is a member of the UK COVID Therapeutics Advisory Panel (UK-CTAP), which is advising the CMO on which compounds need to be prioritised for the RECOVERY+ trial (RECOVERY is funded via NIHR/DHSC).

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Sir Michael Jacobs - Other relevant interest - As part of the academic role at the Liverpool School of Tropical Medicine, Sir Michael is a member of the Study Management Team and antiviral drug prioritisation group for the AGILE proof of concept (phase I/II) platform study. Sir Michael is also part of the team that submits new antiviral compounds against SARS-CoV2 for consideration by NIHR for testing on this platform. No commercial or financial interest in the trial or any of the compounds, or any pharmaceutical or biotechnology company.

Professor Lachmann – Other relevant interest as a volunteer participant in the Oxford vaccine study and no other involvement in the study.

Professor Lehner - Other relevant interest – Professor Lehner previously held a DPAC (Discovery Partnership with Academia) agreement with GSK, but this has been completed. Professor Lehner's participation in his local hospital D and T governance committee deliberations would form the normal activity and professional responsibility in his post and does not interfere with the EWG considerations (Sept 2020).

Dr Misbah - NPNS - Holds honorary Senior Lectureship with University of Oxford & Oxford University Hospitals NHS Foundation Trust

Professor Price - NPNS in GSK and AstraZeneca – which relates to donations provided by both companies to the British Toxicology Society (BTS) to support their Annual Congress and Education and Training of which Professor Price is currently President of the Society (2020-2022)

Dr Riordan - Other relevant interests - Participant in Oxford University's ChAdOx1 nCoV-19 clinical trial –received immunisation 27/8/2020. NPNS - Postgraduate External Examiner for Oxford University (Postgraduate Diploma in Paediatric Infectious Diseases)

Professor Solomon - Other relevant interests – Professor Solomon provides clinical care for patients with Covid-19; chaired the MRC/NIHR committee which awarded funding for development of the Oxford Vaccine.

Professor Weir - Other relevant interest arising from link to the Lothian NHS Board. NHS Lothian R&D has partially funded Professor Weir's post at University of Edinburgh, since 2010, so that he could provide methodological advice on health services research studies and clinical trials.

CTBV

Professor Park - NPNS in GSK Research & Development Ltd. and in Janssen as I received a research grant in the past two years. The grant has been handed over to a colleague in 2020 and the grant is due to finish in 2020. Professor Park received no direct payment. In addition, Professor Park have two active IMI grants for Transbioline and Quantitatve Systems Toxicology, he is the PI on the TransBioline grant for the University of Liverpool. Both grants are paid directly to the University of Liverpool.

Professor Turner – NPNS interest. Professor Turner is a Non Executive Director (non-remunerated) on the Board of the Cell and Gene Therapy Catapult (CGT).
CGT have been tasked by UK Government with re-purposing a factory in Braintree to manufacture either a vaccine or a therapeutic mAb. No decision has been made as to whether or what product CGT Braintree may be asked to manufacture and that decision will be made by UK Government. Professor Turner does not believe that CGT Board will have any material input into the decision as to what product may be manufactured.

CPS

Mr V'lain Fenton-May – None

Mr Robert Lowe – None

Professor Yvonne Perrie - NPNS in Pfizer & AstraZeneca arising from a contract for a grant (March 2018), which includes contributions from these companies to the University of Strathclyde, Janssen in writing a grant for a PhD (now funded), GSK – arising from an EU grant to University of Strathclyde (Jan 2019-Dec 2019)

Professor Kevin Taylor – None

Dr Susannah Walsh – None

Observer – Chair of CHM

Professor Ralston – NPNS – Sanofi, Pfizer, Janssen, AstraZeneca & Other relevant interests in NHS Lothian and Oxford University. Professor Ralston has an honorary consultant contract with NHS Lothian but has not been involved in any trials relating to COVID-19. He also has agreed to be an external examiner for Oxford University clinical trials MSc; however, this has not yet started.

1.4 The Chair welcomed:

Invited Experts of the CTBV and CPS Expert Advisory Groups, and Observer, Professor Ralston, Chair of the Commission on Human Medicines (CHM)

1.5 Apologies have been received from Professor Shah for this meeting.

1.6 MHRA gave the group training on how to access the links and manoeuvre around the dossiers.

2. AZD1222 Quality, Clinical & Batch Release Testing Review

2.1 The EWG heard an update on the quality, clinical and batch release testing aspects of AZD1222. The EWG heard that several different batches of vaccine have been produced for the clinical trials with different manufacturing scales and process. This difference in scale had led to a change in purification process which has given different vial particle concentration. The EWG agreed the company should use a single assay [redacted] The EWG discussed whether two different purification protocols could also be contributing an effect as well as the difference in dose. The EWG agreed the company should be asked whether the ratio of particles containing nucleic acid is known and the effect this may have on the final composition of the product.

2.2 The EWG agreed the company should be asked to provide data on the number of vials tested in this study and the standard deviation.

2.3 The EWG noted that the company is using [redacted] for Processes 1 and 2 and [redacted] for Process 3.

2.4 The EWG heard that the process has been refined since the issues were observed in May 2020, and so there is a question now whether the initial results are reproducible.

2.5 The EWG heard discussion on the issues around the preparation of the doses given to subjects in the AZD1222 trials with different dilutions and volumes administered according to SOPs changes with each batch. The EWG was explained the reason for a lower dose (LD) being administered after the change of manufacturer. The EWG heard that the company intend to submit the application for the SDSD dose regimen, i.e., two standard doses of $5x10^{10}$ viral particles. The EWG discussed whether to consider the study as intention to treat as proposed in the Company SAP (SDSD + LDSD with SDSD as a key subgroup), with the LDSD as an unplanned subgroup, or to disregard the low dose completely. The EWG agreed that the company could use LDSD as pilot data for another proper prospective study to confirm the efficacy finding.

2.6 The EWG noted that dosing regimens in the AZ trials had a lot of heterogeneity in the length of the dosing interval which may cause issues with the interpretation of the data. The EWG heard MHRA will receive an analysis by dosing interval shortly. The EWG heard the company have proposed a dosing window of 25-35 days and MHRA will check how it corresponds to that used in the clinical trial. The EWG considered that the dosing schedule may drive the immunogenicity more than the viral particle dose.

2.7 The EWG noted that in the Phase II part of the COV002 study for immunogenicity the interval between dose 1 and 2 is 28 days whereas in Phase III for efficacy in Study COV002 the median interval is 69 days for the SDSD group and in Study COV003 it is 6 weeks. The EWG considered that this may influence immunogenicity. The EWG noted that there was no immunogenicity data for the LDSD dose regimen in the Phase II part of COV002 and that the immunogenicity data for the LDLD dose regimen and SDSD dose regimen are very similar. The EWG considered that there is no intrinsic difference in immunogenicity between LD and SD. The EWG considered that there is no biological finding to support the high efficacy observed in the LDSD group.

The EWG noted the lower age in the LDSD group as it included only subjects 18 – 55 years old. The EWG heard the subgroup analyses (including by age) are expected 21 December 2020.

2.8 The EWG discussed an appropriate upper limit for the timing of the second dose. The EWG heard the aim would be to achieve the best protection in the shortest period of time. For example, if 50/60% protection is achieved at the first dose, then a longer interval (e.g. 6 weeks) would be appropriate for the second dose. Conversely if less protection was seen in the first few weeks, then the second dose could be at 4 weeks; however, clinical efficacy data would be required to support that.

2.9 The EWG heard that NIBSC have received all 3 batches and have tested 2 which met the defined specifications.

3. Update on Hypersensitivity reactions

3.1 The EWG heard an update on the hypersensitivity reactions observed in 3 individuals (2 reports of anaphylaxis and one suspected allergic reaction) following vaccination with the Pfizer/BioNTech vaccine.

3.2 The EWG heard that a warning has been included in Section 4.4 of the 'Information for Healthcare Professionals' for persons with history of immediate-onset anaphylaxis to a vaccine, medicine or food. The statement includes a warning that the second dose should not be given if there is anaphylactic reaction to the first dose. The EWG heard that a statement has also been included in Section 6.1 of the SmPC to inform that the vaccine contains polyethylene glycol/macrogol (PEG) as part of ALC-0159. The EWG heard that a statement has been included in Section 2 of the 'Information for Recipients' with regard to a history of serious allergic reaction to a previous vaccine, medicine or food. The EWG heard that a clarifying statement that the vaccine contains PEG as part of ALC-0159 has also been added to Section 6 of the 'Information for Recipients'.

3.3 The EWG heard that the broad warning regarding previous reactions to food, vaccine and medicines was added as a precaution. The EWG heard that it is not yet proven that PEG is the cause of the anaphylaxis and allergic reactions observed. The EWG noted that the advice will likely change over time as more evidence becomes available.

3.4 The EWG heard that the three patients who had reactions should be investigated, through NHS England, in allergy clinics such as the Cambridge clinic to determine whether PEG is the causal agent in this case.

3.5 The EWG heard that only healthcare professionals are currently administering the vaccine in appropriate settings with the appropriate equipment to manage anaphylaxis or other reactions.

3.6 The EWG heard that the contraindications (anaphylaxis) may be excluding approximately 5% of the population.

4. Future Steps / Any Other Business

4.1 The EWG heard MHRA-NIBSC have released two further batches of the Pfizer/BioNTech vaccine so Pfizer/BioNTech can now provide vaccine from 3 batches.

4.2 The EWG were asked whether people who have been vaccinated are allowed to donate blood/tissues or should this be deferred. Would the mRNA or lipid component be transmissible? Under normal circumstances individuals who have taken a non-live vaccine would not be deferred.

4.3 The EWG were informed that the company have provided non-clinical data from a second distribution study in the rat using radiolabelled LNP. Following a single IM dose of 50µg, over a 48-hour period, the distribution from the injection site was extensive with the majority of the tissues exhibiting low levels of radioactivity. Drug related radioactivity was detected in the brain, but only at very low levels, i.e. 0.02% of administered dose at 2 hours post-dose falling to 0.009% at 4 hours post-dose. The majority (18% of the administered dose) was located in the liver.

5. Date and time of next meeting

Monday 14th December 2020 at 12:30

The Meeting started at 14:31 and ended at 16:12.

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Observers

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COMMISSION ON HUMAN MEDICINES (CHM)

COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP - Quality ad hoc Group

Minutes of the meeting held on **Thursday 17th December 2020** at **10:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan
Professor N French
Professor D Goldblatt
Ms S Hunneyball
Professor K Hyrich
Sir M Jacobs
Professor P J Lehner
Dr S Misbah
Professor S Price
Dr A Riordan
Professor C Robertson
Professor P Shah
Professor T Solomon
Dr R Thorpe
Mrs M Wang
Professor C Weir

Apologies

Professor H J Lachmann

Members of the CTBV Expert Advisory Group

Professor B K Park

Apologies

Professor M Turner

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted] - LD

Supporting specific items

[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - VRMM
[redacted] - LD

MHRA Observers

Ms R Arrundale - Policy
[redacted] - VRMM
Dr S Branch - VRMM
Dr P Bryan - VRMM
[redacted] - LD
[redacted] - MHRA-NIBSC
[redacted] _ VRMM
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[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
Dr N Rose - MHRA-NIBSC
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD

Members of the CPS Expert Advisory Group

Mr VI G Fenton-May
Mr R Lowe[1]
Professor Y Perrie
Professor K M G Taylor (Chair of CPS)
Dr S Walsh

[redacted]

18th January 2021

Observer

Professor S Ralston (Chair of CHM)

Secretariat

[redacted]

[1] Joined during item 2

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CPS

Mr V'lain Fenton-May – None

Mr Robert Lowe – None

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Professor Kevin Taylor – None

Dr Susannah Walsh – None

Observer – Chair of CHM

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1.4 The Chair welcomed:

Invited Experts of the CTBV and CPS Expert Advisory Groups, and Observer, Professor Ralston, Chair of the Commission on Human Medicines (CHM)

1.5 Apologies have been received from Professors Lachmann and Turner for this meeting.

2. Pfizer/BioNTech new batches

2.1 The EWG heard an update on the new batches of Pfizer/BioNTech vaccine considered for release.

2.2 The EWG discussed the low level of RNA integrity in the Emergency Use (EU) batches and why they are lower than that seen in the CT batches as there appears to be no clear reason for this difference. The EWG considered shearing (non-intact RNA particles) as a possible reason for the low RNA integrity. The EWG heard that the EU batches are close to the edge of failure at release in terms of the RNA integrity specification. The EWG heard that RNA integrity decreases with decreasing stability. The EWG considered whether a loss of RNA integrity will lead to a reduction in immunogenicity.

2.3 The EWG heard that data from NIBSC on batch release has been more consistent than that provided by the company. The EWG heard that NIBSC have reported higher potency for EE and EK batches than the company reported. The EWG discussed possible issues with regard to the potency assay the company are using. [redacted]

2.4 The EWG heard that MHRA and NIBSC will contact PHE with regard to batch testing for immunogenicity.

2.5 The EWG agreed that batches EE and EK could be released, however, as concerns have been noted liaison with PHE is important to evaluate whether immunogenicity testing can be performed on the batches.

3. Update on BNT162b2 risk of anaphylaxis

3.1 The EWG discussed how to bench mark the numbers of reactions and compare to the number of reactions seen following flu vaccination. The EWG considered the rates of anaphylaxis in the community and the following paper was referenced which showed that rates of anaphylaxis are lower in those aged 65 years and over: https://www.sciencedirect.com/science/article/pii/S0091674902001641?via%3Dihub

3.2 The EWG agreed that Professor Solomon should liaise with VRMM to ensure that neurological events are collected properly and to evaluate whether any such events are related to the vaccine or not.

3.3 The EWG agreed that individuals who had mild AEs following their first dose should still take their second dose but that the monitoring post dose should be increased to half an hour. The EWG agreed the company should be asked whether any individuals who had mild events following the first dose have had issues following their second dose.

3.4 The EWG heard that an expert from the allergy community may join Vaccine BR EWG in next few weeks.

4. AZD1222 Clinical Assessment Report – Efficacy

4.1 The EWG heard an update on the efficacy aspects of AZD1222. The EWG heard that broadly MHRA has received all efficacy data required now.

4.2 The EWG heard that WHO criteria are met in terms of efficacy; however uncertainty remains around the level of dose and timing between the two doses. More information on the dosing interval is expected from the company on 22 December 2020. The EWG noted that the subset for efficacy is a relatively small proportion of the whole population and there is a need for assurance that the data seen is reflective of the overall data. The EWG agreed the company should be asked how many events are awaiting adjudication in study COV001 and COV005. The EWG agreed MHRA should perform a tipping analysis to see if the WHO criteria are still met in a worst-case scenario. The EWG heard that the company have not performed an analysis including these 2 studies as the SAP stated they would not include any study that had less than 5 Covid-19 cases. However, the EWG agreed the company can be asked to provide the data on these events.

4.3 The EWG noted there is no information yet on asymptomatic transmission. The EWG heard that the asymptomatic analysis the company have provided is not adequate and MHRA have requested an analysis on all cases (symptomatic, asymptomatic and no disease together) and not asymptomatic cases in isolation.

The EWG discussed the lack of data on severe cases of Covid-19 and the lack of data in the elderly. The bulk of efficacy data is in the 18-55 years of age group. A subgroup analysis in the group 18-55 years vs the group > 55 years should be requested from the Company. The EWG agreed to return to the issue of age once these data are received.

4.4 The EWG discussed the disconnect between immunogenicity (antibodies and T-cells) and efficacy. The EWG noted that in terms of immunogenicity there is not much difference between the LD/LD and SD/SD groups, nor between age groups.

4.5 The EWG agreed that as the vaccine contains polysorbate the company should be asked for further details around the cases of anaphylaxis that occurred with the AZ vaccine. The EWG heard further safety data (e.g. narratives and listings) will be received 21 December 2020. The EWG heard that over 1000 cases are in the age range 65 years and over for the safety data.

4.6 The EWG agreed data gaps in racial diversity, efficacy in severe cases (due to limits in sample size), and seropositivity at baseline could be accepted although the company should be asked to address these points with the next efficacy analysis in the future.

5. AZD1222 Quality update

5.1 The EWG heard an update on the quality aspects of AZD1222. The EWG heard that data for the three Reg 174 batches are expected 21 and 28 December 2020 and 18 January 2021.

5.2 The EWG heard the quality data will be fully presented at the next EWG meeting 22 December 2020.

5.3 The EWG noted a lack of specifications such as infectivity. The EWG considered there does not seem to be an assay with regard to expression of the spike protein. The EWG heard the [redacted] assay was only used for characterisation and not as a release assay. The EWG agreed to discuss in detail at the next EWG. The EWG heard that NIBSC have noted this with the company.

5.4 The EWG heard that NIBSC tests on the three batches for appearance, identity and the cell-based test were all in specification.

6. <u>Future Steps / Any Other Business</u>

6.1 Quality aspects of the Moderna vaccine

6.1.1 The EWG heard an update on the Moderna vaccine. The EWG was informed that the non-clinical dossier was almost complete. The company had provided sufficient results from the animal reproductive toxicology studies to allow the EWG to assess the potential use of this vaccine in pregnancy and during breast-feeding based on a benefit:risk consideration.

6.1.2 The EWG heard an update on the quality aspects of the rolling review of the Moderna vaccine. The EWG heard that the data received and reviewed so far is for product manufactured in the US; it was noted that product from US manufacturing sites will only be supplied to the US. [redacted]

6.1.3 The EWG heard that data for the first EU batch is expected Friday 18 December 2020. The EWG heard that currently this product is being assessed under a rolling review and a Regulation 174 has not been requested.

7. <u>Date and time of next meeting</u>

Tuesday 22nd December 2020 at 11:30

The Meeting started at 10:34 and ended at 13:18

Members are reminded that the content of papers and proceeding of the meetings are to be treated as 'Official – sensitive commercial'. Members are also reminded that, in accordance with the Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members must also declare any other matter which could reasonably be perceived as affecting their impartiality. Detailed guidance is set out in the Code of Practice

Annex I

Conflict of Interest Policy for CHM COVID-19 Vaccine Benefit Risk EWG

Chair and Members

- May not hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
- May not currently be or have previously been involved in the development of COVID-19 vaccines

Invited to all meetings, receives all papers and presentations and is permitted full participation in discussion, including drawing up conclusions and recommendations

Invited experts

- May hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
- May currently be or have previously been involved in the development of COVID-19 vaccines

May be invited to all relevant meetings, receives all papers and presentations and is permitted to participate in discussions when invited by the Chair. Does not contribute to conclusions and recommendations

Observers

Are invited to attend all meetings. Will not participate in drawing up conclusions and recommendations.

COMMISSION ON HUMAN MEDICINES (CHM)

COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Tuesday 22nd December 2020** at **11:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan
Professor N French
Professor D Goldblatt
Ms S Hunneyball
Professor K Hyrich
Sir M Jacobs
Professor H J Lachmann
Professor P J Lehner
Dr S Misbah
Professor S Price
Dr A Riordan
Professor C Robertson[1]
Professor P Shah
Professor T Solomon[2]
Dr R Thorpe
Mrs M Wang
Professor C Weir

Members of the CTBV EAG

Professor B K Park
Professor M Turner

Members of the CPS EAG

Mr VI G Fenton-May
Mr R Lowe
Professor Y Perrie
Professor K M G Taylor (Chair of CPS)
Dr S Walsh

Observer

Professor S Ralston[3] (Chair of CHM)

Invited Experts supporting item 2

[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted] - LD

Supporting specific items

[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted]
[redacted] - LD

MHRA Observers

[redacted] - Government Legal Team
Ms R Arrundale - Policy
Dr S Atkinson – Dir
[redacted] - VRMM
[redacted] - LD
Dr S Branch - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - MHRA-NIBSC
[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
Dr SP Lam - LD
Mr K McDonald - LD
Ms T Moore - IE&S
[redacted] - LD
[redacted] - Government Legal Team
[redacted] - LD
[redacted] - MHRA-NIBSC
Dr J Raine - MHRA CEO
[redacted] - LD

Observers for specific items

[redacted] – Public Health England
[redacted] – Public Health Scotland

Dr N Rose - MHRA-NIBSC
[redacted] - LD
[redacted] - LD
[redacted] - MHRA-NIBSC
[redacted] - LD
[redacted] - LD

Representative from University of Oxford

[redacted]

Secretariat

[redacted]

[1] Joined during item 3
[2] Joined left after item 5
[3] Joined during item 2

Key
LD = Licensing Division
NIBSC = National Institute for Biological Standards & Control
VRMM = Vigilance & Risk Management of Medicines
CTBV = Clinical Trials, Biologicals & Vaccines EAG
CPS = Chemistry, Pharmacy & Standards EAG
CHM = Commission on Human Medicines
MHRA CEO = Chief Executive
Dir = Director of Operational Transformation
IE&S = Inspection, Enforcement & Standards
EAG = Expert Advisory Group

[redacted]

18th January 2021

1. Introduction and Announcement

1.1 The Chair reminded Members that the content of papers and proceeding of the meeting are strictly confidential and should be treated as 'Official – sensitive commercial' and should not be disclosed. There is no consent for members / participants to record the meeting, take screenshots or photographs of presentations. The meeting was recorded by the MHRA Secretariat for minute taking purposes only. The Chair & Members including all participants gave full consent to the recording prior to the start of the meeting.

1.2 Conflict of Interest Policy (Annex I to the minutes)

The Chair reminded members and participants that, in accordance with the CHM Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members were also reminded to declare any other matter which could reasonably be perceived as affecting their impartiality.

1.3 The following members, invited experts and observers declared interests and other relevant interests for this meeting:

Professor Sir Munir Pirmohamed - NPNS AstraZeneca - Research grant to UOL to support PhD in drug interactions.
Other relevant interests in Pfizer, Janssen, Sanofi – Sir Munir is part of an EU-funded IMI consortium on gene therapy, and these companies are partners in the project. The University of Liverpool will get funding from the EU (but not from the partners), this IMI project commences on 3rd November 2020.
AGILE – this is a Liverpool early phase trial platform (between University of Liverpool and Liverpool School of Tropical Medicine). It is funded by the Wellcome Trust and UKRI/DHSC/NIHR. It is NOT evaluating vaccines, but only drugs to treat COVID-19. Sir Munir is not on the trial management group, and he is not directly involved in choosing the compounds for the study. Sir Munir has no involvement with any of the developers of the compounds to be studied (academic or industrial).
Sir Munir is a member of the UK COVID Therapeutics Advisory Panel (UK-CTAP), which is advising the CMO on which compounds need to be prioritised for the RECOVERY+ trial (RECOVERY is funded via NIHR/DHSC).

Professor Breuer – NPNS – Professor Breuer is joining the data safety monitoring committee, DSMB, a study looking at combining vaccines being run by Matthew Snape in Oxford. There does not appear to be any involvement of the vaccine manufacturers and is for already licensed vaccines. The study is funded by the NIHR (Dec 2020).

Professor French - Other relevant interest **-** Provides clinical care when in covering the acute medical wards where patients with COVID-19 are cared. NPNS in GSK - In September 2020 a sub-contract was signed with the Liverpool School of Tropical Medicine to undertake work evaluating the safety and effectiveness of GSK's RTS's malaria vaccine in Malawi. GSK are the primary funders to the LSTM.

Ms Hunneyball - Other relevant interest – writes articles published in the Chemist and Druggist magazine, a trade magazine for pharmacists, but receives no payment for these articles. The information referred to in the articles is in the public domain. Ms Hunneyball makes it clear that these are her personal views and reflections and reference all sources of information used.

Professor Hyrich – NPNS - Professor Hyrich was co-I on an investigator-initiated research grant exploring predictors of outcome in rheumatoid arthritis. NPNS Pfizer- she is a Co-I on a grant exploring adherence to JAK inhibitors in rheumatoid arthritis. NPNS in Abbvie, Professor Hyrich gave some lectures at an education conference on effectiveness of treatment for rheumatoid arthritis.

Sir Michael Jacobs - Other relevant interest - As part of the academic role at the Liverpool School of Tropical Medicine, Sir Michael is a member of the Study Management Team and antiviral drug prioritisation group for the AGILE proof of concept (phase I/II) platform study. Sir Michael is also part of the team that submits new antiviral compounds against SARS-CoV2 for consideration by NIHR for testing on this platform. No commercial or financial interest in the trial or any of the compounds, or any pharmaceutical or biotechnology company.

Professor Lachmann – Other relevant interest as a volunteer participant in the Oxford vaccine study and no other involvement in the study.

Professor Lehner - Other relevant interest – Professor Lehner previously held a DPAC (Discovery Partnership with Academia) agreement with GSK, but this has been completed. Professor Lehner's participation in his local hospital D and T governance committee deliberations would form the normal activity and professional responsibility in his post and does not interfere with the EWG considerations (Sept 2020).

Dr Misbah - NPNS - Holds honorary Senior Lectureship with University of Oxford & Oxford University Hospitals NHS Foundation Trust

Professor Price - NPNS in GSK and AstraZeneca – which relates to donations provided by both companies to the British Toxicology Society (BTS) to support their Annual Congress and Education and Training of which Professor Price is currently President of the Society (2020-2022).

Dr Riordan - Other relevant interests - Participant in Oxford University's ChAdOx1 nCoV-19 clinical trial –received immunisation 27/8/2020. NPNS - Postgraduate External Examiner for Oxford University (Postgraduate Diploma in Paediatric Infectious Diseases).

Professor Solomon - Other relevant interests – Professor Solomon provides clinical care for patients with Covid-19; chaired the MRC/NIHR committee which awarded funding for development of the Oxford Vaccine.

Professor Weir - Other relevant interest arising from link to the Lothian NHS Board. NHS Lothian R&D has partially funded Professor Weir's post at University of Edinburgh, since 2010, so that he could provide methodological advice on health services research studies and clinical trials.

CTBV

Professor Park - NPNS in GSK Research & Development Ltd. and in Janssen as I received a research grant in the past two years. The grant has been handed over to a colleague in 2020 and the grant is due to finish in 2020. Professor Park received no direct payment. In addition, Professor Park have two active IMI grants for Transbioline and Quantitatve Systems Toxicology, he is the PI on the TransBioline grant for the University of Liverpool. Both grants are paid directly to the University of Liverpool.

Professor Turner – Other relevant interest. Professor Turner is a Non Executive Director (non-remunerated) on the Board of the Cell and Gene Therapy Catapult (CGT).
CGT have been tasked by UK Government with re-purposing a factory in Braintree to manufacture either a vaccine or a therapeutic mAb. No decision has been made as to whether or what product CGT Braintree may be asked to manufacture and that decision will be made by UK Government. Professor Turner does not believe that CGT Board will have any material input into the decision as to what product may be manufactured.

CPS

Mr V'lain Fenton-May – None

Mr Robert Lowe – None

Professor Yvonne Perrie - NPNS in Pfizer & AstraZeneca arising from a contract for a grant (March 2018), which includes contributions from these companies to the University of Strathclyde, Janssen in writing a grant for a PhD (now funded), GSK – arising from an EU grant to University of Strathclyde (Jan 2019-Dec 2019)

Professor Kevin Taylor – None

Dr Susannah Walsh – None

Observer – Chair of CHM

Professor Ralston – NPNS – Sanofi, Pfizer, Janssen, AstraZeneca & Other relevant interests in NHS Lothian and Oxford University. Professor Ralston has an honorary consultant contract with NHS Lothian but has not been involved in any trials relating to COVID-19. He also has agreed to be an external examiner for Oxford University clinical trials MSc; however, this has not yet started.

Invited Experts for this meeting

[redacted] – NPNS - in AstraZeneca and a PNS interest in AstraZeneca and was permitted to participate in the meeting to answer direct questions from the Chair only

[redacted] - NPNS interest in Imperial College London

Observer for this meeting

[redacted] - NPNS interest in Pfizer

1.4 The Chair welcomed:

Invited Experts of the CTBV and CPS Expert Advisory Groups, and Observer, Professor Ralston, Chair of the Commission on Human Medicines (CHM)

Invited Experts who participated for the anaphylaxis item 2:

[redacted] MA(Hons) Cantab., MSc, BS, DCH, FRCPCH, FHEAm Dip. Allergy Consultant Paediatric Allergist, Guy's and St Thomas' Hospitals, London; Reader in Paediatric Allergy, King's College London

[redacted] MB BS, MD, FRCP Consultant in Allergy and Asthma, Cambridge University Hospitals NHS Foundation Trust

[redacted] MBBS, MD, MRCP(UK), MBA, FRCP, FRCPath Consultant Immunologist, Sheffield Teaching Hospitals; Chair of the Speciality Advisory Committee for Immunology, Joint Royal Colleges of physicians Training Board

[redacted] Honorary Consultant in Paediatric Allergy and Immunology, London; MRC Clinician Scientist in Paediatric Allergy and Immunology, Imperial College London

The invited experts left after item 2.

Representatives of the Public Health Bodies attending as observers:

[redacted] – Public Health England

[redacted] – Public Health Scotland

The observers left after item 3.

1.5 At 13:14, the Chair welcomed

[redacted] FRCPCH PhD FMedSci
Professor of Paediatric Infection and Immunity, [redacted], Department of Paediatrics, [redacted], [redacted] University of Oxford

[redacted]

Who gave a slide presentation on ChAdOx1 nCoV-19. The representatives answered questions from the Group, then left the meeting.

2. Update on BNT162b2 risk of anaphylaxis

2.1 The EWG heard there were two cases of anaphylaxis reaction on the first day of the UK vaccination campaign. The EWG heard there was also a case of supraventricular tachycardia, and investigations are still on-going, but the latest information suggests this case is unlikely to be associated with an allergic reaction. Currently ~½ million people have been vaccinated with BNT162b2 in UK and a further ~½ million have been vaccinated in the US.

2.2 The EWG heard the FDA have received reports of two cases of anaphylaxis: one severe and one of probable anaphylaxis, and a further two confirmed cases, one in Texas and another in Mississippi. MHRA are in discussions with FDA for how best to share the pharmacovigilance information about adverse events (AE) of interest such as anaphylaxis.

2.3 Subsequent to the two cases referred to above, the MHRA has received five more reports of anaphylaxis and three cases reporting “early anaphylaxis” or anaphylactoid reactions.

Three of these cases report treatment with intramuscular adrenaline and one reports treatment with adrenaline with the route of administration not provided. Detailed onset time are not available in three of the cases, and the remaining cases report events initiating in 20 minutes or less of administration of the vaccine. Including the original two cases, none of the cases have been fatal.

2.4 The EWG heard the information on previous allergies was reviewed, 3 cases included some history of allergy either to medicine, food, or related to an insect sting, 5 cases did not report previous allergic reactions.

2.5 The EWG heard that CPRD epidemiological data has identified 14 patients prescribed AAIs in the past year, who have also received the vaccine. Initial analysis has not identified the allergies which these auto-injectors have been prescribed for, nor the outcomes in these patients although data on any recorded events following these vaccinations should be available through data linkage in the future. There has not been significant reporting in Yellow Cards of allergic reactions in patients with AAI prescriptions. Detailed follow up further information requests have been made on the Yellow Card reports to determine the specific details of the suspected anaphylactic reactions, as well as steps taken to conduct further immunological analysis.

2.6 The EWG heard the company have conducted analysis of the medical history of BNT162b2 clinical trial participants in relation to allergy and hypersensitivity, and unblinded data on reports of drug hypersensitivity events. Overall, there was little evidence of an increased risk of anaphylaxis from the clinical trial data.

2.7 The EWG recalled that polyethylene glycol (PEG) was previously considered as a potential causative agent of the two allergic reactions seen in the vaccination campaign. The MHRA have conducted a review of other injectable medicines and some oral medicines that include PEG to see if similar adverse reactions have been reported. Caelyx pegylated liposomal, a liposome formulation of doxorubicin hydrochloride encapsulated in liposomes with surface-bound methoxypolyethylene glycol (MPEG), was considered to be the product most closely related to the vaccine in terms of the excipient formulation. The EWG heard there have been a significant number of anaphylaxis reports with Caelyx pegylated liposomal; however, due to the potential confounding with infusion reactions with this product it was currently not possible to establish causality. The EWG heard that other injectable pegylated products include warnings on hypersensitivity in their product information, although the contribution of PEG to the warnings is unknown, and the UK ADR reports do not show a consistent pattern of prior history of multiple allergic reactions. The EWG heard there is a paucity of data in the literature on PEG and allergic reactions, but it may exist as an under recognised condition. The EWG heard that the very limited number of Yellow Cards received that cite hypersensitivity or allergic reactions, given the high exposure (½ million doses administered), provides reassurance that cases of anaphylaxis remain rare, including when factoring in the known limitations of YC reporting.

2.8 The EWG noted that it is important to be clear that there is no difference between anaphylaxis and anaphylactoid reactions. Anaphylactoid reactions is an outdated term used to describe non-IgE-mediated anaphylaxis. Major international allergy associations do not recommend use of this term anymore to avoid confusion.

2.9 The EWG noted that incidence of anaphylaxis appears low and investigations of the UK cases of anaphylaxis are on-going; for one of the cases there is no signal that PEG is responsible. The EWG noted of the US cases, one patient had a possible route of sensitisation to PEG through potential contact with pegylated liposomal doxorubicin as part

of her professional duties as an oncology nurse. Overall, investigations are on-going, and are presently inconclusive as to whether PEG is the causative agent.

2.10 The EWG noted that prescription of an AAI does not preclude use of the vaccine, as there are other reasons to require one other than drug sensitivity, e.g. risk of anaphylaxis due to insect stings, latex, or other allergens.

2.11 The EWG noted a paper which identified the incidence of anaphylactic reactions to PEG to be uncommon; there have been 37 cases reported to the MHRA, but causality is not confirmed for all (Sellaturay and Nasser et al, 2020; J Allergy Clin Immunol Practice). Of the 5 cases of PEG allergy studied in the paper, some individuals reacted to injectable PEG, but anaphylactic reactions also occurred with orally administered medications containing high molecular weight PEG. In three of five patients clinically assessed, anaphylaxis was induced through intradermal testing with a minute quantity of PEG. The EWG also noted that anaphylaxis to PEG appears difficult to treat as the condition seems to persist and does not respond well to adrenaline.

2.12 The EWG noted blood from two of the three vaccinated UK patients who experienced anaphylaxis had been obtained, and the third is due 22nd December 2020. Testing will be delayed until after Christmas due to delays in obtaining the vaccine in the form needed. The EWG noted the FDA have prepared an assay for [redacted] and are collaborating with the UK in terms of immunological testing, but data is only expected after the New Year.

2.13 The EWG noted the possibility to conduct a differential analysis of infusion products containing PEG versus those that do not, such as rituximab. The data may assist with the understanding of causality in terms of infusion reactions versus allergic reactions.

2.14 The EWG was reassured that the signal of anaphylaxis does not appear to be strong.

2.15 The EWG noted that the food allergy may have adverse impact on vaccine uptake but there is little evidence for increased susceptibility to adverse reactions in this population. The EWG noted that patients with food allergies should not be deterred from taking the vaccine. In contrast patients with a history of allergy to PEG, must avoid the vaccine. The EWG heard that the SmPC section 6.1 and the section of the PIL for HCPs has been updated to make it explicitly clear that the product contains PEG while also listing the alternative name of the excipient, Macrogol.

2.16 The EWG noted that, the current pharmacovigilance data does not indicate an increased risk in those with a history of allergies to other vaccines, foods or medicines and therefore, this advice can be updated and aligned with the EMA advice. The EWG noted it was important to avoid causing confusion by updating the product information too regularly, but on this occasion, it was considered appropriate due to the number of doses administered since the original advice.

2.17 The EWG noted the importance of promptly referring YC reports to the immunology experts to enable additional investigation where agreed with the reporter. The EWG noted delays have been due the additional time needed to request further details as many of the original YC reports only included sparse detail.

2.18 The EWG noted skin reactions such as urticaria at a site or sites distant from the injection site would be termed systemic, as would any suspicion of IgE manifestation. A systemic reaction is likely to preclude giving a second dose of BNT162b2. The EWG noted if the signs of allergy are localised and also continuous with the injection site the second dose should be given. The EWG noted that any patient who has experienced a systemic allergic reaction

to the first dose of BNT162b2 should only receive a second dose on specialist advice, as dispensed by the clinic. The EWG also noted that a single dose of BNT162b2 gives a degree of protection against COVID-19, and so the benefit-risk of giving the second dose in cases where the patient is potentially sensitised to an ingredient/s in BNT162b2 is limited. Patients with suspected allergies to BNT162b2 need to be also warned against switching to the Moderna vaccine for the second dose as this vaccine also contains PEG. The EWG noted it is yet to be determined if the causative agent/s may differ between reported cases, and other excipients present in BNT162b2 are still being considered; therefore, it is currently premature to form opinions on vaccine switching.

2.19 The EWG heard the MHRA has also considered trace production excipients and concluded that these are unlikely to be causative agents. Further details will be provided to the immunology experts.

2.20 The EWG noted it is currently unknown if patients who have an allergic immunogenic response to the vaccine are protected.

2.21 The EWG noted that specialist expertise is required to accurately diagnose anaphylaxis, and there is a risk of error with use of the existing product information wording which places the onus on front-line healthcare professionals to make an assessment of the allergy history of the intended recipient. This also adds an unnecessary burden because the incidence of hypersensitivity and anaphylaxis appears to be very rare. The EWG noted it would be appropriate to align with the advice from EMA, Health Canada, and the FDA, this will have the added benefit of providing a consistent message. The 15-minute observation window will remain in keeping with the EMA label.

3. Paresis and facial paralysis with Pfizer-BioNTech COVID-19 vaccine

3.1 The EWG heard there are differences in the product information between that associated with the EMA centralised authorisation and UK authorisation under a regulation 174 in terms of capturing the adverse events (AEs) of facial paralysis reported in the clinical trial. The EWG heard 4 reports of facial paralysis occurred in the vaccine arm of the BNT162b2 trial with zero cases in the placebo arm, and one report of facial paresis occurred in the placebo arm with zero cases in the vaccine arm. The cases had varying times to onset from 2, 8, 36, and 47 days post vaccination.

3.2 The EWG heard that during the consideration of the Regulation 174 approval, events of facial paralysis were identified to be within the range of the background incidence rate, predicating the absence of an increased risk of acquiring facial paralysis due to the vaccine.

3.3 The EWG heard facial paralysis has been included, as an adverse event of special interest (AESI) under the term Bell's Palsy. The EWG heard on a related note, Guillain Barre Syndrome (GBS) is also an AESI due to previous concerns with the H1N1 vaccine; although subsequent epidemiological studies did not substantiate these concerns.

3.4 The EMA concluded there was at least a reasonable possible causal association with the vaccine, due to the imbalance between cases in the vaccine arm versus placebo, even though the frequency was within the background incidence rate. Therefore, the EMA included facial paralysis in the SmPC (4.8 undesirable effects) and one-sided facial drooping in the package leaflet, the SmPC includes a foot note stating the figures and onsets of these events as per the clinical trial data. The EMA have implemented the same pharmacovigilance measures as the MHRA in relation to these events.

3.5 The EWG heard that the YC data includes one report of facial paralysis submitted by a healthcare professional and one report of facial weakness submitted by a patient. Checks are being undertaken to confirm if the reports are duplicates, as the subject age and initials match. The results of an MRI scan are awaited, but a CT scan ruled out stroke. The EWG heard presently the rate of facial paralysis appears to be very low considering the exposure, but onset of the condition can be delayed to ~6 weeks post vaccination.

3.6 The EWG heard, in the Moderna clinical trial there have been 3 cases of facial paralysis in the vaccine arm versus no cases in the placebo arm.

3.7 The EWG noted the numbers are within the background rate, but this does not preclude the vaccine being the trigger. The EWG noted Bell's palsy and GBS are associated with viral infection and have been considered potential risks with other vaccines; GBS has been associated with other vaccines previously, although this was not supported by subsequent epidemiological investigation. The EWG noted that including the adverse event term in the UK product information may, beneficially lead to increased reporting of neurological events.

3.8 The EWG noted that Bell's palsy was associated with a liposomal vaccine administered intranasally for influenza, but this may not be connected (Mutch et al, 2004; NEJM).

3.9 Overall, the EWG noted that due to the imbalances seen in both the Pfizer and Moderna trials, and the additional YC report (possibly two), on a precautionary basis the UK Information for Healthcare Professionals and other relevant product information should be aligned with that produced by the EMA. The EWG noted that amendment of the current Risk Management Plan (RMP) was not required.

4. Update on BNT162b2 vaccine for use in pregnancy

4.1 The EWG heard that on 21 December 2020 the EMA granted a conditional Marketing Authorisation for the BNT162b2 vaccine. The information included in section 4.6 (fertility, pregnancy and lactation) and 5.3 (pre-clinical data) of the EU SmPC is marginally different to that found in the same sections of SmPC for the UK 174 authorisation and the text proposed for the UK Marketing Authorisation.

4.2 The EWG heard that the differences arise due to a preclinical reproductive toxicity study that was finalised after the authorisation under regulation 174. The study was conducted in female rats with BNT162b2 given by intramuscular (IM) injection prior to mating with an un-dosed male; the vaccine was also given on two occasions during pregnancy. The study design included caesarean section on gestation day 21 which would allow embryo-fetal malformations, if present, to be identified. A further group of rats was followed to litter and the behaviour and features of the offspring observed to post-natal day 21. The EWG heard the report concluded that the vaccine did not affect any of the parameters investigated in relation to reproductive health. The EWG heard the study supports breast feeding in women and raises no concerns for female fertility as there was no impact on: the ability of the rats to get pregnant, or on pregnancy viability. This provides reassurance of the safety and absence of effects from the nanolipid particles (NLPs) and the vaccine antigen.

4.3 The EWG heard immunogenic responses were seen in the dams, and the fetuses (at gestation day 21), and the pups (with exposure by occurring through lactation intake). The EWG heard in rats, exposure to the maternal antibody does not occur to any significant degree until late into pregnancy and this was identified as a possible caveat to the relevance of the study to pregnant humans. The EWG heard that rat organogenesis takes place approximately between day 10 to 15 and during this window there is probably minimal exposure of the fetus to the maternal antibodies generated in response to the vaccine.

Importantly, and in contrast to rats, the antibody exposure window in human embryos is earlier and in terms of vaccine-induced antibody exposure, the use of a rat model may not recapitulate the conditions needed to test if vaccine induced antibodies have an adverse effect on human fetal development.

4.4 The EWG heard there was an absence of a teratogenic effect in the rat fetuses, but the significance of this finding may be uncertain as regards human risk, considering there was likely to be little or no exposure to the vaccine induced antibody during organogenesis.

4.5 The EWG heard the EMA raised the issue in earlier questions to the company, and the company based their response on a meta-analysis (Bowman et al 2013, Birth Defects Research (Part B) 98:459–485). The meta-analysis found that placental antibody transfer (IgG) levels are relatively low during development after organogenesis but the ratio of maternal blood: fetal concentrations approach one by the end of gestation in multiple species including rat, rabbit, monkey, and human. The EWG heard the meta-analysis data collection commenced on gestation day 15, notably after the period of organogenesis ends in rat development. The EWG heard neither the study nor the meta-analysis support direct exposure of the antibody to the rat fetus during the period of organogenesis, consequently the statement “the vaccine is not teratogenic arising from its induced antibodies” cannot be excluded.

4.6 The EWG heard further studies in other species are not advised as the clinical data from incidental pregnancies in vaccinated individuals will be of greater scientific relevance.

4.7 The EWG heard the UK product information (that which is not applicable to the regulation 174) must align with the EMA, as the vaccine has now been authorised through the centralised route and the UK are currently within the EU; however divergence is acceptable if supported by evidence. The EWG heard the content in both versions of SmPC section 4.6 is similar and would not precipitate any change in clinical outcomes. The EWG heard section 5.3 includes additional information which is at a higher level of detail than is expected typically for this section, although the additional information is not contentious.

5. EWG discussion

5.1 The EWG noted the structure of the data provided does not include exposure data in the window of gestation day 6 to 15. The EWG noted that relevance to humans of the outcomes of the study have not been fully established. The EWG noted in terms of the preclinical regulatory requirements for a Marketing Authorisation, data would also be sought from other sources such as toxicokinetic information which has the potential to allay concerns about teratogenic effects.

5.2 The EWG noted that the degree of reassurance a negative signal in an animal model of reproductive toxicology gives is difficult to translate in terms of relevance to humans. The EWG noted that the importance of stating in the product information that the level of knowledge in terms of the interpretation of the reproductive pre-clinical data is limited.

5.3 The EWG noted in the field of paediatric immunology the current consensus is that placental IgG from the mother starts to be seen at gestation week 12 or 13 in humans. Organogenesis in humans ends by approximately week 8, and thus has elapsed prior to fetal exposure to maternal antibody, as such the risk of maternal vaccine induced antibody teratogenicity is likely to be low. The EWG, however, maintained that the direct relevance of the data from the rat study in terms of human pregnancy is nevertheless, uncertain.

5.4 The EWG noted antibodies to the spike protein will be generated through natural exposure to SARS-CoV-2, and this form of registry data may have some use to the topic discussed, but differences between antibodies produced by variants would need to be considered, as would differences in the vaccine induced antibodies versus antibodies generated due to natural exposure.

5.5 The EWG noted after the 31 December, Northern Ireland need to adhere to EMA labelling and product information, whereas Great Britain has the option to produce alternative text. The EWG noted that, wherever appropriate, it is important to maintain consistency.

5.6 Overall, the EWG noted that both the MHRA version of the SmPC and the EMA SmPC state there is insufficient evidence of exposure to the vaccine in pregnancy, but only the EMA SmPC provides for use in patients with an elevated benefit for receiving the vaccine e.g. pregnant women who are critically vulnerable to COVID-19. The EWG noted that there is no elevated risk to the public by aligning with the EMA wording, with the provision that it is made clear that relevance of the non-clinical reproductive data in human pregnancy is unclear, and that use during pregnancy must be an informed decision by the individual supported by the advice of a clinically qualified person/s.

5.7 The EWG noted that the UK information mentions that women of childbearing age should be advised to avoid pregnancy for at least two months after their second dose. The EWG heard the two-month period arose due to the time to clearance of the NLPs, but the clinical relevance to the embryonic or fetal development remains to be established. The EWG noted that this text should be removed due to the importance of a delivering consistent message. The EWG noted that to err on the side of caution, information on this topic could be communicated in other documents such as the patient group directions and immunisation protocols. Overall, the EWG noted that alignment of the product information and label was appropriate. The EWG noted, as part of the standard governing process, alignment of the product information and label will need to be considered at CHM.

6. AZD1222 clinical discussion and Q and A.

6.1 The EWG heard ChAdOx1 nCoV-19 vaccine uses a replication deficient chimpanzee adenovirus as a vector with the full-length gene for the SARS-CoV-2 spike protein inserted.

6.2 The EWG heard pre-phase I modelling suggested a single dose would be most effective to gain a signal of efficacy due to the high number of cases predicted at the time. Phase I commenced in April, however the number of COVID-19 cases was much lower than expected due to lockdown, and so the sample size was insufficient to give a signal of efficacy. However, a positive signal of stronger immune responses on neutralizing antibody was noted in a two-dose sub study so development was switched to a two-dose programme. An extended programme was conducted that confirmed the findings as well as the existence of T-cell responses to the spike protein.

6.3 The EWG heard phase II studies found little difference in the neutralising antibody titres between age groups induced with two doses; although levels were lower with a single dose, they were still similar between groups. Phase II and III studies were initiated in the UK, Brazil and South Africa plus a small phase I/II in Kenya which was not discussed. In the UK 11,000 participants are enrolled with 20% over 55, in Brazil 10,000 with 20% over 55. The partnership with AstraZeneca enabled 30,000 participants to be enrolled in the US with 25% over 65, in addition to small immunogenicity studies in Russia and in Japan, and India (completed). The EWG heard AstraZeneca share the vision to create a not-for-profit vaccine.

6.4 The EWG heard there was a manufacturing delay, which in turn delayed administration of the second dose to participants in the phase III studies, particularly to younger UK trial participants. Due to a lack of manufacturing capacity, the phase III trial material in the UK was sourced from a different manufacturer, a contract manufacturing organisation (CMO). The EWG heard the release assay for concentration of virus used by the CMO was different to that used by Oxford (PCR versus absorbance). The EWG heard a decision was taken to also apply absorbance testing to CMO produced batches as it is the most cautious approach and is consistent with the method used to release the Phase I material. The EWG heard participants in the phase III trial receiving the product from batches manufactured by the CMO had lower reactogenicity compared to phase I participants, and further investigations suggested carry over of polysorbate 80 interfered with the absorbance measure, the carry over resulted in a subgroup of 3000 participants receiving a half first dose termed low dose (LD), followed by a full second standard dose (SD), the subgroup is identified by the initialism (LD/SD). The majority of participants received a standard dose followed by a second standard dose (SD/SD group).

6.5 The EWG heard the efficacy endpoints are based on PHE and WHO symptom definitions published in February, with infection confirmed in symptomatic participants by PCR testing. Weekly swab-based PCR testing for all UK trial participants is also being undertaken to monitor asymptomatic infection. The EWG heard there is also an endpoint of serological evidence of infection that is yet to be analysed.

6.6 The EWG heard that 4th November 2020 was the data cut-off for the interim analysis with a database lock of 21st November. The EWG heard the results clearly showed that the reactogenicity of the vaccine which was more pronounced with the first dose. The other adverse events were evenly balanced between the vaccine arms and the control arms. The EWG heard serious adverse events across the 4 studies were 175 events in 168 participants, and three of these were considered possibly related to the experimental vaccine or the control vaccine. The first event was a case of haemolytic anaemia in the control group of the phase I/II study. The second was a case of transverse myelitis that was seen in a UK trial participant 14 days after the second dose (booster) of the experimental vaccine. This adverse event was considered possibly related to the vaccination by the investigator; the independent neurological committee review considered the most likely diagnosis was idiopathic short segment spinal cord demyelination. The third adverse event was a case of fever over 40^{o}C in a trial participant in South Africa; the fever resolved without hospitalisation and the participant received a second dose without a similar reaction. Due to blinding, it is currently unknown if the participant was in the control or experimental vaccine arm. The EWG heard there were two cases of neurological AEs that were determined to be unlikely to be related to the vaccine (control or experimental) by the independent neurological committee. One of the cases occurred 10 days after the first dose of the experimental vaccine, and on imaging, old lesions were identified consistent with the pathology of previously unrecognised, but pre-existing multiple sclerosis. The other case was in the control group.

6.7 The EWG heard the data from the phase I UK study and SA study was not included in the efficacy interim analysis due to too few COVID-19 cases post second dose. Overall efficacy results were 70% (from participants seronegative at baseline), LD/SD 90%, SD/SD: 60% in UK trial, and 64% Brazil trial. The EWG heard hospitalisation and severe COVID-19 data is available from the two clinical trials. Two cases in the vaccine group in first three weeks after first dose, one on the day of vaccination, the other at day 10, all subsequent cases were in the control group.

6.8 The EWG heard the package to support a potential Marketing Authorisation is based on the SD/SD regimen. The EWG heard protection was seen from 3 weeks after the first dose. The

EWG heard a post first dose interval of >4 weeks is supported by the data, up to 12 weeks; there was a trend that a longer interval may was associated with greater efficacy, and this is also supported by immunogenicity (serological antibody) data. The EWG heard there are relatively few older adults in the efficacy analysis, but further data is expected.

6.9 The EWG heard asymptomatic infection data in the LD/SD subgroup, saw a point estimate for VE of 58%, but with wide confidence intervals; in the SD/SD group there was a similar number of asymptomatic cases in each group.

6.10 The EWG heard the over 65s will be better represented in future analyses, as they were enrolled to the trial later. In the present analysis there are too few cases to draw firm conclusions on the point estimates of VE in the over 65s (8 control group versus 2 in vaccinated group from dose 1), but bridging antibody data to that reported from the Brazil trial leads to an estimated VE of 60%.

6.11 The EWG heard the results of the PCR testing have suggested the new SARS-CoV-2 variant is present in some UK trial participants and further analysis is being undertaken.

7. Questions and Answers

7.1 The EWG asked about the immunological basis of high VE in the LD/SD subgroup compared to the VE seen in the SD/SD group. The EWG heard immunogenicity analysis suggest that the high VE was more likely to be associated with the extended length of the interval rather than the dosing regimen.

7.2 The EWG heard the serological data consistently showed no strong association between anti-vector neutralising antibodies and the immune response to spike protein, but T-cell responses have yet to be excluded.

7.3 The EWG asked about implications for the differences in the purification procedure between the CMO and the Oxford site. The EWG heard differences were expected to be limited to null, as batches produced are comparable in terms of immunogenicity by batch, and amount of neutralising antibody. The EWG heard the vaccine given in the LD/SD and SD/SD groups of the UK trial are sourced from the same manufacturing batch.

7.4 The EWG asked about details and the outcome of a potential neurological AE reported in India. The EWG heard the independent neurological committee is currently reviewing the case. The committee's evaluations currently find a causal association between the study vaccination and clinical presentation to be uncertain. The clinical diagnosis put forth by the committee was of an acute and self-limiting non-specific encephalitis / encephalopathy with full recovery. Although, the committee is deliberating if the case is truly encephalopathic, as full recovery was seen without the use of immunomodulators—only antibiotics and antivirals. Further investigations are still on-going. The committee found high titres of anti-ribonucleotide (RNP) antibodies which may indicate lupus erythematosus (SLE); however, the committee identified no other clinical or systemic signs of SLE. Currently, two of the possible diagnoses are autoimmune disorders, or condition/s which respond to antivirals and/or antibiotics, but alternative diagnoses are not precluded at this stage.

7.5 The EWG asked if viral load in the SD/SD asymptomatic group had been measured to see if there was a reduction. The EWG heard normalising PCR against QC controls needs to be completed before analysis can be conducted in a robust manner. The EWG heard the new variant seems to be seen at higher viral loads, and how precisely, to factor this into the analysis also needs to be determined. The EWG heard that future data will potentially be

subject to confounding due to healthcare professionals in the control arm of the trial receiving the Pfizer/BioNTech mRNA vaccine (BNT162b2).

7.6 The EWG asked if the investigations of the case of transverse myelitis included measuring anti-neuronal antibodies and anti-vector antibodies. The EWG heard, there was extensive investigation of the case, there were no significant findings in terms of assessing auto-antibodies to the central nervous system (anti-neuronal antibodies not found). The EWG heard some members of the independent neurological committee correlate the pathology with a possible ischaemic event, which would align with a trip/fall reported by the participant.

7.7 The EWG heard serological testing revealed the presence of anti-vector antibodies but this finding was unremarkable as most vaccinated individuals possess anti-vector antibodies; how best to further interpret the data is currently not known. The EWG heard the changes were very anterior in the spinal cord and are only present in a single segment; of note the cerebral spinal fluid was also non-inflammatory. Overall, the findings are unusual, but an association with vaccine cannot be presently be excluded. A member of the EWG who was involved in the care of the patient, explained that the clinical pattern of disease onset and recovery was consistent with an inflammatory event rather than an ischaemic one, but the detailed information about the patient's recovery may still need to reach the independent neurological committee.

7.8 The EWG asked about the age distribution of the trial participants. The EWG heard that data from most of the over 65s was not available until beyond the cut-off for the interim analysis. The EWG heard the US study is enrolling 30,000 patients (including in Chile and Peru) and the target is 25% who are 65 and over. The data for the next analysis should be ready January / February.

7.9 The EWG asked about the immunogenicity in the context of duration post first or post second dose. The EWG heard that operation warp speed postulated that the difference in efficacy between the LD/SD and SD/SD was due to differences in immune responses to the vaccine in young versus old participants. The EWG heard this was likely to be incorrect because numbers of older patients included in the SD/SD group were very limited. The EWG heard the interval data support efficacy from an interval of 4 weeks and above, and there is a trend towards an incremental increase of efficacy with a longer interval between doses, and this is consistent with some other vector vaccines.

7.10 The EWG asked if the data to support use of prophylactic paracetamol were available. The EWG heard the study data from the phase II show that paracetamol does not have a detectable effect on immune responses to the vaccine.

8. AZD1222 Quality update

8.1 The EWG heard the content discussed relate to the application for a conditional MA; the batch specific release of AZD1222 under regulation 174 is to be discussed at a later meeting.

8.2 The EWG heard the material used in the clinical trials was derived from three manufacturing sites, and for each of the sites, the company have provided sufficient details of batch scale-ups and manufacturing process changes, as well as satisfactory justifications for significant changes.

8.3 To characterise the clinical trial product from the three sites, numerous analytical methods were employed by the company; [redacted]

[redacted] Assays of clinical trial product from each of the three processes results in functional S protein [redacted]. A comparability study demonstrated that the commercial Process 4 drug substance (DS) is comparable to DS from Process 1, 2 and 3 [redacted] although the limits are wide. The EWG heard other criteria are also very wide, however the data appear acceptable. The EWG advised that the company should commit to [redacted] for routine batch release.

8.4 The EWG heard an explanation of the process steps used to create the viral vector. The EWG heard the production steps were adequately described and the control of materials was acceptable. The EWG heard master virus seed (MVS) and working virus seed (WVS) for commercial manufacture were derived from a different lot of pre-GMP starting material to that used for the clinical trial lots, but at an earlier stage the material is traced back to the same protein & viral genome D8 isolate. The EWG heard this can be considered acceptable if DS lots are confirmed to be comparable. The EWG heard the company recently provided reassurance of comparability by undertaking additional DS characterisation in the form of NGS sequencing of the whole vector (including the S protein) and the results demonstrated 100% alignment with the reference sequence. Other forms of reassurance include the release specification parameters and other extended characterisation data.

8.5 The Company have also been asked to confirm the manufacturing site/s to supply the product to the UK, although this has been confirmed for the batch that may be procured under Regulation 174.

8.6 The EWG heard the DS control procedures appear adequate although full DS validation results expected soon are required.

8.7 The EWG heard an explanation of the drug product manufacturing process and controls, covering three separate manufacturing sites. The EWG heard the process and controls are adequately described, and the controls are appropriate although full DP validation data is also pending.

8.8 The EWG heard material of human origin and the materials of animal origin have been adequately described and the documentation including applicable risk assessments were considered suitable. The EWG heard that the adventitious agent screening and testing was comprehensive.

8.9 The EWG heard about the DS and drug product (DP) specifications. The EWG heard the specifications were considered appropriate, but all specifications will be revisited after additional manufacturing experience has been gained.

8.10 The EWG heard about the DP stability data programme: The EWG heard stability studies were conducted to establish DP shelf life at the long-term storage condition of 2-8°C. Data are available for up to 4 months at a storage condition of 2-8°C, for three clinical lots (Process 3) which are designated the primary stability lots, with supporting stability data from clinical lots derived from the other processes (1-2). The EWG heard stability studies have been initiated for seven Process 4 (commercial) DP lots. The EWG heard the proposed shelf life for the Drug Product is 6 months, the same as for the frozen DS. The EWG heard the shelf life is considered to be acceptable, but decreasing infectivity and increasing virus particles

vs infectious virus ratio, have occurred under accelerated stability testing and this was been noted as a potential aspect requiring further attention in case the company decides to extend the DP shelf-life beyond 6 months in the future.

8.11 The EWG heard the company had proposed an in-use shelf-life of 6 hours at room temp up to 30ºC and 48 hours in a refrigerator at 2-8ºC. The in-use shelf life was primarily supported by data from a microbial attribute study. The company have been advised by the MHRA to include an amendment to state that after first use the product should be used as soon as practically possible. The EWG heard the in-use shelf life should also be updated to clarify that the vaccine may be stored at 2-30ºC during the in-use period.

8.12 The EWG noted for an unpreserved product the best practise is to not go beyond a 6 hours in-use shelf life and that it is problematic to accurately record and track usage beyond 6 hours. The EWG noted that the 30ºC was not the room temperature value used in the stability studies, and 25ºC aligns with the Pfizer vaccine. The EWG noted the product should be used as soon as practically possible, to a maximum in-use shelf-life of 6 hours at 2-25ºC. The EWG noted that this in-use shelf-life corresponds to the most likely real-world in-use vaccination setting.

8.13 The EWG considered the [redacted] to be the most important measure of potency available, and therefore the [redacted] need to be introduced for the CMA. The EWG noted as a commitment to the conditional MA the DS and DP specifications (parameters and limits) must be appropriately configured in order to assure robust quality control.

9. Moderna Clinical Update

9.1 The EWG heard the vaccine (mRNA-1273) developed by Moderna consists of mRNA encapsulated in PEGylated lipid nanoparticles, with novel lipid excipients that are different to those in the Pfizer/BioNTech vaccine (BNT162b2). The EWG heard the vaccine includes a single mRNA sequence encoding the pre-fusion stabilised Spike (S) protein of the SARS-CoV-2 virus.

9.2 The company have applied for a conditional Marketing Authorisation for their vaccine. The proposed indication is active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by the SARS-CoV-2 virus in individuals18 years of age and older. The vaccine is given as two intramuscular doses of 100 micrograms with an interval of 1 month between each dose.

9.3 The EWG heard immunogenicity data are available from phase I and II studies, but the phase I study was sponsored by National Institutes of Health (NIH), and therefore reports on the validation and qualification of the methods are not available. The data was still considered to hold importance, due to the extended duration covered; three months post second dose. The EWG heard that a dose response was seen between 25 and 100 micrograms, and the proposed dose of 100 micrograms was based on these data.

9.4 The EWG heard there was a reduction in levels of binding and neutralising antibodies at 3 months post dose 2 in the older participants, but the levels still exceeded those of convalescent sera.

9.5 The EWG heard the cellular response data has been requested from the Company.

9.6 The EWG heard of a phase 2a, randomised, observer-blind, placebo-controlled safety and reactogenicity study of mRNA-1273 SARS-CoV-2 vaccine in healthy adults aged 18 years

and older, sponsored by the applicant. Two age group cohorts were planned: ≥18 to <55 years (n=300) and ≥55 years (n=300). The EWG heard participants were randomised to three dose groups (1:1:1): mRNA-1273 50 µg (n=200), mRNA-1273 100 µg (n=200) and 0.9% sodium chloride placebo (n=200), i.e. 100 participants were planned for each age/dose group. Vaccine or placebo was administered by 2 injections of 0.5 mL into the deltoid muscle 28 days apart. The EWG heard humoral data from the study are presently available. The EWG heard that there was not a large difference in neutralisation responses between the age cohorts, the EWG heard at the at the 100µg level, a large humoral response is seen two weeks after dose two, and the data to 1 month shows this response is sustained.

9.7 The EWG heard clinical efficacy data have been generated from a single pivotal Phase III study that was a standard design similar to those employed by other companies developing vaccines to protect against COVID-19. The study was only conducted in US and has enrolled ~30,000 participants aged 18 years and older with no known history of SARS-CoV-2 infection rather than COVID-19, the equivalent exclusion criterion employed by the Pfizer BioNTech study. Clarification has been sought to confirm if all-comers are included in the Moderna trial. The participants were randomised 1:1 to receive 100µg of mRNA-1273 vaccine or placebo, as 2 doses separated by 28 days. The EWG heard the trial did not include immunosuppressed patients and those receiving concomitant vaccination were excluded.

9.8 The EWG heard the applicant has been asked to clarify if history of allergy, anaphylaxis, or urticaria, is to any agent, or specific to the vaccine / any of the vaccine's ingredients. The EWG heard baseline medical history will also be requested to assess how many participants have a history of allergies, due to the contextual background of two anaphylaxis cases occurring shortly after vaccination with the lipid nanoparticle mRNA Pfizer/BioNTech vaccine.

9.9 The EWG heard more than 50% of participants randomised have completed 2-month post second dose follow-up; within this 25% are over the age of 65 and some patients over 75, the proportion of SARS-CoV-2 positive participants was similar to that seen in the Pfizer/BioNTech trial, but an increase to 5% is predicted to be confirmed by further results. The EWG heard that key patient groups were well represented in the study population.

9.10 The EWG heard that at the final analysis,196 cases of COVID-19 have been reported in the trial: 11 in the experimental vaccine group and 185 placebo group (out of ~14,000 total participants per group). The vaccine efficacy (VE) is calculated to be 94.1% similar to that seen in the interim analysis, and within the confidence limits and VE target set by WHO.

9.11 The EWG heard VE of 86.4% (4 experimental vaccine, 29 placebo) was reported from the subgroup of participants age 65 and above (3500 participants per group). The EWG heard VE was found to be similar in the age 75 and above (0 experimental vaccine, 7 placebo) (650 subjects per group)

9.12 The EWG heard in non-white participants the VE is also high at 97.5% (5000 subjects per group).

9.13 The EWG heard VE was also high in subjects at high risk of severe disease ~90%, the VE values are also included in the data package associated by each risk factor, individually. The EWG heard further VE data is requested following dose one.

9.14 The EWG heard all cases (30) of severe disease have occurred in the placebo arm, and the one death from COVID-19 has occurred in the placebo arm.

9.15 The EWG heard about the clinical safety data. EWG heard that the Phase I and II studies predominately enrolled healthy volunteers, whereas the pivotal phase III study enrolled a boarder population. The phase III study was identified as the most important source of reactogenicity data. The EWG heard two datasets were reviewed, one with a data-cut point of 11 November 2020, median follow-up of 49 days after the second dose, and 25 November 2020, median follow-up 63 days after the second dose. The company plan a database lock on 25 December 2020; and corresponding study report to be finalised by March 2021. The SmPC will currently reflect the 11 November cut off as the 25 November is still under review. If a conditional Marketing Authorisation is granted, the subsequent safety data from the cut off of 25 Nov and database lock on 25 Dec will be introduced by a variation procedure.

9.16 The EWG heard the Phase III recorded solicited adverse reactions (ARs) from 14,500 participants in each treatment group. The EWG heard there was a high incidence of local reactions: pain, swelling, erythema, and ipsilateral axillary lymphadenopathy. Zero grade 4 local reactions were reported and of the grade 3 local reactions, the most severe was pain at the injection site. The EWG heard the incidence of systemic reactions was also high. The systemic ARs included 14 grade 4 events of which 13 were cases of fever in the vaccine arm vs three cases in the placebo arm, and one was a case of nausea and vomiting in the vaccine arm vs none in the placebo arm.

9.17 The EWG heard most ARs were mild to moderate and occurred on day 1-2 of vaccination and lasted for a median of 2-3 days, with some reactions persisting beyond 7 days. ARs were more frequent after the second dose. The EWG heard overall, the safety profile of mRNA-1273 is consistent with that of BNT162b2, especially in terms of the pattern of ARs myalgia, pain (injection site), fever, chills, and fatigue.

9.18 The EWG heard that the incidence of serious adverse events (SAEs), fatalities and discontinuations due to AEs were similar in the vaccine arm and placebo arm. Analysis of related SAEs identified two cases of facial swelling in participants who had previously received cosmetic facial injections (case 1: botox, case 2: hyaluronic acid) are likely to be related to the vaccine, this information will be included in section 4.8 and 4.4 of the SmPC.

9.19 The EWG heard there are some adverse events of special interest (AESIs): Bell's palsy (3 active, 1 placebo, two of the cases in the vaccine arm had co-infections) and arthritis (11 active 3 placebo, two in the vaccine group considered possibly related), the AESIs could not be confirmed or excluded to be related to the vaccine with certainty and these should be reviewed closely in future safety updates. The EWG heard there was also a slight imbalance in cases of hypersensitivity reactions (1.5% vaccine 1.1% placebo) mainly explained by injection site urticaria and injection site erythema. The EWG heard that to date, there have been no reports of anaphylaxis which have occurred in the immediate aftermath of administration of the vaccine. There was one report of anaphylaxis 11 days after first dose considered not related. There were 233 cases of allergic or hypersensitivity reactions; of these cases seven patients were withdrawn from receiving the second dose. The clinical features of the seven cases were: swollen lips, or urticaria, or a rash at the injection site immediately after administration or one that persisted for a long duration. Of the 233 cases, 10 had events reported after the second dose but with no increase in severity of the reaction/s.

9.20 The EWG heard there were no specific safety concerns, including no evidence of enhanced COVID-19, and adverse events were well balanced between the active arm and placebo with a greater proportion of AEs occurring in the younger among the clinical trial population compared to the older sub-groups; reassuringly AEs were less frequent and less severe in seropositive individuals.

9.21 The EWG heard that overall, the safety profile has been adequately characterised and is found to be acceptable. A few areas of uncertainty such as long-term safety and safety in populations excluded from the studies need to be monitored in the ongoing studies and in the post-authorisation setting.

9.22 The EWG heard of the measures and content associated with the RMP.

9.23 The EWG noted slight differences in the product information wording regarding use in pregnancy between the COVID-19 vaccines developed by Moderna and Pfizer and advised that international regulatory consistency should be strived for across the vaccines. The EWG noted that pre-clinical data is yet to be reviewed by the EWG.

9.24 The EWG noted the impressive rates of VE, especially those seen in the elderly. In agreement with the assessment team, the EWG noted drug hypersensitivity exclusion criterion should be clarified. The EWG also noted that~17% of recipients in the phase II trial are recorded as having baseline drug hypersensitivity, further investigation of this group may give a better understanding of the propensity for the vaccine to induce allergic reactions in those with a history of medicine allergy.

9.25 The EWG noted VE was high including across subgroups such as those with risk factors for severe disease. The EWG noted there is a variety of measures of VE employed by the different Sponsors of vaccines, the EWG noted that the VE seen in the Phase III was substantiated by the use of a secondary analysis which utilised another measure of efficacy, in addition to the primary measure (hazard ratios). The EWG noted it would be useful to investigate the 11 cases of vaccine failure, as this could improve the characterisation and limitations of the protection acquired through use of the vaccine.

9.26 The EWG noted the clinical data supporting mRNA-1273 and that supporting BNT162b2 appears consistent across many aspects and drawing conclusions on comparability is feasible.

9.27 The EWG noted that Professor Tom Solomon should be contacted for his views on cases of facial palsy.

10. Future Steps / Any Other Business

10.1 None.

11. Date and time of next meeting

Thursday 24th December 2020 at 10:30

The Meeting started at 11:30 and ended at 15:30

Members are reminded that the content of papers and proceeding of the meetings are to be treated as 'Official – sensitive commercial'. Members are also reminded that, in accordance with the Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members must also declare any other matter which could reasonably be perceived as affecting their impartiality. Detailed guidance is set out in the Code of Practice

Annex I

Conflict of Interest Policy for CHM COVID-19 Vaccine Benefit Risk EWG

Chair and Members

- May not hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
- May not currently be or have previously been involved in the development of COVID-19 vaccines

Invited to all meetings, receives all papers and presentations and is permitted full participation in discussion, including drawing up conclusions and recommendations

Invited experts

- May hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
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Observers

Are invited to attend all meetings. Will not participate in drawing up conclusions and recommendations.

COMMISSION ON HUMAN MEDICINES (CHM)

COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Thursday 24th December 2020** at **10:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan
Professor N French
Professor D Goldblatt
Ms S Hunneyball
Professor K Hyrich
Sir M Jacobs
Professor H J Lachmann
Professor P J Lehner
Dr S Misbah
Professor S Price
Dr A Riordan
Professor C Robertson
Professor T Solomon
Dr R Thorpe
Mrs M Wang
Professor C Weir

Apologies

Professor P Shah

Members of the CTBV Expert Advisory Group

Professor B K Park
Professor M Turner

Members of the CPS Expert Advisory Group

Mr VI G Fenton-May
Mr R Lowe
Professor Y Perrie
Professor K M G Taylor (Chair of CPS)
Dr S Walsh

Observer

Professor S Ralston (Chair of CHM)

Secretariat

[redacted]

Professional Staff of MHRA Present

Principal Assessors[1]

Dr J Bonnerjea - LD
[redacted] - LD

Supporting specific items[1]

[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD

MHRA Observers

Ms R Arrundale - Policy
Dr S Atkinson - Dir
[redacted] - VRMM
[redacted] - LD
Dr S Branch - VRMM
Dr P Bryan - VRMM
[redacted] - MHRA-NIBSC
[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
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[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
Dr SP Lam - LD
Mr K McDonald - LD
Ms T Moore - IE&S
[redacted] - LD
[redacted] - Government Legal Team
[redacted] - MHRA-NIBSC
[redacted] - LD
Dr J Raine - MHRA CEO
Dr N Rose - MHRA-NIBSC
[redacted] - MHRA-NIBSC
[redacted] - LD
[redacted] - MHRA-NIBSC

[1] supporting specifc items [redacted] - LD

Key
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NIBSC = National Institute for Biological Standards & Control
VRMM = Vigilance & Risk Management of Medicines
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CPS = Chemistry, Pharmacy & Standards EAG
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Dir = Director of Operational Transformation
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[redacted]

22nd January 2021

1. Introduction and Announcement

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1.2 Conflict of Interest Policy (Annex I to the minutes)

The Chair reminded members and participants that, in accordance with the CHM Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members were also reminded to declare any other matter which could reasonably be perceived as affecting their impartiality.

1.3 The following members, invited experts and observers declared interests and other relevant interests for this meeting:

Professor Sir Munir Pirmohamed - NPNS AstraZeneca - Research grant to UOL to support PhD in drug interactions.
Other relevant interests in Pfizer, Janssen, Sanofi – Sir Munir is part of an EU-funded IMI consortium on gene therapy, and these companies are partners in the project. The University of Liverpool will get funding from the EU (but not from the partners), this IMI project commences on 3rd November 2020.
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Sir Munir is a member of the UK COVID Therapeutics Advisory Panel (UK-CTAP), which is advising the CMO on which compounds need to be prioritised for the RECOVERY+ trial (RECOVERY is funded via NIHR/DHSC)

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CPS

Mr V'lain Fenton-May – None

Mr Robert Lowe – None

Professor Yvonne Perrie - NPNS in Pfizer & AstraZeneca arising from a contract for a grant (March 2018), which includes contributions from these companies to the University of Strathclyde, Janssen in writing a grant for a PhD (now funded), GSK – arising from an EU grant to University of Strathclyde (Jan 2019-Dec 2019)

Professor Kevin Taylor – None

Dr Susannah Walsh – None

Observer – Chair of CHM

Professor Ralston – NPNS – Sanofi, Pfizer, Janssen, AstraZeneca & Other relevant interests in NHS Lothian and Oxford University. Professor Ralston has an honorary consultant contract with NHS Lothian but has not been involved in any trials relating to COVID-19. He also has agreed to be an external examiner for Oxford University clinical trials MSc; however, this has not yet started.

1.4 The Chair welcomed Invited Experts of the CTBV and CPS Expert Advisory Groups, and Observer, Professor Ralston, Chair of the Commission on Human Medicines (CHM).

1.5 Apologies were received from Professor Shah for this meeting.

2. AZD1222 Deployment Model (For information)

2.1 The EWG heard that NHS England have supplied a one slide framework which is similar to the Pfizer/BioNTech vaccine but without the cold storage temperature requirements. The models for all the home countries are ready but the slide decks have not yet been supplied. The EWG heard they are likely to be similar to that supplied for NHSE.

2.2 The EWG heard there is a roving model, so the vaccine can be supplied to nursing homes and private homes. The EWG agreed stability will be important with regard to the roving model.

3. AZD1222 Quality assessment - update

3.1 The EWG heard an update of the quality assessment and NIBSC testing of AZD1222.

3.2 The EWG heard that AZ have complied with the MHRA request to reduce the in-use shelf-life to 6 hours, and this has been reflected in the product information which is now complete from a quality point of view.

3.3 The EWG heard that all testing by NIBSC for batches AB0001, AB0002, AB0003 falls into specification and NIBSC are prepared to issue certificates. The EWG heard that NIBSC are content with the performance of the potency assay.

3.4 The EWG heard that each batch contains approximately 450,000 doses.

3.5 The EWG noted that in this case we are not checking against approved specifications, we are comparing against clinical trial batches. This is valid but must remember it is not usual procedure. The EWG agreed it is important to ensure continuity between clinical trial batches and commercial batches. The EWG noted that specifications will be tightened in time.

The EWG heard there are outstanding other concerns which the company should respond to by mid-January 2021. These responses are not required to reach a decision for this batch. The EWG heard there are no major concerns relating to this batch for a Regulation 174.

The EWG were reassured that the [redacted] have GMP certification in place and have sufficient experience in manufacturing vaccines/sterile products. They have a manufacturer import authorisation (MIA) in place which covers this process. The EWG heard that media fill data have been supplied to show the site can produce product aseptic product. No specific validation is required as it is fulfilled in the matrix.

The EWG heard a second batch for this vaccine will be submitted by Monday 28th December 2020. The EWG agreed they only need to see data on this batch if there are any concerns. The EWG endorsed the quality data presented and agreed with the Regulation 174 proposal with regard to the quality aspects.

4. Non-clinical update on AZD1222 – reproductive toxicity focus

4.1 The EWG heard an update with regard to the non-clinical aspects of AZD1222.

4.2 The EWG heard the preliminary reproductive toxicity study has been completed in mice and no major issues arose.

4.3 The EWG discussed the reproductive toxicity and the precautionary text that should go into the SmPC as the animal data is not yet complete. The EWG discussed whether the text should be aligned with that for the Pfizer/BioNTech vaccine.

4.4 The EWG agreed with the wording 'The full relevance of animal studies to human risk with vaccines for COVID-19 remains to be established.'

The EWG agreed that for pregnant women where the risk of not having the vaccine is greater than the risk of having it, a clinical decision will need to be made.

4.5 The EWG discussed how long the adenovirus/drug substance persists in the body and heard this will be addressed by the company in a kinetic study for up to 29 days. The expectation is distribution will be local and that, in principle, the exposure should decrease over time. The EWG endorsed the non-clinical data presented.

5. Verbal update on AZD1222 clinical data

5.1 The EWG heard an update on the clinical aspects of AZD1222. The EWG noted that comparisons of the low and standard doses are non-randomised comparisons and the apparent differences are likely to be because of confounding factors, such as dose interval. The confounding was generated by the low dose being given by error early in the trial, a

protocol amendment which affected the timing of the second dose, and older subjects being introduced late in the trial. The exploratory analyses suggesting improved efficacy with increasing dose interval are also subject to confounding but have support from immunogenicity data.

Overall, the EWG endorsed the efficacy assessment of MHRA.

5.2 The EWG discussed the lack of subjects aged 55 and over and aged 65 and over in the trial. The EWG heard that the best direct evidence of efficacy for those aged over 65 is looking at all cases following the first dose. The EWG noted that there is no hard data that immunogenicity drops in individuals at higher ages, over 55 years and over 65 years. The EWG discussed the risk of vaccine escape and vaccine evolution if the vaccine has low efficacy in vulnerable groups. The EWG also noted the risks of not vaccinating in these groups.

The EWG noted that more data in older populations is expected from future analyses. The EWG agreed that the trend suggests the vaccine would be efficacious in the older populations.

The EWG agreed the vaccine should be licensed in those over 18 years of age and discussed the inclusion of appropriate wording with regard to the lack of efficacy data in the older age groups.

The EWG noted there is precedent for giving licences to medicines with limited data in elderly patients, e.g. statins.

The EWG agreed the references to the low dose should not be included in the regulatory document (product information).

5.3 The EWG agreed that there is evidence that protection after a single dose is maintained up to 12 weeks after dosing. The EWG agreed that there is reasonable evidence that a longer dosing interval gives better protection after dose 2. The EWG agreed a dosing interval of 4-12 weeks with MHRA to decide the wording around this to indicate the likely better results with dose intervals 8-12 weeks before the EWG meeting on Tuesday 29th December 2020.

5.4 The EWG noted that public health need is part of the assessment in relation to a Regulation 174 procedure. The EWG heard that conditions of the approval can be changed and amended as more information becomes available.

5.5 The EWG heard that the committee agree the parameters for use of the vaccine and JCVI can only supply the vaccine in line with these parameters.

5.6 The EWG were in agreement with a broader indication with regard to age (individuals ≥18 years old).

The EWG agreed the term ‘demyelinating disorders’ in Section 4.4 of the product information, should be changed to ‘neuroinflammatory disorders’.

The EWG noted that AZD1222 contained the excipient polysorbate 80 which, rarely, has been associated with anaphylactic reactions. The EWG noted that polysorbate 80 is included in many biological products, including other vaccines. In particular, Fluad contains more than double the amount of polysorbate than this vaccine and Fluad is indicated in the over 65-year age group. The EWG agreed that the standard contraindication and warning in sections 4.3 and 4.4 regarding hypersensitivity/anaphylaxis in the product information was sufficient.

The EWG agreed that, currently there was insufficient evidence to recommend prophylactic use of paracetamol. However, the inclusion of wording in the product information regarding symptomatic use of paracetamol was supported.

The EWG discussed the potential risk of neuroinflammatory disorders, including the small number of cases observed in the clinical trials. It was agreed that a causal relationship has not been established between vaccination and these cases.

The EWG discussed vaccine associated enhanced disease and noted that the period of follow-up is too short to determine the risk, however, it was noted that VED is a theoretical risk which has not yet been observed in humans.

6. Dose interval discussion for BNT162b2 – Q from NHS/DHSC

6.1 The EWG discussed a slide presentation of a statistical analysis performed on data from the initial Pfizer submission in order to evaluate the efficacy provided by the first dose. The EWG agreed that the vaccine efficacy (VE) reported by Pfizer of 52.4% (95% Confidence Interval of 29.5 to 68.4) is likely to be an underestimate since little protection is expected within 14 days following the first dose. The EWG agreed that calculation of the efficacy of the first dose discounting COVID-19 cases in the first 14 days would be more accurate.

6.2 The EWG heard the Pfizer analysis of COVID-19 cases taken from the second dose to 7 days after the second dose is expected to be a better estimate of the efficacy of the first dose. This analysis estimated vaccine efficacy (VE) as 90.5% (CI 61.0, 98.9) based on 2 COVID-19 cases in the vaccine arm of the study compared to 21 COVID-19 cases in the placebo arm.

6.3 The EWG also discussed the results of the MHRA analysis of VE taken from interim raw data. This analysis found a VE of 91% (CI 63, 98) from day 14 to before dose 2 was given, based on 2 COVID-19 cases on vaccine compared to 23 COVID-19 cases on placebo. From Day 21 to before dose 2 was given there were no COVID-19 cases on vaccine compared with 8 COVID-19 cases in the placebo group. The EWG agreed that there was evidence that protection was strong at 21 days after dose 1 and was not declining at that point.

6.4 The EWG also reviewed a Tabled Paper submitted by PHE on an independent analysis of the full Pfizer data. This analysis found a VE of 89% (CI 52, 97) from day 15 to day 21 after the first dose based on 2 COVID-19 cases on vaccine compared to 18 COVID-19 cases on placebo. The VE increased to 91% (CI 74, 97) from day 15 to day 28 based on 4 COVID-19 cases on vaccine compared to 42 COVID-19 cases on placebo. The EWG agreed the data suggest there is no decline in the level of protection at 28 days and that there is no biologically plausible reason to expect that it would decline rapidly. Immunological principles and experience with other types of vaccines suggest that immunogenicity may be improved with more prolonged intervals between doses in the primary immunisation series.

6.5 The EWG were reminded of the condition of the authorisation that it must be ensured that two doses are given to each patient. The EWG agreed that immunologically there is no concern if the second dose of vaccine is from a different batch than the first.

6.6 The EWG considered the risks of a partially immunised community if the dosing interval is too long and individuals only take one dose.

6.7 The EWG heard that the ever-changing public health need can be taken into consideration when making a decision. The EWG agreed that the dosing recommendation should be ‘at

least 21 days apart' without specifying an upper bound. The EWG noted this is also in line with the EMA recommendation.

7. Moderna non-clinical assessment

7.1 The EWG heard an update on the non-clinical assessment of the Moderna vaccine. The EWG heard that there are no major objections.

7.2 The EWG agreed the company should provide more information on the pregnancy rates observed.

7.3 The EWG discussed the use of an alternative mRNA to that in mRNA-1273 in the tissue distribution study.

The study was conducted using mRNA-1647, and not mRNA-1273, the clinical product. mRNA-1647 is a novel vaccine that contains 6 distinct mRNA sequences. Since mRNAs that are within an LNP of the same composition (i.e. mRNA-1273 and mRNA-1647) are expected to distribute similarly, this approach is acceptable with the proviso that information on particle size and other factors that can influence the distribution of the LNP e.g. surface charge is provided to demonstrate that the two mRNA constructs are sufficiently similar to enable "read across" from MRNA-1647 to mRNA-1273.

Further information on their disposition, distribution, persistence and fate on the two novel lipid nanoparticles (SM-102 and PEG2000-DMG) should be provided since they have not been used previously in a pharmaceutical product.

The EWG heard that this vaccine has now been approved by the FDA.

7.4 The EWG endorsed the non-clinical questions posed to the company. The EWG agreed the overall package appears to be more extensive than the Pfizer one.

7.5 The EWG agreed that although there are some concerns, there are no major objections.

8. <u>Future Steps / Any Other Business</u>

8.1 None.

9. <u>Date and time of next meeting</u>

Tuesday 29th December 2020 at 10:30

The Meeting started at 10:32 and ended at 14:41

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Annex I

Conflict of Interest Policy for CHM COVID-19 Vaccine Benefit Risk EWG

Chair and Members

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COMMISSION ON HUMAN MEDICINES (CHM)

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Supporting specific items[1]

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MHRA Observers

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Mr V'lain Fenton-May – None

Mr Robert Lowe – None

Professor Yvonne Perrie - NPNS in Pfizer & AstraZeneca arising from a contract for a grant (March 2018), which includes contributions from these companies to the University of Strathclyde, Janssen in writing a grant for a PhD (now funded), GSK – arising from an EU grant to University of Strathclyde (Jan 2019-Dec 2019)

Professor Kevin Taylor – None

Dr Susannah Walsh – None

Observer – Chair of CHM

Professor Ralston – NPNS – Sanofi, Pfizer, Janssen, AstraZeneca & Other relevant interests in NHS Lothian and Oxford University. Professor Ralston has an honorary consultant contract with NHS Lothian but has not been involved in any trials relating to COVID-19. He also has agreed to be an external examiner for Oxford University clinical trials MSc; however, this has not yet started.

1.4 The Chair welcomed Invited Experts of the CTBV and CPS Expert Advisory Groups, and Observer, Professor Ralston, Chair of the Commission on Human Medicines (CHM)

1.5 Apologies were received from Professor Shah for this meeting.

2. AZ: Summary of safety review & AEs

2.1 The EWG heard a summary of the safety review and adverse events for AZD1222.

2.2 The EWG agreed, based on the data currently available, not to include hypersensitivity as an adverse drug reaction (ADR). The EWG agreed that those who experience hypersensitivity following a first dose of vaccine are contraindicated for the second dose as detailed in Section 4.3 of the SmPC. The EWG noted that systemic urticaria is considered a hypersensitivity reaction. The group agreed this should be made clear to those healthcare practitioners administering the vaccine via information in the green book. The EWG agreed that MHRA can raise with PHE the concern that systemic urticaria may not be understood to be a hypersensitivity reaction.

2.3 The EWG agreed that no specific precautions are required for the administration of the vaccine in individuals that have a clinical history of COVID-19 (+/- PCR confirmation) or in

those with no history of COVID-19 illness but a positive COVID-19 antibody test.. This is in line with the advice for the Pfizer/BioNTech vaccine.

3. AZ: Information for Healthcare Professionals and for Vaccine Recipient documents

3.1 The EWG heard a presentation on the Information for Healthcare Professionals for Vaccine Recipient documents.

3.2 The EWG discussed the statement that increasing the dosing interval increases efficacy of the vaccine in Section 5.1 of the SmPC. The EWG agreed to amend the wording to reflect the uncertainty around the exploratory analyses.

The EWG discussed how to encourage the timing of the second dose to 8 weeks rather than 4 weeks. The EWG considered whether to acknowledge the lower amount of data seen at the lower dosing interval (4 weeks).

The EWG discussed whether to include a general statement that protection following vaccine administration is not immediate.

The EWG agreed to delete the sentence 'In this subpopulation, efficacy has been inferred from immunogenicity data, see below.' from Section 5.1 of the SmPC.

The EWG noted the wording of the dosing interval needs to be consistent between the SmPC and the PIL. It was also questioned whether it should be mentioned in the product information that this information will be updated as more data becomes available.

The EWG heard that the QR code links to the equivalent of the SmPC and PIL and the adverse event reporting form.

3.3 The EWG noted the lack of information about the 7-day gap between COVID-19 vaccine and the flu vaccine in Section 2 of the PIL.

The EWG considered whether information about colds, i.e. that it is still fine to take the vaccine if you have a cold, should be included in the PIL. This had already been requested.

3.4 The EWG agreed that the proposed wording regarding neuroinflammatory disorders in section 4.4 of the HCP information should be moved to section 4.8. The EWG discussed how to include information about neuroinflammatory disorders in the PIL in lay terms. The EWG agreed to review the wording off-line.

3.5 The EWG agreed that the pregnancy/fertility/reproductive wording in the product information reflects the current non-clinical data.

4. AZ: Risk Management Plan

4.1 The EWG heard an update on the Risk Management Plan.

4.2 The EWG agreed to ask the company how they propose to evaluate patients taking immunosuppressant medications and individuals with primary immunodeficiency to demonstrate vaccine safety in this population. The EWG also noted patients with conditions such as inflammatory bowel disease and inflammatory skin disease would fall into these categories.

4.3 The EWG noted that individuals are given a vaccine card which holds the batch number of each vaccine and from this it will be possible to determine the immunogenicity of each batch an individual has taken.

4.4 The EWG discussed assessment of immunogenicity and how it varies from batch to batch and how PHE are assessing it, if they are. The EWG heard that MHRA have communicated with PHE with regard to the Pfizer/BioNTech vaccine and are awaiting a response. The EWG suggested this approach also be taken with the AZ vaccine.

The EWG agreed to recommend to CHM approval for use of the AZ vaccine under a Regulation 174.

5. Future Steps / Any Other Business

5.1 None.

6. Date and time of next meeting

Thursday 31st December 2020 at 10:30

The Meeting started at 09:31 and ended at 10:36

Members are reminded that the content of papers and proceeding of the meetings are to be treated as 'Official – sensitive commercial'. Members are also reminded that, in accordance with the Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members must also declare any other matter which could reasonably be perceived as affecting their impartiality. Detailed guidance is set out in the Code of Practice

Annex I

Conflict of Interest Policy for CHM COVID-19 Vaccine Benefit Risk EWG

Chair and Members

- May not hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
- May not currently be or have previously been involved in the development of COVID-19 vaccines

Invited to all meetings, receives all papers and presentations and is permitted full participation in discussion, including drawing up conclusions and recommendations

Invited experts

- May hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
- May currently be or have previously been involved in the development of COVID-19 vaccines

May be invited to all relevant meetings, receives all papers and presentations and is permitted to participate in discussions when invited by the Chair. Does not contribute to conclusions and recommendations

Observers

Are invited to attend all meetings. Will not participate in drawing up conclusions and recommendations.

COMMISSION ON HUMAN MEDICINES (CHM)

COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Thursday 31st December 2020** at **10:00** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer[1]
Professor G Dougan
Professor N French
Professor D Goldblatt
Ms S Hunneyball
Professor K Hyrich
Sir M Jacobs
Professor H J Lachmann
Professor P J Lehner
Dr S Misbah
Professor S Price
Dr A Riordan
Professor C Robertson
Dr R Thorpe
Mrs M Wang
Professor C Weir

Apologies

Professor P Shah
Professor T Solomon

Members of the CTBV Expert Advisory Group

Professor B K Park
Professor M Turner

Members of the CPS Expert Advisory Group

Mr VI G Fenton-May[1]
Mr R Lowe
Professor Y Perrie
Professor K M G Taylor (Chair of CPS)
Dr S Walsh

Observer

Professor S Ralston (Chair of CHM)

Secretariat

[redacted]

Professional Staff of MHRA Present

Principal Assessors[2]

Dr J Bonnerjea - LD
[redacted] - LD

Presenters supporting specific items

[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - Government Legal Team
Dr N Rose - MHRA-NIBSC
[redacted] - LD

MHRA Observers

Dr S Atkinson - Directorate
Dr M Bailey - MHRA-NIBSC
Dr S Branch - VRMM
[redacted] - MHRA-NIBSC
[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
Dr SP Lam - LD
Mr K McDonald - LD
[redacted] - MHRA Policy
Ms T Moore - IE&S
[redacted] - LD
[redacted] - LD
[redacted] - MHRA-NIBSC
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - VRMM
[redacted] - LD

[1] joined during item 2
[2] supporting specifc items

Key
LD = Licensing Division
NIBSC = National Institute for Biological Standards & Control
VRMM = Vigilance & Risk Management of Medicines
CTBV = Clinical Trials, Biologicals & Vaccines EAG
CPS = Chemistry, Pharmacy & Standards EAG
CHM = Commission on Human Medicines
Directorate = Director of Operational Transformation
IE&S = Inspection, Enforcement & Standards

[redacted]

19th July 2021

1. Introduction and Announcement

1.1 The Chair reminded Members that the content of papers and proceeding of the meeting are strictly confidential and should be treated as 'Official – sensitive commercial' and should not be disclosed. There is no consent for members / participants to record the meeting, take screenshots or photographs of presentations. The meeting was recorded by the MHRA Secretariat for minute taking purposes only. The Chair & Members including all participants gave full consent to the recording prior to the start of the meeting.

1.2 Conflict of Interest Policy (Annex I to the minutes)

The Chair reminded members and participants that, in accordance with the CHM Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members were also reminded to declare any other matter which could reasonably be perceived as affecting their impartiality.

1.3 The following members, invited experts and observers declared interests and other relevant interests for this meeting:

Professor Sir Munir Pirmohamed - NPNS AstraZeneca - Research grant to UOL to support PhD in drug interactions.
Other relevant interests in Pfizer, Janssen, Sanofi – Sir Munir is part of an EU-funded IMI consortium on gene therapy, and these companies are partners in the project. The University of Liverpool will get funding from the EU (but not from the partners), this IMI project commences on 3rd November 2020.
AGILE – this is a Liverpool early phase trial platform (between University of Liverpool and Liverpool School of Tropical Medicine). It is funded by the Wellcome Trust and UKRI/DHSC/NIHR. It is NOT evaluating vaccines, but only drugs to treat COVID-19. Sir Munir is not on the trial management group, and he is not directly involved in choosing the compounds for the study. Sir Munir has no involvement with any of the developers of the compounds to be studied (academic or industrial).
Sir Munir is a member of the UK COVID Therapeutics Advisory Panel (UK-CTAP), which is advising the CMO on which compounds need to be prioritised for the RECOVERY+ trial (RECOVERY is funded via NIHR/DHSC).

Professor Breuer – NPNS – Professor Breuer is joining the data safety monitoring committee, DSMB, a study looking at combining vaccines being run by Matthew Snape in Oxford. There does not appear to be any involvement of the vaccine manufacturers and is for already licensed vaccines. The study is funded by the NIHR (Dec 2020).

Professor French - Other relevant interest **-** Provides clinical care when in covering the acute medical wards where patients with COVID-19 are cared. NPNS in GSK - In September 2020 a sub-contract was signed with the Liverpool School of Tropical Medicine to undertake work evaluating the safety and effectiveness of GSK's RTS's malaria vaccine in Malawi. GSK are the primary funders to the LSTM.

Ms Hunneyball - Other relevant interest – writes articles published in the Chemist and Druggist magazine, a trade magazine for pharmacists, but receives no payment for these articles. The information referred to in the articles is in the public domain. Ms Hunneyball makes it clear that these are her personal views and reflections and reference all sources of information used.

Professor Hyrich – NPNS - Professor Hyrich was co-I on an investigator-initiated research grant exploring predictors of outcome in rheumatoid arthritis. NPNS Pfizer- she is a Co-I on a grant exploring adherence to JAK inhibitors in rheumatoid arthritis. NPNS in Abbvie, Professor Hyrich gave some lectures at an education conference on effectiveness of treatment for rheumatoid arthritis.

Sir Michael Jacobs - Other relevant interest - As part of the academic role at the Liverpool School of Tropical Medicine, Sir Michael is a member of the Study Management Team and antiviral drug prioritisation group for the AGILE proof of concept (phase I/II) platform study. Sir Michael is also part of the team that submits new antiviral compounds against SARS-CoV2 for consideration by NIHR for testing on this platform. No commercial or financial interest in the trial or any of the compounds, or any pharmaceutical or biotechnology company.

Professor Lachmann – Other relevant interest as a volunteer participant in the Oxford vaccine study and no other involvement in the study.

Professor Lehner - Other relevant interest – Professor Lehner previously held a DPAC (Discovery Partnership with Academia) agreement with GSK, but this has been completed. Professor Lehner's participation in his local hospital D and T governance committee deliberations would form the normal activity and professional responsibility in his post and does not interfere with the EWG considerations (Sept 2020).

Dr Misbah - NPNS - Holds honorary Senior Lectureship with University of Oxford & Oxford University Hospitals NHS Foundation Trust.

Professor Price - NPNS in GSK and AstraZeneca – which relates to donations provided by both companies to the British Toxicology Society (BTS) to support their Annual Congress and Education and Training of which Professor Price is currently President of the Society (2020-2022).

Dr Riordan - Other relevant interests - Participant in Oxford University's ChAdOx1 nCoV-19 clinical trial –received immunisation 27/8/2020. NPNS - Postgraduate External Examiner for Oxford University (Postgraduate Diploma in Paediatric Infectious Diseases)

Professor Weir - Other relevant interest arising from link to the Lothian NHS Board. NHS Lothian R&D has partially funded Professor Weir's post at University of Edinburgh, since 2010, so that he could provide methodological advice on health services research studies and clinical trials.

CTBV

Professor Park - NPNS in GSK Research & Development Ltd. and in Janssen as I received a research grant in the past two years. The grant has been handed over to a colleague in 2020 and the grant is due to finish in 2020. Professor Park received no direct payment. In addition, Professor Park have two active IMI grants for Transbioline and Quantitative Systems Toxicology, he is the PI on the TransBioline grant for the University of Liverpool. Both grants are paid directly to the University of Liverpool.

Professor Turner – NPNS interest. Professor Turner is a Non Executive Director (non-remunerated) on the Board of the Cell and Gene Therapy Catapult (CGT).
CGT have been tasked by UK Government with re-purposing a factory in Braintree to manufacture either a vaccine or a therapeutic mAb. No decision has been made as to whether or what product CGT Braintree may be asked to manufacture and that decision

will be made by UK Government. Professor Turner does not believe that CGT Board will have any material input into the decision as to what product may be manufactured.

CPS

Mr V'lain Fenton-May – None

Mr Robert Lowe – None

Professor Yvonne Perrie - NPNS in Pfizer & AstraZeneca arising from a contract for a grant (March 2018), which includes contributions from these companies to the University of Strathclyde, Janssen in writing a grant for a PhD (now funded), GSK – arising from an EU grant to University of Strathclyde (Jan 2019-Dec 2019)

Professor Kevin Taylor – None

Dr Susannah Walsh – None

Observer – Chair of CHM

Professor Ralston – NPNS – Sanofi, Pfizer, Janssen, AstraZeneca & Other relevant interests in NHS Lothian and Oxford University. Professor Ralston has an honorary consultant contract with NHS Lothian but has not been involved in any trials relating to COVID-19. He also has agreed to be an external examiner for Oxford University clinical trials MSc; however, this has not yet started.

1.4 The Chair welcomed:

Invited Experts of the CTBV and CPS Expert Advisory Groups, and Observer, Professor Ralston, Chair of the Commission on Human Medicines (CHM)

1.5 Apologies were received from Professors Shah and Solomon for this meeting.

1.6 The EWG received the following message of thanks from [redacted], [redacted]

"Please pass on my thanks on behalf of the MHRA Board to all of the members of the Expert Committees, CHM and the Agency who have been involved in the decisions to approve two of the major, international COVID-19 vaccines before any other regulator in the world. I recognise that this has involved many hours of extra work, usually at short notice, right up to and over the Christmas period, so everyone should be rightly proud of their contribution to protecting public health and saving many lives as a result of this incredible achievement. Of course, the work does not stop here with the continuing demands on batch release, safety vigilance and security of the supply chain, as well as further analysis of new data on these and other new vaccines as they become available. However, this does feel like the "end of the beginning" as we work towards our common goal of beating this virus and that does feel like a good way to bring 2020 to a close and look forward to a brighter New Year".

2. Moderna Vaccine:

2.1 Legal aspects of Moderna Vaccine (mRNA-1273) decision

2.1.1 The EWG heard their discussion needs to cover a broader scope than was initially planned due to uncertainties over the particular batch to be supplied to the UK (an alternative batch may be available to that considered previously). The EWG were asked to shift their focus from a batch specific proposal to a conditional MA approval and the EWG was asked to consider the additional information required to ascertain if the vaccine meets the requirements for a Regulation 174 authorisation. The EWG were also asked to give specific consideration to the dosing interval.

2.2 Batch testing

2.2.1 The EWG heard the National Institute for Biological Standards and Control (NIBSC) very recently received the materials required to commence laboratory testing. Testing protocols at NIBSC are in development and some documentation is outstanding. The EWG heard that the novel tests will take more time to set-up. In the interim, to address independent control of batch/s being considered for temporary authorisation under Regulation 174 of the HMRs, the Austrian Official Medicines Control Laboratory (OMCL) has been contacted to discuss data sharing and/or testing on behalf of NIBSC.

2.3 Quality

2.3.1 The mRNA-1273 product development and initial production has been performed in the US, and manufacturing activities were subsequently expanded to sites in the EU. US sites will supply the US regions and countries proximal to the US; in a similar format, the EU sites will supply the EU/EEA and Great Britain. Data from a single commercial batch produced within the EU is available (drug substance (DS) site: [redacted]; drug product (DP) site: [redacted]

2.3.2 The EWG heard about the manufacturing process of the mRNA active substance and the lipid elements of the product. The dossier is structured with three drug substance sections (DS 1: mRNA, DS 2: SM-102 LNP, DS 3: mRNA-1273 LNP) and one drug product section (the lipid-nanoparticle (LNP) formulated mRNA-1273 vaccine filled into vials). The product includes one active substance i.e., the mRNA, although the Applicant had presented three drug substance sections; two of these should have been included in the drug product section and will need to be corrected when seeking a full marketing authorisation.

2.3.3 The EWG heard details of the manufacture of mRNA active substance, with the purified mRNA element of the drug substance stored in polyethylene storage bags at -15°C to -25°C (or forward processed without freezing), although there is currently limited data to support the proposed shelf-life.

2.3.4 The EWG heard about manufacture of the lipid nanoparticles (SM-102 LNP) including [redacted] The LNP dispersion is stored at -[redacted] C to [redacted]°C, supported by real-time stability data for 6 months for one batch.

2.3.5 The novel excipients (i.e. SM-102 and PEG 2000-DMG) used for the manufacture of the LNP without mRNA are different to those included in the other mRNA vaccine considered by the Commission. In the SM-102 LNP, the proportion of PEG 2000-DMG to SM-102 is relatively low.

2.3.6 The EWG heard mRNA-1273 LNP is stored in a buffer solution and long-term stability data ([redacted]°C to [redacted]°C) for one developmental batch (4 months) and one Phase I//II clinical batch (3 months) has been provided. Stability data was reassuring when stored at [redacted]°C to [redacted]°C.

2.3.7 There are some amendments required to the specifications for both the SM 102 LNP and mRNA-1273 LNP [redacted]

2.3.8 The EWG heard that the manufacture of drug product is [redacted] in a multiple dose vial (10 doses per vial), without preservative. Only one commercial batch at 60,000 – 70,000 vial scale has been produced in the EU [redacted] The EWG heard the batch manufactured in the EU was produced too recently to generate any stability data, and therefore US batch stability data is being used to support the shelf life claim. The applicant proposed a shelf life of 6 months at [redacted]°C, 30 days at [redacted]°C, an in-use (unopened product) time of up to 12 hours at [redacted]5°C. There were only limited stability data to date to support this.

2.3.9 The EWG heard the key outstanding issues from cycle 4 of the rolling review, after responses were received on 30-12-2020. The applicant has committed to provide DS and DP process validation data from the EU sites by 31 March 2021. Full comparability data for current commercial batches from EU sites to US material used in clinical trials is expected by 31 March 2021; these data will be required in order to confirm a full demonstration of comparability throughout product development. The EWG heard that the aseptic fill summary report has been provided and was deemed acceptable.

2.3.10 The EWG heard DS and DP release and shelf-life specification acceptance criteria are wider than justified by the batch data ([redacted]); only one batch is manufactured at the EU sites, reliance is placed on individual batch data from the EU sites. This will need to be clear in the conditions of the temporary authorisation under Regulation 174 of the HMR 2012. DS specifications are to be finalised, with more commercial scale experience, by 30 June 2021. [redacted]. The EWG heard that in relation to the PEG2000-DMG manufacturing process, a tightening of the specifications for both novel excipients have been requested.

2.3.11 [redacted]

2.3.12 [redacted]

[redacted]

2.3.13 [redacted]

2.3.14 [redacted].

2.3.15 The EWG discussed the bacterial challenge filter data and noted that the product is stated to be bactericidal without dilution. The MHRA informed the EWG that the reports provided indicate that proper controls for testing sterility of a bactericidal product are in place.

2.3.16 The applicant proposed to have different shelf-life assignments dependent on purity of drug product at release, but it is not acceptable for shelf life to be applied to batches individually, based on a calculated 50% purity at the point of vaccination.

2.3.17 The EWG heard that the assessment team consider the applicant's proposal for storage at [redacted]°C for up to 30 days at point-of-care site as a point of concern. The EWG considered the practical benefits for deployment, with storage at [redacted]°C after thawing the vials, to outweigh the risk of mRNA degradation. The MHRA also mentioned the spiking studies demonstrated that E. coli growth begins to increase at 12 hours, therefore a 12-hour shelf life once the vial is punctured is not appropriate. The EWG noted that an in-use shelf life of 6 hours after the vial has been punctured would also be consistent with the other COVID-19 vaccines. For an unpreserved product, the shelf life of the unopened vial (after removal from refrigerated conditions of 12 hours) could present a risk in terms of errors when understanding the different shelf lives, e.g. in terms of an unopened product being returned to refrigerated conditions. The EWG noted the odds of this occurring could be minimised by informative and clear labelling. The EWG also considered the benefits of a 12-hour unopened shelf life, in terms of distribution from central locations to remote areas. The MHRA informed the EWG that the current intention is to transport the product frozen. Once thawed the product could be more vulnerable to stress and shaking forces; further stability data has been requested to verify this. The request for stability data covers all modes of transport currently included in the deployment models, including data at [redacted]°C. The MHRA

added that for the product to be transported at room temperature, additional supportive data would need to be provided.

2.3.18 The EWG heard the GMP certification that was outstanding has now been provided.

2.3.19 The EWG noted issues suggest authorisation under Regulation 174 should be considered, rather than a Marketing Authorisation.

2.3.20 The EWG reached a consensus that issues were outstanding that require further data or further justification before a batch-specific release could be authorised; once these issues have been satisfactorily resolved a Regulation 174 authorisation could be considered.

2.4 Clinical

2.4.1 The EWG heard following vaccination with the first dose, VE is low for ~14 days, but after this period VE increases to ~94% (35 vs 2 cases) prior to the second dose. The regulation 174 letter requested specific guidance on whether, and to what extent, an extended interval between first and second doses can be allowed, giving operational flexibility and potentially allowing increased prioritisation of the first dose for as many people as possible. The EWG heard the primary analysis population (per protocol set) received the second dose 3-6 weeks after the first dose and there was very limited efficacy data for an interval greater than 6 weeks (~0.6% of participants). The majority of participants in the Pfizer/BioNTech (BNT162b2) trial received a 2nd dose close to or on day 21, though the range was also 3-6 weeks; whereas in the phase III trial of mRNA-1273 most participants received a second dose on day 29. In accordance with the product information for Pfizer/BioNTech (BNT162b2) the second dose is to be given at least 21 days after first dose. The product information for mRNA-1273 presently states the second dose is to be given one month after first dose, the EWG was asked to consider if this should be changed to, at least one month after first dose, or more precisely at least 28 days after first dose.

2.4.2 The Chair mentioned the indication and whether an interval at least 28 days apart was appropriate for mRNA 1273.

2.4.3 The EWG noted the data on Moderna vaccine support a dosing interval of at least 28 days and was reassured that immunologically it would be very unlikely that efficacy would drop substantially if the interval was to extend beyond 28 days.

2.4.4 The EWG asked for a breakdown of cases of COVID-19 occurring between the second dose and 14 days after the second dose to identify if the cases are occurring within the first 7 days, where protection could be attributed to the first dose, or the next 7 days, where the second dose could also be contributing to the efficacy seen. The MHRA informed the EWG that data breakdown by 7 days post second dose has been requested, though it should be noted that during the whole 14 day period cases were only seen on the placebo arm.

2.4.5 The EWG noted there is a disconnect between the immunogenicity data and the vaccine efficacy data. The increase in the neutralising antibody levels just prior to the second dose is ~5 fold, increasing shortly after the second dose to ~38 fold (spike-IgG binding). However, the correlates of protection are yet to be determined; the ~5 fold increase despite appearing comparatively low, may still be sufficient to drive the vaccine efficacy seen in post first dose data.

2.4.6 The Chair noted that post-vaccination effectiveness studies with 3-month interval data including those from academic groups e.g. SIREN, should be made available to the EWG. Once completed, the findings from these studies may help to inform the optimum interval

between doses for the other COVID-19 vaccines and to confirm if longer intervals provide sufficient vaccine efficacy in the real-world setting.

2.4.7 The EWG heard anaphylaxis has been upgraded from an important potential risk to an important identified risk due to a post-marketing case report of anaphylaxis. The risk minimisation measures include warnings about anaphylaxis; pharmacovigilance includes expedited reporting and follow-up of any cases. If the mRNA 1273 vaccine is authorised MHRA will be closely monitoring the post marketing data for anaphylaxis and hypersensitivity reactions in the same manner undertaken for the Pfizer/BioNTech vaccine.

2.4.8 The EWG heard use in patients with immunosuppression (missing information in the RMP) will be included in the long-term effectiveness study which will rely on a database from Kaiser Permanente (Southern California), but the study protocol is yet to be received. The EWG heard the other RMP issues are minor and do not preclude an authorisation.

2.4.9 The EWG noted it would be more helpful to a vaccinator to use product information wording on anaphylaxis used in Pfizer/BioNTech product information as it is more descriptive of the clinical features of anaphylaxis, hypersensitivity reactions and generalised urticaria. The CDC have unified advice on both mRNA vaccines (Pfizer and Moderna), therefore MHRA could also consider a common set of guidance.

2.4.10 The EWG noted the product information currently includes a statement to the effect of 'mRNA-1273 is not recommended for use for pregnant or breastfeeding women'. An amendment is required to reflect limited experience with use of the vaccine in pregnant women, and a recommendation that the vaccine is only used in this group following a benefit risk discussion with the potential recipient. The EWG advised inclusion of the following statement 'The full relevance of animal studies to human risk with vaccines for COVID-19 remains to be established.' in section 5.3. The EWG also noted that the pregnancy registry will be an important form of post-marketing surveillance.

2.4.11 The imbalance in cases of facial palsy in the trial was noted and, therefore, facial palsy and how it presents, should be included in the product information on a precautionary basis notwithstanding the limited number of events. The EWG noted the importance of consistent use of lay language where applicable, across vaccines, and also that the symptoms are often more important to the lay reader who might not infer anything from the name of a medical condition alone. The MHRA informed the EWG that certain sections of the product information could be aligned with the text used for Pfizer/BioNTech.

2.4.12 The Chair noted the clinical issues are resolvable, but the quality issues require further data.

2.4.13 The EWG asked about when and how further data will be submitted to the UK post Brexit. The MHRA mentioned, when the company submit information to the EMA, they have been asked to provide the same information to the MHRA.

2.5 Viral Variants and the Moderna Vaccine

2.5.1 The EWG heard Moderna have provided to the MHRA a document that details their plans to evaluate the vaccine's efficacy against the SARS-CoV-2 viral variant first identified in Kent. The variant has 17 mutations in the viral genome, 8 of which encode parts of the spike protein. Moderna have tested animal sera and are intending to extend testing to sera from vaccinated human subjects, using functional testing in a [redacted] assay using a pseudovirus, developed to be a copy of the Kent viral variant. Moderna have already undertaken testing of mice and monkey sera with a number of variants that are closely homologous / share some of the same mutations as the Kent variant: these results suggest

that neutralising responses are similar to those produced when sera were challenged with the wildtype strain.

2.5.2 The EWG noted the laboratory data were encouraging, and noted that one of the variants tested, the mink sequence, includes a deletion which causes an S gene drop-out. The 501 mutation is of interest as it is responsible for increased virus-host receptor binding; it is beneficial that this sequence is included in the testing programme.

2.5.3 The EWG heard that PHE-Porton and NIBSC are coordinating to test new variants. The EWG noted the Genotype-Phenotype correlation aspect of COG-UK work could also serve as a useful resource.

2.5.4 The EWG noted that the multiple lineages of SARS-CoV-2 and continued testing of variants as they are identified, is key piece of work to be advanced forward. The EWG asked about the process to handle changes to the authorisations if the vaccines need to be modified in response to variants. The Chair informed the panel that this issue is due to be revisited.

3. Any Other Business

3.1 Oxford/AstraZeneca AZD1222 vaccine human leukocyte antigen (HLA) sensitisation to Human embryonic kidney 293 cells (HEK 293)

3.1.1 The EWG heard that NHS-BT have asked the MHRA if the AZD1222 vaccine could carry a risk of HLA sensitisation, and if there could be clinical consequences for patients on the transplant waiting list if they receive the vaccine. AZD1222 is developed using the HEK 293 cell line. The example of some clinical trial recipients of a cytomegalovirus (CMV) vaccine sensitised to HLA proteins mapped back to the HEK cell line was noted, although the data are limited. The EWG heard this is currently only a theoretical consideration for AZD1222, and any root-cause analysis has not yet been made available to MHRA. The letter asked the MHRA to confirm the absence of residual traces of HEK 293 cell components. As with any biological product derived from a cell line, levels of host cell proteins (HCPs) are well controlled (in each batch of AZD1222) but are not absent. AstraZeneca were provided with a copy of the NHS-BT letter and have informed the MHRA of their intention to urgently liaise with the medical director for the CMV vaccine trial to gain more knowledge about the cell line and HCP levels. AstraZeneca have also confirmed HLA antigens were not detected in AZD1222 batches, and further studies of the issue are planned.

3.1.2 The EWG heard currently available batch data shows the batches are well within HCP limits. However, the established limits approach used to inform these specifications is largely based on levels of HCPs from other vaccines, but of these vaccines only few use HEK cell lines.

3.1.3 The Chair asked the EWG if any urgent action is required given that the vaccine roll-out is starting 4th of January.

3.1.4 The EWG noted the approach that AstraZeneca have taken so far appears to be the correct one; spectrophotometry did not appear to show any HLA proteins. According to the batch data the levels of HCPs are very low, but it would be beneficial to compare the levels to historical CMV vaccine batch data. The EWG noted that a benefit-risk evaluation needs to be undertaken before deferring vaccination. The EWG noted that adenoviruses are non-enveloped, and therefore the scope to carry host proteins such as HLA antigens is highly limited. The EWG noted that more data are required including the sensitivity limits of the spectroscopy method.

3.1.5 The EWG noted that sensitisation is a potential serious previously unidentified risk and suggested alternative vaccines could possibly be used for those on the transplant waiting list. The Chair mentioned enabling patients to gain access to the Pfizer BioNTech vaccine may not be logistically feasible, because many of these patients cannot leave their homes and the cold chain needs to be maintained for this particular vaccine; availability may also be another caveat. The EWG heard that, in order to inform on the benefit-risk of the situation more accurately, the MHRA are rapidly seeking more data from the manufacturer of the CMV vaccine, as well as meeting with NHS-BT and AstraZeneca.

3.1.6 The EWG noted that patients with chronic renal failure are extremely vulnerable to COVID, and therefore extreme caution should be exercised when considering not to vaccinate this group.

4. Future Steps / Any Other Business

None.

5. Date and time of next meeting

Monday 4th January 2021 at 09:30

The Meeting started at 10:02 and ended at 12:57

Members are reminded that the content of papers and proceeding of the meetings are to be treated as 'Official – sensitive commercial'. Members are also reminded that, in accordance with the Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members must also declare any other matter which could reasonably be perceived as affecting their impartiality. Detailed guidance is set out in the Code of Practice

Annex I

Conflict of Interest Policy for CHM COVID-19 Vaccine Benefit Risk EWG

Chair and Members

- May not hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
- May not currently be or have previously been involved in the development of COVID-19 vaccines

Invited to all meetings, receives all papers and presentations and is permitted full participation in discussion, including drawing up conclusions and recommendations

Invited experts

- May hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
- May currently be or have previously been involved in the development of COVID-19 vaccines

May be invited to all relevant meetings, receives all papers and presentations and is permitted to participate in discussions when invited by the Chair. Does not contribute to conclusions and recommendations

Observers

Are invited to attend all meetings. Will not participate in drawing up conclusions and recommendations.

COMMISSION ON HUMAN MEDICINES (CHM)

COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Sunday 3rd January 2021** at **15:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor H J Lachmann
Professor P J Lehner
Dr S Misbah

Members of the CTBV Expert Advisory Group

Professor M Turner

Professional Staff of MHRA Present

Principal Assessor

Dr J Bonnerjea - LD

Presenters supporting specific items[1]

[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - LD

Secretariat

[redacted]

[1] supporting specific items

MHRA Observers

Dr S Atkinson - Directorate
Dr S Branch - VRMM
[redacted] – LD
Dr SP Lam - LD
[redacted] – Government Legal Team
[redacted] - MHRA-NIBSC
[redacted] - LD
Dr J Raine – MHRA CEO
[redacted] - LD
[redacted] - LD

[redacted]

19th July 2021

Key
LD = Licensing Division
NIBSC = National Institute for Biological Standards & Control
VRMM = Vigilance & Risk Management of Medicines
CTBV = Clinical Trials, Biologicals & Vaccines EAG
CPS = Chemistry, Pharmacy & Standards EAG
CHM = Commission on Human Medicines
Directorate = Director of Operational Transformation
IE&S = Inspection, Enforcement & Standards

1. Introduction and Announcement

1.1 The Chair reminded Members that the content of papers and proceeding of the meeting are strictly confidential and should be treated as 'Official – sensitive commercial' and should not be disclosed. There is no consent for members / participants to record the meeting, take screenshots or photographs of presentations. The meeting was recorded by the MHRA Secretariat for minute taking purposes only. The Chair & Members including all participants gave full consent to the recording prior to the start of the meeting.

1.2 Conflict of Interest Policy (Annex I to the minutes)

The Chair reminded members and participants that, in accordance with the CHM Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members were also reminded to declare any other matter which could reasonably be perceived as affecting their impartiality.

1.3 The following members, invited experts and observers declared interests and other relevant interests for this meeting:

Professor Sir Munir Pirmohamed - NPNS AstraZeneca - Research grant to UOL to support PhD in drug interactions.
Other relevant interests in Pfizer, Janssen, Sanofi – Sir Munir is part of an EU-funded IMI consortium on gene therapy, and these companies are partners in the project. The University of Liverpool will get funding from the EU (but not from the partners), this IMI project commences on 3rd November 2020.
AGILE – this is a Liverpool early phase trial platform (between University of Liverpool and Liverpool School of Tropical Medicine). It is funded by the Wellcome Trust and UKRI/DHSC/NIHR. It is NOT evaluating vaccines, but only drugs to treat COVID-19. Sir Munir is not on the trial management group, and he is not directly involved in choosing the compounds for the study. Sir Munir has no involvement with any of the developers of the compounds to be studied (academic or industrial).
Sir Munir is a member of the UK COVID Therapeutics Advisory Panel (UK-CTAP), which is advising the CMO on which compounds need to be prioritised for the RECOVERY+ trial (RECOVERY is funded via NIHR/DHSC).

Professor Lachmann – Other relevant interest as a volunteer participant in the Oxford vaccine study and no other involvement in the study.

Professor Lehner - Other relevant interest – Professor Lehner previously held a DPAC (Discovery Partnership with Academia) agreement with GSK, but this has been completed. Professor Lehner's participation in his local hospital D and T governance committee deliberations would form the normal activity and professional responsibility in his post and does not interfere with the EWG considerations (Sept 2020).

Dr Misbah - NPNS - Holds honorary Senior Lectureship with University of Oxford & Oxford University Hospitals NHS Foundation Trust.

CTBV

Professor Turner – NPNS interest. Professor Turner is a Non Executive Director (non-remunerated) on the Board of the Cell and Gene Therapy Catapult (CGT).

CGT have been tasked by UK Government with re-purposing a factory in [redacted] to manufacture either a vaccine or a therapeutic mAb. No decision has been made as to whether or what product CGT [redacted] may be asked to manufacture and that decision will be made by UK Government. Professor Turner does not believe that CGT Board will have any material input into the decision as to what product may be manufactured.

2. HLA Sensitisation Issue – MHRA and AZ Risk Assessments

2.1 The EWG was presented with a risk assessment of the potential signal of HLA sensitisation for recipients of the Covid-19 vaccine AstraZeneca which had been raised following cases of HLA sensitisation in subjects in a clinical trial of CMV vaccine.

2.2 The EWG noted the following points:

2.2.1 Covid19 vaccine AstraZeneca uses an adenovirus vector, which is non-enveloped. This is in contrast with the CMV virus vaccine which raised the signal (which uses a Lymphocytic Choriomeningitis Virus vector which is enveloped) and the other vaccine for which sensitisation has been reported which is HIV, also an enveloped virus. Therefore, host cell HLA is unlikely to be incorporated into Covid19 vaccine AstraZeneca virion particles as it would during the formation of an envelope during the budding off of an enveloped virion.

2.2.2 Details of the [redacted] performed by AstraZeneca to test a Covid19 vaccine AstraZeneca product batch for Host Cell Proteins and HLA did not find any HLA protein/peptides and the detection levels achieved were sufficiently sensitive.

2.2.3 Analysis of samples from 595 male subjects from Covid-19 vaccine AstraZeneca trials did not identify any sensitisation of vaccine recipients. All potentially HEK293 HLA-reactive antibodies detected in post vaccination samples were present in baseline samples taken prior to vaccination.

2.3 The EWG endorsed the findings of the risk assessment and considered that the available data does not present evidence of a risk and therefore should not be a barrier to transplant candidates and recipients receiving Covid-19 vaccine AstraZeneca.

2.4 The EWG made the following recommendations:

2.4.1 The EWG supported the proposal that AstraZeneca, as an additional pharmacovigilance measure, should conduct analysis of further samples from a larger proportion of trial participants, with comparison to samples from participants who received active control, on the basis of a valid statistical plan.

2.4.2 The EWG also supported the proposal that AstraZeneca, as additional pharmacovigilance, should perform LC-MS analysis of a small additional number of Covid19 vaccine AstraZeneca product batches. Further details should also be provided of the methods used for LC-MS including the relative sensitivities to detect membrane-bound and soluble proteins.

2.4.3 These additional pharmacovigilance measures should be performed as soon as possible and completed within a timescale to be determined by MHRA.

2.4.4 The EWG recommended that no update to the Covid19 vaccine AstraZeneca product information was required and that no proactive communications were required to patients and healthcare professionals.

2.5 The EWG reflected on the risks that Covid-19 infection poses to transplant candidates and recipients and the importance of their access to Covid-19 vaccination.

3. Future Steps / Any Other Business

None.

4. Date and time of next meeting

TBC

The Meeting started at 15:35 and ended at 16:22

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COMMISSION ON HUMAN MEDICINES (CHM)
COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Wednesday 13th January 2021** at **15:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan
Professor N French
Professor D Goldblatt
Ms S Hunneyball
Professor K Hyrich
Sir M Jacobs
Professor H J Lachmann
Professor P J Lehner
Dr S Misbah
Dr A Riordan
Professor C Robertson
Professor P Shah[1]
Dr R Thorpe
Mrs M Wang[1]
Professor C Weir

Apologies

Professor S Price
Professor T Solomon

Members of the CTBV Expert Advisory Group

Professor B K Park
Professor M Turner

Members of the CPS Expert Advisory Group

Mr VI G Fenton-May
Mr R Lowe
Professor Y Perrie
Professor K M G Taylor (Chair of CPS)
Dr S Walsh

Secretariat

[redacted]

Minute Taker

[redacted] - LD - Medical Writer

[1] Joined at item 2
[2] supporting specific items

Professional Staff of MHRA Present

Principal Assessors[2]

Dr J Bonnerjea - LD
Dr P Bryan - VRMM

Presenters supporting specific items[2]

[redacted] - VRMM
[redacted] - VRMM
[redacted] - VRMM
Dr N Rose - MHRA-NIBSC

MHRA Observers

[redacted] - VRMM
[redacted] - VRMM
[redacted] - MHRA-NIBSC
[redacted] - LD
Dr S Branch - VRMM
[redacted] - LD
[redacted] - VRMM
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[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
[redacted] - MHRA-NIBSC
[redacted] - LD
[redacted] - VRMM
[redacted] - VRMM
Mr P Tregunno - VRMM
[redacted] - Government Legal Team
[redacted] - MHRA-NIBSC
[redacted] - LD
[redacted] - LD

Key
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VRMM = Vigilance & Risk Management of Medicines
CTBV = Clinical Trials, Biologicals & Vaccines EAG
CPS = Chemistry, Pharmacy & Standards EAG

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Sir Munir is a member of the UK COVID Therapeutics Advisory Panel (UK-CTAP), which is advising the CMO on which compounds need to be prioritised for the RECOVERY+ trial (RECOVERY is funded via NIHR/DHSC).

Professor Breuer – NPNS – Professor Breuer is joining the data safety monitoring committee, DSMB, a study looking at combining vaccines being run by Matthew Snape in Oxford. There does not appear to be any involvement of the vaccine manufacturers and is for already licensed vaccines. The study is funded by the NIHR (Dec 2020).

Professor French - Other relevant interest **-** Provides clinical care when in covering the acute medical wards where patients with COVID-19 are cared. NPNS in GSK - In September 2020 a sub-contract was signed with the Liverpool School of Tropical Medicine to undertake work evaluating the safety and effectiveness of GSK's RTS's malaria vaccine in Malawi. GSK are the primary funders to the LSTM.

Ms Hunneyball - Other relevant interest – writes articles published in the Chemist and Druggist magazine, a trade magazine for pharmacists, but receives no payment for these articles. The information referred to in the articles is in the public domain. Ms Hunneyball makes it clear that these are her personal views and reflections and references all sources of information used.

Professor Hyrich – NPNS - Professor Hyrich was co-I on an investigator-initiated research grant exploring predictors of outcome in rheumatoid arthritis. NPNS Pfizer- she is a Co-I on a grant exploring adherence to JAK inhibitors in rheumatoid arthritis. NPNS in Abbvie, Professor Hyrich gave some lectures at an education conference on effectiveness of treatment for rheumatoid arthritis.

Sir Michael Jacobs - Other relevant interest - As part of the academic role at the Liverpool School of Tropical Medicine, Sir Michael is a member of the Study Management Team and antiviral drug prioritisation group for the AGILE proof of concept (phase I/II) platform study. Sir Michael is also part of the team that submits new antiviral compounds against SARS-CoV2 for consideration by NIHR for testing on this platform. No commercial or financial interest in the trial or any of the compounds, or any pharmaceutical or biotechnology company.

Professor Lachmann – Other relevant interest as a volunteer participant in the Oxford vaccine study and no other involvement in the study.

Professor Lehner - Other relevant interest – Professor Lehner previously held a DPAC (Discovery Partnership with Academia) agreement with GSK, but this has been completed. Professor Lehner's participation in his local hospital D and T governance committee deliberations would form the normal activity and professional responsibility in his post and does not interfere with the EWG considerations (Sept 2020).

Dr Misbah - NPNS - Holds honorary Senior Lectureship with University of Oxford & Oxford University Hospitals NHS Foundation Trust.

Dr Riordan - Other relevant interests - Participant in Oxford University's ChAdOx1 nCoV-19 clinical trial –received immunisation 27/8/2020. NPNS - Postgraduate External Examiner for Oxford University (Postgraduate Diploma in Paediatric Infectious Diseases)

Mrs Wang – Other relevant interest arising from being highly sensitive to insect stings, and plant products such as Hyacinth bulbs, which are recorded on Mrs Wang's medical records. This declared interest is only specific for this meeting.

Professor Weir - NPNS - Imperial College and Other relevant interest arising from his department collaborates with Imperial College on a number of clinical trials.

CTBV

Professor Park - NPNS in GSK Research & Development Ltd. and in Janssen as I received a research grant in the past two years. The grant has been handed over to a colleague in 2020 and the grant is due to finish in 2020. Professor Park received no direct payment. In addition, Professor Park have two active IMI grants for Transbioline and Quantitative Systems Toxicology, he is the PI on the TransBioline grant for the University of Liverpool. Both grants are paid directly to the University of Liverpool.

Professor Turner – NPNS interest. Professor Turner is a Non Executive Director (non-remunerated) on the Board of the Cell and Gene Therapy Catapult (CGT).
CGT have been tasked by UK Government with re-purposing a factory in Braintree to manufacture either a vaccine or a therapeutic mAb. No decision has been made as to whether or what product CGT Braintree may be asked to manufacture and that decision will be made by UK Government. Professor Turner does not believe that CGT Board will have any material input into the decision as to what product may be manufactured.

CPS

Mr V'lain Fenton-May – None

Mr Robert Lowe – None

Professor Yvonne Perrie - NPNS in Pfizer & AstraZeneca arising from a contract for a grant (March 2018), which includes contributions from these companies to the University of Strathclyde, Janssen in writing a grant for a PhD (now funded), GSK – arising from an EU grant to University of Strathclyde (Jan 2019-Dec 2019)

Professor Kevin Taylor – None

Dr Susannah Walsh – None

1.4 Apologies have been received from Professor Price and Professor Solomon for this meeting.

2. mRNA COVID-19 vaccines – Safety data in those with prior COVID-19 infection

2.1 The EWG heard a paper on safety in those with prior COVID-19 infection.

The EWG discussed the potential for increased reactogenicity, particularly with the Pfizer vaccine, in those who have previously had COVID-19 infection. The EWG agreed that although there may be a theoretical reason to anticipate a lower magnitude of antibody response in the AZ vaccine compared with the Pfizer vaccine, at present both vaccines can be considered similar in this respect. The EWG noted the lack of standardised assays and head to head studies to evaluate whether the vaccines induce a different magnitude of antibody response. The EWG also noted that a small percentage of individuals in clinical trials were seropositive at baseline and data from clinical trials did not indicate an increased risk of reactogenic events in these individuals.

2.2 The EWG noted that immune-complex type reactions, including serum sickness and vasculitides, were also theoretical and no risk was observed in the clinical trials. The EWG noted that the risk of immune-complex deposition was unlikely and would be more likely to occur in the event of prolonged antigen production, for example with a live vaccine.

2.3 The EWG discussed possible approaches for continued monitoring and noted that patients with previous COVID-19 infections may have a higher immune response with symptomatic disease than with asymptomatic disease.

2.4 The EWG agreed that given the evolving landscape with COVID-19 to enhance current monitoring, the MHRA should include immune-complex events as Adverse Events of Special Interests (AESIs). These would include events such as glomerulonephritis and vasculitis.

2.5 The EWG considered that the correlates or the true biological markers of protection are still unknown. The EWG noted the need for ongoing studies in order to understand if the immune response to each individual batch is the same and a baseline blood sample would be useful to carry this out and to link the subsequent reactions in those with pre-existing antibodies. The EWG considered that such a study might be coordinated by PHE and would likely have a number of individuals with pre-existing antibodies.

2.6 The EWG briefly discussed long COVID-19 and noted it would be useful to know if individuals are collecting data on this.

2.7 The EWG noted the issue of antibody enhancement of disease. There EWG heard there is potential concern that poor levels of neutralising antibodies may lead to enhancement of

disease when individuals encounter COVID-19 if they are naïve at the time of vaccination. In cases where the second dose is delayed in mRNA vaccines, high levels of IgG are observed post dose 1; however, the levels of neutralising antibodies stay low which theoretically is a situation that could lead to enhancement.

2.8 The EWG heard that approximately 300000 individuals have had the second dose and noted a proportion of them would have had a prior infection. The EWG discussed whether the second dose could induce the same kind of immune complex disease in those individuals that have not previously had COVID-19. The EWG also considered that a greater antibody response might be expected after two doses. The EWG noted that there is some evidence, i.e. from the Moderna study, that the second dose induces more of a response.

2.9 The EWG were relatively reassured for the present time by the results of the clinical trial data in terms of both reactogenicity and immune-complex events in individuals who were seropositive at baseline who have received the vaccine but noted the need for continued vigilance.

3. Risk of anaphylaxis with Pfizer/BioNTech and Moderna COVID-19 vaccines

3.1 The EWG heard a paper of the risk of anaphylaxis with Pfizer/BioNTech and Moderna COVID-19 vaccines. The EWG were reassured that the rate of anaphylaxis remained similar to that previously reported. The EWG agreed the 15-minute observation period should be maintained.

3.2 The EWG noted that the patient group directions (PGDs) for Oxford/AstraZeneca and Pfizer vaccines should be the same with respect to contraindications due to pre-existing allergies and that some patients have been incorrectly refused vaccination due to, for example, penicillin allergy. MHRA agreed to raise this with PHE.

4. Update on the Safety Data for the Pfizer/BioNTech COVID-19 vaccine
Example Publication to get view on structure

4.1 The EWG heard a paper on an update on the safety data for the Pfizer/BioNTech COVID-19 vaccine. The EWG agreed that the data were broadly reassuring.

4.2 The EWG were assured that low levels of lymphadenopathy were observed, and this event is listed in Section 4.8 of the SmPC.

4.3 The EWG heard there were no cases of appendicitis.

4.4 The EWG heard there are risk windows for each of the adverse events of special interest. For Bell's Palsy the window is between 7- and 42-days post dose 1 vaccination. These windows are then compared to the rates of Bell's Palsy in unexposed populations.

4.5 The EWG discussed the risk of lack of care in individuals following their first dose of vaccine has led to a number of cases of COVID-19 disease. The EWG also noted that some cases of COVID-19 could be contracted in the vaccine centre.

The EWG discussed individuals who contract a fever post vaccination. The EWG heard that most were healthcare professionals, and some did report symptoms of fever and joints aches/pains. A proportion of these did report positive COVID-19 tests.

4.6 MHRA informed 500 yellow cards have been received concerning the AZ vaccine which do not indicate any signals.

The EWG reviewed an example COVID-19 vaccine adverse reaction summary publication.

The EWG gave advice to MHRA on the language, content and structure of the example publication. Some members of the EWG offered their time to input further on the publication, including lay members, to ensure the publication is understood in the context of the number of doses of vaccine administered.

5. Future Steps / Any Other Business

5.1 Update on Independent Batch Release

5.1.1 The EWG heard an update on Independent Batch Release from NIBSC on Pfizer (12 batches) and AZ vaccines (5 batches) of which 10 Pfizer batches and 3 AZ batches have been certificated.

5.1.2 The EWG heard that approximately 7 million doses of COVID-19 vaccines have now been certificated. The number of doses that have been batch tested and are awaiting manufacturers testing data to allow certification is approximately another 6 million.

5.1.3 The EWG heard that by the end of January 2021 batches representing approximately 5.5 million doses are expected to have been submitted to NIBSC for testing.

5.1.4 Overall, the number of batches tested and released by the end of January by NIBSC will represent between 15 and 20 million doses in total, depending on the manufacturers' data (Lot Release Protocol) submission dates.

5.1.5 The EWG heard that the duration of the longest test is 4 days for the AZ vaccine, and 5-6 days for the Pfizer vaccine.

5.2 Members were reminded that:

The content of papers and proceeding of the meeting are strictly confidential and should not be disclosed.

All enquiries, approaches, interview requests and requests for comments made directly to the members from the media or stakeholders, verbal or written, should be declined and referred to the agency's news centre in the first instance.

6. Date and time of next meeting

The next meeting is scheduled to take place on Monday 18th January 2021 at 10:30

The Meeting today started at 15:34 and ended at 16:58

[redacted]

24th March 2021

Members are reminded that the content of papers and proceeding of the meetings are to be treated as 'Official – sensitive commercial'. Members are also reminded that, in accordance with the Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members must also declare any other matter which could reasonably be perceived as affecting their impartiality. Detailed guidance is set out in the Code of Practice

COMMISSION ON HUMAN MEDICINES (CHM)
COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Monday 18th January 2021** at **10:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan
Professor N French
Professor D Goldblatt
Ms S Hunneyball
Professor K Hyrich
Sir M Jacobs
Professor H J Lachmann
Dr S Misbah
Professor S Price
Dr A Riordan
Professor C Robertson
Professor P Shah
Professor T Solomon
Dr R Thorpe
Mrs M Wang
Professor C Weir

Apologies

Professor P J Lehner

Members of the CTBV Expert Advisory Group

Professor B K Park
Professor M Turner

Members of the CPS Expert Advisory Group

Mr VI G Fenton-May
Mr R Lowe
Professor Y Perrie
Professor K M G Taylor (Chair of CPS)
Dr S Walsh

PHE Representatives

[redacted]

COG-UK Representatives

[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
Dr P Bryan - VRMM
[redacted] - LD

MHRA Presenters supporting specific items[2]

[redacted] - LD

MHRA Observers

[redacted] - LD
Dr M Bailey - MHRA-NIBSC
[redacted] - VRMM
[redacted] - VRMM
[redacted] - MHRA-NIBSC
[redacted] - LD
Dr S Branch - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD - Medical Writer
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - MHRA-NIBSC
Ms N Rose - MHRA-NIBSC
[redacted] - LD
[redacted] - IE&S
[redacted] - MHRA-NIBSC
[redacted] - LD
[redacted] - LD

[redacted]

24th March 2021

Secretariat

[redacted]

[1] Left after item 2
[2] Left after item 4
[3] supporting specific items

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VRMM = Vigilance & Risk Management of Medicines
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CPS = Chemistry, Pharmacy & Standards EAG
PHE = Public Health England
COG-UK = COVID-19 Genomics UK Consortium
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Other relevant interests in Pfizer, Janssen, Sanofi – Sir Munir is part of an EU-funded IMI consortium on gene therapy, and these companies are partners in the project. The University of Liverpool will get funding from the EU (but not from the partners), this IMI project commences on 3rd November 2020.
AGILE – this is a Liverpool early phase trial platform (between University of Liverpool and Liverpool School of Tropical Medicine). It is funded by the Wellcome Trust and UKRI/DHSC/NIHR. It is NOT evaluating vaccines, but only drugs to treat COVID-19. Sir Munir is not on the trial management group, and he is not directly involved in choosing the compounds for the study. Sir Munir has no involvement with any of the developers of the compounds to be studied (academic or industrial).
Sir Munir is a member of the UK COVID Therapeutics Advisory Panel (UK-CTAP), which is advising the CMO on which compounds need to be prioritised for the RECOVERY+ trial (RECOVERY is funded via NIHR/DHSC).

Professor Breuer – NPNS – Professor Breuer is joining the data safety monitoring committee, DSMB, a study looking at combining vaccines being run by Matthew Snape in Oxford. There does not appear to be any involvement of the vaccine manufacturers and is for already licensed vaccines. The study is funded by the NIHR (Dec 2020).

Professor French - Other relevant interest **-** Provides clinical care when in covering the acute medical wards where patients with COVID-19 are cared. NPNS in GSK - In September 2020 a sub-contract was signed with the Liverpool School of Tropical Medicine to undertake work evaluating the safety and effectiveness of GSK's RTS's malaria vaccine in Malawi. GSK are the primary funders to the LSTM.

Ms Hunneyball - Other relevant interest – writes articles published in the Chemist and Druggist magazine, a trade magazine for pharmacists, but receives no payment for these articles. The information referred to in the articles is in the public domain. Ms Hunneyball makes it clear that these are her personal views and reflections and references all sources of information used.

Professor Hyrich – NPNS - Professor Hyrich was co-I on an investigator-initiated research grant exploring predictors of outcome in rheumatoid arthritis. NPNS Pfizer- she is a Co-I on a grant exploring adherence to JAK inhibitors in rheumatoid arthritis. NPNS in Abbvie, Professor Hyrich gave some lectures at an education conference on effectiveness of treatment for rheumatoid arthritis.

Sir Michael Jacobs - Other relevant interest - As part of the academic role at the Liverpool School of Tropical Medicine, Sir Michael is a member of the Study Management Team and antiviral drug prioritisation group for the AGILE proof of concept (phase I/II) platform study. Sir Michael is also part of the team that submits new antiviral compounds against SARS-CoV2 for consideration by NIHR for testing on this platform. No commercial or financial interest in the trial or any of the compounds, or any pharmaceutical or biotechnology company.

Professor Lachmann – Other relevant interest as a volunteer participant in the Oxford vaccine study and no other involvement in the study.

Dr Misbah - NPNS - Holds honorary Senior Lectureship with University of Oxford & Oxford University Hospitals NHS Foundation Trust.

Professor Price - NPNS in GSK and AstraZeneca – which relates to donations provided by both companies to the British Toxicology Society (BTS) to support their Annual Congress and Education and Training of which Professor Price is currently President of the Society (2020-2022).

Dr Riordan - Other relevant interests - Participant in Oxford University's ChAdOx1 nCoV-19 clinical trial –received immunisation 27/8/2020. NPNS - Postgraduate External Examiner for Oxford University (Postgraduate Diploma in Paediatric Infectious Diseases).

Professor Solomon - Other relevant interests – Professor Solomon provides clinical care for patients with Covid-19; chaired the MRC/NIHR committee which awarded funding for development of the Oxford Vaccine.

Professor Weir - NPNS - Imperial College and Other relevant interest arising from his department collaborates with Imperial College on a number of clinical trials.

CTBV

Professor Park - NPNS in GSK Research & Development Ltd. and in Janssen as I received a research grant in the past two years. The grant has been handed over to a colleague in 2020 and the grant is due to finish in 2020. Professor Park received no direct payment. In addition, Professor Park have two active IMI grants for Transbioline and Quantitative Systems Toxicology, he is the PI on the TransBioline grant for the University of Liverpool. Both grants are paid directly to the University of Liverpool.

Professor Turner – NPNS interest. Professor Turner is a Non Executive Director (non-remunerated) on the Board of the Cell and Gene Therapy Catapult (CGT).
CGT have been tasked by UK Government with re-purposing a factory in Braintree to manufacture either a vaccine or a therapeutic mAb. No decision has been made as to whether or what product CGT Braintree may be asked to manufacture and that decision will be made by UK Government. Professor Turner does not believe that CGT Board will have any material input into the decision as to what product may be manufactured.

CPS

Mr V'lain Fenton-May – None

Mr Robert Lowe – None

Professor Yvonne Perrie - NPNS in Pfizer & AstraZeneca arising from a contract for a grant (March 2018), which includes contributions from these companies to the University of Strathclyde, Janssen in writing a grant for a PhD (now funded), GSK – arising from an EU grant to University of Strathclyde (Jan 2019-Dec 2019)

Professor Kevin Taylor – None

Dr Susannah Walsh – None

1.4 Apologies have been received from Professor Lehner for this meeting.

1.5 The Chair welcomed [redacted] (Consultant epidemiologist) & [redacted] (Scientific Lead) from PHE. The Chair also welcomed [redacted] and [redacted] from COG-UK.

2. Presentation by PHE

2.1 Early assessment of COVID-19 vaccine effects using Pillar1 and 2 data

2.1.1 The EWG viewed slides and heard a presentation from PHE on the early assessment of COVID-19 vaccine effects using Pillar1 and Pillar 2 data.

2.1.2 The EWG questioned the possibility that individuals are becoming infected in vaccination centres themselves. PHE confirmed that in their enhanced surveillance they are adding questions around the vaccination visit in order to understand more.

2.1.3 The EWG noted it is concerning that the dynamics in first week post-vaccination follow what is known about infections with COVID-19.

2.1.4 PHE informed there are a group of people being tested as they developed symptoms post vaccination.

2.1.5 The EWG heard that in terms of comparison with data from other countries who also rolled vaccine out quickly such as Israel or the US, UK data may be consistent with Israel but more data is needed to make a comparison.

2.1.6 The EWG noted that in cases where those that have been vaccinated and show symptoms, there is a need to check carefully for virus escape. People who are asymptomatic can become carriers of the disease. It is particularly important to keep the asymptomatic under review in the elderly population. PHE informed that this may form part of what ONS are doing.

2.1.7 The EWG discussed the possibility that the apparent increase in risk of disease in the short time period immediately after vaccination could theoretically be due to an antibody sump which then dissipates when the vaccine takes effect.

2.1.8 The EWG heard that overall, these results are similar to those seen in Scotland, with the exception of the increase 2–3 days post vaccination.

2.1.9 The EWG noted concern about deaths observed in the few days after vaccination in care home residents and heard there are specific studies set up to look at these. The VIVALDI study will be used to look at this, but all care homes will be incorporated into an analysis.

2.1.10 The EWG heard that the initial group of data from PHE includes a significant number of people who have received their second dose at 21 days.

2.1.11 The EWG questioned whether there is increased testing in people who have had the vaccine by virtue of being symptomatic to the vaccine itself? PHE stated there is no dramatic rise but overall, the numbers tested do go up a little in the period 3-13 days post vaccination.

2.1.12 The EWG noted that some of these vaccines are quite novel and questioned whether after vaccination each individual might be expressing the antigen in body fluids and that vaccination could be giving false positives. The EWG noted that PCR tests involve multiple sites on virus but could theoretically capture vaccine mRNA depending on protocol used; however, it is unlikely the vaccine could be responsible for false positives.

2.1.13 The EWG heard that PHE does also hold information on lateral flow test results but these are not presented here.

2.1.14 The EWG found the data presented of great interest and looked forward to hearing more from future analyses.

2.2 Analysis of reinfections from the SIREN cohort

2.2.1 The EWG viewed slides and heard a presentation on interim analysis of the SIREN study.

2.2.2 The EWG heard that those who had symptoms had less severe symptoms from the initial review but PHE informed that this will be looked at in more detail going forward.

2.2.3 The EWG queried whether an inverse analysis had been performed on reinfections to evaluate whether the first infection was symptomatic or asymptomatic and see if it was linked to the second infection. PHE informed that they know all cases that were symptomatic in first infection; however, work still needs to be done with regard to asymptomatic infections.

2.2.4 The EWG noted that it is important to link with COG-UK and follow asymptomatic and symptomatic infections and questioned whether these cases are reinfections or re-emergence of original infection. PHE informed that this work is on-going and some may be reclassified at a later stage to ‘persistent’.

2.2.5 Results from interim analysis has all been done at hospital sites and is qualitative. PHE will carry out a quantitative analysis. PHE collect medical histories at enrolment.

3. Presentation by COG-UK

3.1 The EWG viewed slides and heard a presentation by COG-UK.

3.2 The EWG noted it is important to look at the genotype of the virus as demonstrated by COG-UK.

3.3 The EWG noted it is important to do forecasting and evaluate how to do it and how accurately it can be done. The significance of mutations is not known and the role of combinations or consolation of mutations as well as single mutations was discussed.

3.4 The EWG heard that COG-UK are ahead in terms of collating mutations but that there was a long way to go to translate that into what it really means for the future. Excellent surveillance methods are required to keep track of the incidence of severe disease and death and mechanisms to pick up people who are re-infected after vaccination or natural infections and mechanism to see if there is a surge in cases. The transmissibility with impairment to immunity will be most concerning.

3.5 The EWG discussed how vaccine companies get access to data and how to feedback from COG-UK and PHENO to discuss with the companies what they need if they should need to redesign their vaccines. The EWG heard much information is freely available on COG-UK website and COG-UK are happy to engage with companies but in an organised structured way. The EWG heard access to data in real time is important. MHRA will talk to vaccine companies this week and plan to discuss the regulatory approach to tweaking the vaccines. MHRA informed that a paper will come to EWG in the near future.

3.6 The EWG discussed the potential adaptation of coronavirus vaccines to mutations. We do not have an example of another virus where there is escape from the vaccine apart from flu which changes rapidly. The EWG heard that coronavirus mutates much more slowly than the flu virus. The number of transmissions drives the infection rate and what happens in people who are chronically infected. If transmission is stopped then that would reduce the likelihood of escape mutants.

4. Presentation on Agility Project

4.1 The EWG viewed slides and heard a presentation on the CEPI funded Agility Project.

4.2 The EWG heard that the Syrian hamster model was originally developed for SARS-2CoV as being an effective model for this virus and it is an appropriate model to look at vaccines.

4.3 The EWG that heard PHE have sufficient capacity to look at different antivirals and vaccines.

4.4 The EWG discussed the sources of convalescent plasma used. The EWG heard that PHE have eight sera supplied in large volumes from NIBSC sourced from blood transfusion service in the early part of outbreak (no later than summer). The EWG heard the sera used in this study is from healthy volunteers from blood transfusion service.

4.5 The EWG noted it would be interesting to look at virus as it moves back into animal system to see if counter-evolution occurs.

4.6 The EWG heard PHE are doing a [redacted] assay which is not technically intracellular but would be keen to talk about this off-line.

5. EWG discussion on *in vivo* adventitious agent testing for Covid-19 vaccine AZD1222

5.1 The EWG viewed slides and heard a presentation on *in vivo* adventitious agent testing for COVID-19 vaccine AZD1222.

5.2 The EWG had no particular concerns with removing *in vivo* adventitious agent testing for COVID-19 vaccine AZD1222. The EWG noted a test by test analysis may be required at some point.

5.3 The EWG discussed the use of intermittent metagenomics and agreed to ask the company if they are considering this approach for the future.

6. Review of Minutes

6.1 Wednesday 18th November 2020
Saturday 21st November 2020
Tuesday 24th November 2020
Friday 27th November 2020
Saturday 28th November 2020
Monday 7th December 2020
Thursday 10th December 2020
Thursday 17th December 2020
Tuesday 22nd December 2020
Thursday 24th December 2020
Tuesday 29th December 2020

6.1.1 The minutes listed above were approved as a true and accurate record of the proceedings, subject to some amendments to the relevant minutes.

7. Future Steps / Any Other Business

7.1 Members were reminded that:

The content of papers and proceeding of the meeting are strictly confidential and should not be disclosed.

All enquiries, approaches, interview requests and requests for comments made directly to you from the media or stakeholders, verbal or written, should be declined and referred to the agency's news centre in the first instance.

8. Date and time of next meeting

The next meeting is scheduled to take place on Friday 22nd January 2021 at 15:30

The Meeting today started at 10:31 and ended at 12:56

Members are reminded that the content of papers and proceeding of the meetings are to be treated as 'Official – sensitive commercial'. Members are also reminded that, in accordance with the Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members must also declare any other matter which could reasonably be perceived as affecting their impartiality. Detailed guidance is set out in the Code of Practice

COMMISSION ON HUMAN MEDICINES (CHM)
COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Friday 22nd January 2021** at **15:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan
Professor N French
Professor D Goldblatt
Ms S Hunneyball
Professor K Hyrich
Sir M Jacobs
Professor H J Lachmann
Professor P J Lehner
Dr S Misbah
Professor S Price
Dr A Riordan[1]
Professor C Robertson
Professor P Shah
Professor T Solomon
Dr R Thorpe
Mrs M Wang
Professor C Weir

Members of the CTBV Expert Advisory Group

Professor B K Park[1]
Professor M Turner

Members of the CPS Expert Advisory Group

Mr VI G Fenton-May
Mr R Lowe
Professor Y Perrie
Professor K M G Taylor (Chair of CPS)
Dr S Walsh

Observer

Professor S Ralston (Chair of CHM)

Secretariat

[redacted]

Professional Staff of MHRA Present

Principal Assessors[2]

Dr J Bonnerjea - LD
Dr P Bryan - VRMM

MHRA Presenters supporting specific items[2]

[redacted]
[redacted] - COMMS
[redacted]
Dr C Schneider - MHRA-NIBSC
[redacted]

MHRA Observers

[redacted]
Dr S Branch - VRMM
[redacted]
Mr K McDonald - LD
[redacted]
Dr J Raine - MHRA CEO
Ms N Rose - MHRA-NIBSC
[redacted] LD
Mr P Tregunno - VRMM
[redacted]

[1] Joined during item 3
[2] supporting specific items

[redacted]

[redacted]

19th July 2021

Key

LD = Licensing Division
NIBSC = National Institute for Biological Standards & Control
VRMM = Vigilance & Risk Management of Medicines
CTBV = Clinical Trials, Biologicals & Vaccines EAG
CPS = Chemistry, Pharmacy & Standards EAG
CHM = Commission on Human Medicines
MHRA CEO = Chief Executive
IE&S = Inspection, Enforcement & Standards
NIBSC = National Institute for Biological Standards & Control
COMMS = Deputy Director of News, Digital & Content

1. Introduction and Announcement

1.1 The Chair reminded Members that the content of papers and proceeding of the meeting are strictly confidential and should be treated as 'Official – sensitive commercial' and should not be disclosed. There is no consent for members / participants to record the meeting, take screenshots or photographs of presentations. The meeting was recorded by the MHRA Secretariat for minute taking purposes only. The Chair & Members including all participants gave full consent to the recording prior to the start of the meeting.

1.2 Conflict of Interest Policy (Annex I to the minutes)

The Chair reminded members and participants that, in accordance with the CHM Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members were also reminded to declare any other matter which could reasonably be perceived as affecting their impartiality.

1.3 The following members and invited experts declared interests and other relevant interests for this meeting:

Professor Sir Munir Pirmohamed - NPNS AstraZeneca - Research grant to UOL to support PhD in drug interactions.
Other relevant interests in Pfizer, Janssen, Sanofi – Sir Munir is part of an EU-funded IMI consortium on gene therapy, and these companies are partners in the project. The University of Liverpool will get funding from the EU (but not from the partners), this IMI project commences on 3rd November 2020.
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Professor Lachmann – Other relevant interest as a volunteer participant in the Oxford vaccine study and no other involvement in the study.

Professor Lehner - Other relevant interest – Professor Lehner previously held a DPAC (Discovery Partnership with Academia) agreement with GSK, but this has been completed. Professor Lehner's participation in his local hospital D and T governance committee deliberations would form the normal activity and professional responsibility in his post and does not interfere with the EWG considerations (Sept 2020).

Dr Misbah - NPNS - Holds honorary Senior Lectureship with University of Oxford & Oxford University Hospitals NHS Foundation Trust.

Professor Price - NPNS in GSK and AstraZeneca – which relates to donations provided by both companies to the British Toxicology Society (BTS) to support their Annual Congress and Education and Training of which Professor Price is currently President of the Society (2020-2022).

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CTBV

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either a vaccine or a therapeutic mAb. No decision has been made as to whether or what product CGT Braintree may be asked to manufacture and that decision will be made by UK Government. Professor Turner does not believe that CGT Board will have any material input into the decision as to what product may be manufactured.

CPS

Mr V'lain Fenton-May – None

Mr Robert Lowe – None

Professor Yvonne Perrie - NPNS in Pfizer & AstraZeneca arising from a contract for a grant (March 2018), which includes contributions from these companies to the University of Strathclyde, Janssen in writing a grant for a PhD (now funded), GSK – arising from an EU grant to University of Strathclyde (Jan 2019-Dec 2019).

Professor Kevin Taylor – None

Dr Susannah Walsh – None

CHM

Professor Ralston – NPNS – Sanofi, Pfizer, Janssen, AstraZeneca & Other relevant interests in NHS Lothian and Oxford University. Professor Ralston has an honorary consultant contract with NHS Lothian but has not been involved in any trials relating to COVID-19. He also has agreed to be an external examiner for Oxford University clinical trials MSc; however, this has not yet started.

1.4 MHRA Press Interaction

1.4.1 The EWG heard advice from the MHRA Communications Division regarding MHRA Press Interaction. MHRA advice remains that EWG members should not speak on behalf of or as a representative of the EWG/CHM or discuss EWG/CHM business. In these cases, EWG members are advised to pass these queries to the MHRA news centre. MHRA to circulate the contact details to EWG members post meeting.

1.4.2 The EWG were reminded of the code of practice for scientific advisory committees (communication with media is covered in paragraphs 139-142). MHRA to provide link to this document following the meeting.

1.4.3 The EWG heard that where information is already in public domain and decision or advice already been made or given when that advice is in the public domain then members can repeat the outcome to the press.

1.4.4 The EWG were informed that EWG members are not to interact with the press about any live issues that are under consideration or any other issues that could potentially come up in the future.

1.4.5 MHRA advised EWG members to avoid putting themselves in positions where they might get asked questions around COVID-19 vaccines and their role as an EWG member wherever possible. MHRA informed EWG members that the MHRA news centre staff are always available to discuss any press queries members receive with them and to provide support and advice and to agree what can and can't be said.

2. Minutes of the COVID-19 VBR EWG meeting held on Thursday 24th December 2020

2.1 The minutes were agreed as a true and accurate record of the proceedings.

3. Regulatory strategy for authorised Covid-19 vaccines in case of strain changes

3.1 The EWG heard a draft paper about the regulatory strategy for authorised COVID-19 vaccines in case of strain changes.

3.2 The EWG heard the difference between antigen drift and antigen shift, where antigen shift would mean a new gene assortment, and the regulatory concepts associated with both. The EWG heard that at present the coronavirus is mutating in line with what would be considered antigen drift.

3.3 The EWG heard how this antigen drift could be managed along the same lines as the annual flu vaccine updates. The EWG heard the quality requirements MHRA would expect to see in order to update the COVID-19 vaccines in this way.

3.4 The EWG heard that is not yet known if antibody response is a good indicator of a response, and that a challenge study with SAR-Cov2 would be required which would be time consuming. A hamster study would also be required in the post-marketing phase. Cross protection should also be evaluated to ensure any new vaccine would protect against previous versions of the virus as well as recent versions.

3.5 The EWG heard that immunogenicity data would be required as outlined in the draft paper.

3.6 The EWG discussed the human challenge model and whether it has a role to play in the path to rapid approval for new vaccine strains. The EWG heard there are some ethical concerns that may relate to how dangerous any new strain of the virus would be but could be looked at on a case by case basis. The EWG heard that challenge studies may not be necessary if it is possible to bridge via immunogenicity data and an occurrence of disease would not be required. The EWG agreed it would be useful to have a session on human challenge trials at a future meeting.

3.7 The EWG heard that the human challenge studies are a fairly quick process and could provide a route to understand correlates of protection and to measure escape processes of the virus. The EWG heard that already there are different variants in 3 different continents, and it is not known which strain should be targeted by an updated vaccine. Human challenge model may be the only way to find out. The EWG heard any strategy needs to be internationally regulated. The EWG heard there may be similarities between coronavirus and norovirus and how it changes in different continents.

3.8 The EWG discussed whether we have reached the trigger point for manufacturers to start thinking about creating new vaccines to combat the new variants.

3.9 The EWG heard that the live virus will show the full complement of the mutations occurring whereas a pseudovirus will only give some of the mutations but not necessarily any occurring outside the RBD domain.

3.10 The EWG heard that recipients of Pfizer vaccine are able to produce neutralizing antibodies against variant 501; however, the trigger point for production for new vaccine may almost be reached. The EWG also noted the level of IgG produced after vaccination with the Pfizer vaccine. The EWG noted that the role of cellular immunity is not yet fully understood.

The EWG discussed the use of the human challenge studies and their use to determine natural immunity to the virus as well as immunity to the virus following vaccination with a new vaccine.

3.11 The EWG discussed how a new vaccine to be used in challenge studies would be approved. The EWG heard it could be used at Phase II level and would not have to be a licensed vaccine.

3.12 The EWG heard discussion around a sample size of 300 participants being exposed to an updated vaccine and agreed it seemed reasonable that this number might meet adequate levels of precision and practicality.
The EWG discussed the use of multiple virus sequences in the same vaccine to combat variants.

3.13 The EWG discussed whether non-clinical or quality data could be used alone and did not agree that this could be the case.
The EWG discussed the minimum level of evidence required to develop an updated vaccine.
The EWG heard that the paper will be updated and that the next logical step would be to have discussions with WHO being mindful of the impact that any delay might have and any potential changes of the pandemic.

4. Update on fatal ADRs

4.1 The EWG heard an update on the safety data from fatal ADRs. The EWG heard a summary of the fatal cases in Norway following administration of the Pfizer/BioNTech COVID-19 vaccination in frail and elderly patients, and that no connection with the vaccine had been established.

4.2 The EWG heard that the majority of the fatal cases in the UK following vaccination with the Pfizer vaccine are in the 80+ age group. The ADR cases were also summarized and were largely in line with events expected considering the ages and comorbidities in the patients. There were also some cases reporting diarrhoea and vomiting.

4.3 The EWG heard a summary of fatal cases in the UK following vaccination with the AstraZeneca vaccine in those aged 65 – 96 years of age. The events reported in fatal cases for AstraZeneca COVID-19 vaccine were also considered expected due to the age and comorbidities in the patients.

4.4 The EWG heard that currently there is no evidence of an increased risk of fatal events in frail patients and the benefit/risk profile remains the same in these patients.

4.5 The EWG requested more information on the cases of toxic epidermal necrolysis and the fatal cases where the onset of symptoms occurred within 25 minutes of vaccination. The EWG heard that generally speaking the fatalities occurred within a week of vaccination.

4.6 The EWG agreed that there does not seem to be a signal for an increased risk of fatalities in the elderly and frail patients with either the Pfizer COVID-19 vaccine or the AstraZeneca COVID-19 vaccine. The EWG agreed that the regulatory procedures put in place by the MHRA currently seem adequate.

5. <u>Any Other Business</u>

None.

6. Date and time of next meeting

The next meeting scheduled to take place on Monday 25th January has been cancelled.

The next meeting is scheduled to take place on **Friday 29th January 2021** at **13:30**

The Meeting today started at 15:31 and ended at 17:37

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COMMISSION ON HUMAN MEDICINES (CHM)
COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Friday 29th January 2021** at **13:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer[1]
Professor G Dougan
Professor N French
Professor D Goldblatt
Ms S Hunneyball
Professor K Hyrich
Sir M Jacobs
Professor H J Lachmann[2]
Professor P J Lehner
Dr S Misbah[3]
Professor S Price
Dr A Riordan
Professor C Robertson
Professor T Solomon
Dr R Thorpe
Mrs M Wang
Professor C Weir

Apologies

Professor P Shah

Members of the CTBV Expert Advisory Group

Professor B K Park
Professor M Turner

Members of the CPS Expert Advisory Group

Mr VI G Fenton-May
Mr R Lowe
Professor Y Perrie
Professor K M G Taylor (Chair of CPS)
Dr S Walsh

Observers

[redacted] (Imperial)
Professor S Ralston (Chair of CHM)

Invited Experts

[redacted]

Professional Staff of MHRA Present

Principal Assessors[4]

Dr J Bonnerjea - LD
Dr P Bryan - VRMM

MHRA Presenters supporting specific items[4]

[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - VRMM
[redacted] - LD
[redacted] - Government Legal Team
[redacted] - VRMM

MHRA Observers

[redacted] - LD - Medical Writer
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
Dr S Branch - VRMM
[redacted] - MHRA-NIBSC
[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - LD - Medical Writer
[redacted] - VRMM
Dr SP Lam - LD
Mr K McDonald - LD
[redacted] – VRMM
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - MHRA-NIBSC
Ms N Rose - MHRA-NIBSC
[redacted] - MHRA-NIBSC
[redacted] - LD
[redacted] - LD
[redacted] - VRMM
Mr P Tregunno - VRMM
[redacted] - Government Legal Team
[redacted] - MHRA-NIBSC
[redacted] - LD
[redacted] - LD

[redacted] - VRMM
Dr K Wydenbach - LD

Secretariat

[redacted]

[redacted]

19th July 2021

[1] Joined during item 3
[2] left during item 9
[3] left during item 6
[4] supporting specific items

Key
LD = Licensing Division
NIBSC = National Institute for Biological Standards & Control
VRMM = Vigilance & Risk Management of Medicines
CTBV = Clinical Trials, Biologicals & Vaccines EAG
CPS = Chemistry, Pharmacy & Standards EAG
CHM = Commission on Human Medicines

1. Introduction and Announcement

1.1 The Chair reminded Members that the content of papers and proceeding of the meeting are strictly confidential and should be treated as 'Official – sensitive commercial' and should not be disclosed. There is no consent for members / participants to record the meeting, take screenshots or photographs of presentations. The meeting was recorded by the MHRA Secretariat for minute taking purposes only. The Chair & Members including all participants gave full consent to the recording prior to the start of the meeting.

1.2 Conflict of Interest Policy (Annex I to the minutes)

The Chair reminded members and participants that, in accordance with the CHM Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members were also reminded to declare any other matter which could reasonably be perceived as affecting their impartiality.

1.3 The following members and invited experts declared interests and other relevant interests for this meeting:

Professor Sir Munir Pirmohamed - NPNS AstraZeneca - Research grant to UOL to support PhD in drug interactions.
Other relevant interests in Pfizer, Janssen, Sanofi – Sir Munir is part of an EU-funded IMI consortium on gene therapy, and these companies are partners in the project. The University of Liverpool will get funding from the EU (but not from the partners), this IMI project commences on 3rd November 2020.
AGILE – this is a Liverpool early phase trial platform (between University of Liverpool and Liverpool School of Tropical Medicine). It is funded by the Wellcome Trust and UKRI/DHSC/NIHR. It is NOT evaluating vaccines, but only drugs to treat COVID-19. Sir Munir is not on the trial management group, and he is not directly involved in choosing the compounds for the study. Sir Munir has no involvement with any of the developers of the compounds to be studied (academic or industrial).
Sir Munir is a member of the UK COVID Therapeutics Advisory Panel (UK-CTAP), which is advising the CMO on which compounds need to be prioritised for the RECOVERY+ trial (RECOVERY is funded via NIHR/DHSC).

Professor Breuer – NPNS – Professor Breuer is on the data safety monitoring committee, DSMB, a study looking at combining vaccines being run by Matthew Snape in Oxford. There does not appear to be any involvement of the vaccine manufacturers and is for already licensed vaccines. The study is funded by the NIHR (Dec 2020).

Professor Dougan – Personal interest specific to this meeting **–** Works with and is partially paid by the Wellcome Trust. Professor Dougan arranges the invite. At the chair's discretion, Professor Dougan was permitted to participate by answering specific questions from the chair, but not raise spontaneous comments or questions.

Professor French - Other relevant interest **-** Provides clinical care when in covering the acute medical wards where patients with COVID-19 are cared. NPNS in GSK - In September 2020 a sub-contract was signed with the Liverpool School of Tropical Medicine to undertake work evaluating the safety and effectiveness of GSK's RTS's malaria vaccine in Malawi. GSK are the primary funders to the LSTM.

Ms Hunneyball - Other relevant interest – writes articles published in the Chemist and Druggist magazine, a trade magazine for pharmacists, but receives no payment for these articles. The information referred to in the articles is in the public domain. Ms Hunneyball makes it clear that these are her personal views and reflections and references all sources of information used.

Professor Hyrich – NPNS - Professor Hyrich was co-I on an investigator-initiated research grant exploring predictors of outcome in rheumatoid arthritis. NPNS Pfizer- she is a Co-I on a grant exploring adherence to JAK inhibitors in rheumatoid arthritis. NPNS in Abbvie, Professor Hyrich gave some lectures at an education conference on effectiveness of treatment for rheumatoid arthritis.

Sir Michael Jacobs - Other relevant interest - As part of the academic role at the Liverpool School of Tropical Medicine, Sir Michael is a member of the Study Management Team and antiviral drug prioritisation group for the AGILE proof of concept (phase I/II) platform study. Sir Michael is also part of the team that submits new antiviral compounds against SARS-CoV2 for consideration by NIHR for testing on this platform. No commercial or financial interest in the trial or any of the compounds, or any pharmaceutical or biotechnology company. Personal interest specific to this meeting – Sir Michael is a member of the Human Challenge Steering Committee. At the chair's discretion, Sir Michael was permitted to participate by answering specific questions from the chair, but not raise spontaneous comments or questions.

Professor Lachmann – Other relevant interest as a volunteer participant in the Oxford vaccine study and no other involvement in the study.

Professor Lehner - Other relevant interest – Professor Lehner previously held a DPAC (Discovery Partnership with Academia) agreement with GSK, but this has been completed. Professor Lehner's participation in his local hospital D and T governance committee deliberations would form the normal activity and professional responsibility in his post and does not interfere with the EWG considerations (Sept 2020).

Dr Misbah - NPNS - Holds honorary Senior Lectureship with University of Oxford & Oxford University Hospitals NHS Foundation Trust.

Professor Price - NPNS in GSK and AstraZeneca – which relates to donations provided by both companies to the British Toxicology Society (BTS) to support their Annual Congress and Education and Training of which Professor Price is currently President of the Society (2020-2022).

Dr Riordan - Other relevant interests - Participant in Oxford University's ChAdOx1 nCoV-19 clinical trial –received immunisation 27/8/2020. NPNS - Postgraduate External Examiner for Oxford University (Postgraduate Diploma in Paediatric Infectious Diseases)

Professor Solomon - Other relevant interests – Professor Solomon provides clinical care for patients with Covid-19; chaired the MRC/NIHR committee which awarded funding for development of the Oxford Vaccine.

Professor Weir - NPNS - Imperial College and Other relevant interest arising from his department collaborates with Imperial College on a number of clinical trials.

CTBV

Professor Park - NPNS in GSK Research & Development Ltd. and in Janssen as I received a research grant in the past two years. The grant has been handed over to a colleague in 2020 and the grant is due to finish in 2020. Professor Park received no direct payment. In addition, Professor Park have two active IMI grants for Transbioline and Quantitative Systems Toxicology, he is the PI on the TransBioline grant for the University of Liverpool. Both grants are paid directly to the University of Liverpool.

Professor Turner – Other relevant interest. Professor Turner is a Non Executive Director (non-remunerated) on the Board of the Cell and Gene Therapy Catapult (CGT). CGT have been tasked by UK Government with re-purposing a factory in Braintree to manufacture either a vaccine or a therapeutic mAb. No decision has been made as to whether or what product CGT Braintree may be asked to manufacture and that decision will be made by UK Government. Professor Turner does not believe that CGT Board will have any material input into the decision as to what product may be manufactured.

CPS

Mr V'lain Fenton-May – None
Mr Robert Lowe – None
Professor Yvonne Perrie - NPNS in Pfizer & AstraZeneca arising from a contract for a grant (March 2018), which includes contributions from these companies to the University of Strathclyde, Janssen in writing a grant for a PhD (now funded), GSK – arising from an EU grant to University of Strathclyde (Jan 2019-Dec 2019).
Professor Kevin Taylor – None
Dr Susannah Walsh – None

CHM

Professor Ralston – NPNS – Sanofi, Pfizer, Janssen, AstraZeneca & Other relevant interests in NHS Lothian and Oxford University. Professor Ralston has an honorary consultant contract with NHS Lothian but has not been involved in any trials relating to COVID-19. He also has agreed to be an external examiner for Oxford University clinical trials MSc; however, this has not yet started.

1.4 The Chair welcomed the following invited experts for item 3:

[redacted] Human Challenge, Vaccines Taskforce
[redacted] Human Challenge, Vaccines Taskforce
[redacted] University of Southampton & Human Challenge Board Member
Read R.C.
[redacted] Imperial College (Study PI)

The Chair welcomed the following invited experts for item 4:

[redacted]

The Chair also welcomed [redacted] from Imperial who attended as an Observer.

2. Update on off-label prescribing of vaccines (for information)

2.1 The EWG was given an update regarding the previously raised questions about how the Regulation 174 approvals legally interact with the Specials Regime.

2.2 The EWG heard that a clause has now been introduced to the wording of conditions of all Regulation 174 vaccine approvals that covers off-label prescribing. This clause clarifies that an authorisation under Regulation 174 does not displace or preclude the reliance on the specials route of administration in the appropriate situations.

2.3 The EWG heard that the off-label use of vaccines cannot be further recommended or specified by MHRA and that the added clause merely states that the Regulation 174 approval does not displace or preclude the use of specials route of administration where these may appropriate in the judgement of individual prescribers or subject to the recommendations and priorities specified by the JCVI or other similar bodies.

2.4 The EWG were reminded that the added clause does not affect the liabilities of the prescriber as explained under Regulations 345 of the Human Medicines Regulations 2012. The added clause does not amount to a recommendation of use under Regulation 174. A healthcare professional prescribing this product off-label would not be considered to be doing it pursuant to the recommendation made under Regulation 174.

3. Presentation from Imperial/VTF – Human Challenge Study

3.1 The EWG viewed slides and heard a presentation from the Imperial/VTF on the general principles of human challenge studies, their strengths and requirements and how they are expected to accelerate the development of new vaccines. This type of study aims to answer questions such as the effect of vaccines and other treatments on viral shedding, and the effect of previous infections and any protection generated from this on viral shedding.

3.2 The EWG heard that these studies can look at critical challenges that may present themselves such as decisions regarding dosing or interval schedules, reduction of transmission and when to re-vaccinate.

3.3 The EWG heard that this type of study can also include non-vaccine therapies, such as therapeutics used for prophylaxis, antivirals and monoclonal antibodies as the study uses a disease model rather than an infection model.

3.4 The EWG discussed the benefits and limitations of these studies following the presentation from Wellcome on the Human Challenge Study.

4. Presentation from Wellcome – Human Challenge Study

4.1 The EWG viewed slides and heard a presentation from the Wellcome Trust. The EWG heard about the Wellcome programme of human challenge studies, with a goal to establish these studies in a low resource endemic setting so that vaccines can be tailored towards a target population.

4.2 The EWG heard about the programme of human challenge studies for SARS-CoV-2, which include characterisation studies and how they can be conducted ethically and safely. Current risk mitigation strategies in terms of treatment include pre-emptive remdesevir, monoclonal antibody cocktails, and dexamethasone.

4.3 The EWG discussed that there is a need to bridge clinical challenge data from young healthy adult individuals to target populations such as the elderly.

4.4 The EWG noted that the study will need to ensure a duty of care towards the volunteers especially in regard to persistent infections. The EWG noted that the presence of counselling young adult volunteers was reassuring and was the step in the right direction to ensure viral shedding was not taking place in the community.

4.5 The EWG heard that the study will carefully clinically screen individuals to ensure no prior history of recurrent infectious disease was present to exclude subjects with immune defects. The EWG raised concerns about the long-term effects of COVID infection in some individuals (long-COVID).

4.6 The EWG questioned the trigger points for the interventions and rescue therapies for the characterisation study, when a young adult patient is presenting symptoms of severe disease. The EWG heard that the trigger points were based around the physiological responses in those volunteers, such as gas exchange in the individual and untoward pro-inflammatory responses, with the potential use of remdesivir, monoclonal antibodies and dexamethasone in severe manifestations of the disease. Such subjects would be treated in a NHS unit independent from the study.

4.7 The EWG were reassured to hear the steps taken by the team to ensure the involvement of public in terms of public engagement studies which showed immense public support for the human challenge studies. The task force clarified that the work around spreading a clear message to the public is ongoing and continually monitored.

4.8 The EWG discussed the limitations to the challenge study such as the use of viral shedding rather than a disease model, as this does not allow for a clinical readout. The EWG questioned how efficacy will be inferred from viral replication in the upper respiratory tracts and whether this was sufficient for correlation with the efficacy of the vaccines. It was noted that this was the preferred model of choice in order to ensure the safety of the volunteers. To overcome the limitations of the disease model, the invited experts suggested alternative surrogate measures of efficacy, such as pathology seen on radiological imaging to serve as a form of a clinical readout.

4.9 The EWG agreed that challenge models will be critical going forward in understanding the different variants of SARS-CoV-2. The models will also provide an opportunity to determine whether the virus being detected is infectious.

4.10 The EWG noted the need for future discussions regarding the benefits if any of improvements to the approval pathway in terms of the nature and speed of the data these studies can produce for the current pandemic and future diseases.

4.11 The EWG expressed concern that preventing viral replication/load in the model would be a very high bar to set for any vaccine. It was raised that a model based on preventing symptoms of viral infection, especially for the accelerated vaccine development and testing, would be better.

4.12 The EWG felt that we are now moving from a previous situation of a fairly homogenous virus in a naïve population to a population who have had either had virus exposure or vaccination, and a virus that has variants. The human challenge models won't replace current research work but will add value in the nature of the data that it can produce.

5. Janssen non-clinical review

5.1 The EWG viewed slides and heard a presentation on the non-clinical aspects and the rolling review of the Janssen COVID-19 vaccine. The vaccine is an adenovirus type 26 vector.

5.2 The EWG were informed that the European Medicines Agency are reviewing the same dataset and it has been agreed that MHRA will consider what questions MHRA needs to put to the company after reviewing interactions between the European Medicines Agency and the company.

5.3 The EWG heard that the data presented on pharmacodynamics in terms of immunogenicity was reassuring. However, some discordance was noted with regards to the intracellular cytokine studies in mice and Rhesus monkeys. In mice, the intracellular cytokine response is predominantly confined to CD8 rather than CD4 cells. In Rhesus monkeys, the cytokine response is concordant between CD4 and CD8 cells. This may need to be explained by the company, as it is an unexpected finding, although it does not seem to affect the level of protection.

5.4 The EWG noted that the MHRA is awaiting toxicology data to be submitted. The EWG is keen to understand the reproductive toxicity, and whether the difference in lung pathology induced by SARS CoV-2 virus in the challenge study in rhesus monkeys between males and females could be due to lack of age matching between males and females).

5.5 The EWG discussed the possible requirements for future 1-dose and 2-dose studies (e.g. persistence of infection and persistence of antibodies in 1-dose studies). The EWG enquired as to what animal studies could be done to investigate this. The EWG considered whether 1-dose human studies would require longer-term follow-up on immunogenicity.

5.6 The MHRA confirmed that based on the rolling review data submitted in this sequence, there is no indication of whether the company will come to MHRA with a proposal for a 1-dose or 2-dose vaccine.

5.7 The EWG heard that data regarding the effects of SARS CoV2 challenge in vaccinated hamsters will be provided in sequence 2, due by the end of January. The EWG agreed that this data would provide a better understanding of immunogenicity.

The EWG concluded that the non-clinical package submitted so far was promising, but more data would be required, as outlined above.

6. Clinical AR – Update on AZD1222 efficacy and immunogenicity

6.1 The EWG viewed slides and heard a presentation on updated AZD1222 efficacy and additional immunogenicity data.

6.2 The EWG noted that efficacy was approximately 78% at dosing interval of 12 weeks or more and approximately 55% at dosing intervals of 4 to 8 weeks. However, not enough data is available to amend the dosing intervals at this stage. The EWG was concerned that early homologous boosting was confusing the data that were being presented.

6.3 The EWG discussed the available information on the clinical trial participants from South Africa and Brazil with regards to reinfection following vaccination, especially in terms of the new variants in those countries. The EWG noted that current data which depicts this sort of information is not available, however, will be requested from the company.

6.4 The EWG requested long-term data to be made available on the time of events in terms of infection to the time of vaccination in order to analyse the trends in infection rates. The EWG asked if more data would be made available on asymptomatic carriers.

6.5 The EWG noted that PHE are performing weekly analysis and will provide Pillar testing data versus vaccine records by mid-February.

6.6 The EWG concluded that the efficacy results were reassuring. The EWG advised that the product information (Information for Healthcare Professionals, Information for Recipients of the Vaccine and UK Public Assessment Report) should be amended to include updates on the age and dosage interval efficacy data based on the study data submitted; however, it was advised to wait for further data from the US (due in March) before considering a change in the dose interval recommendation in section 4.2 of the HCP information.

7. Verbal update on trends in reactogenic adverse reactions with the Pfizer and AZ vaccines

7.1 The EWG heard an update on the reactogenic adverse reactions in participants who received the Pfizer/BioNTech and the AZ COVID-19 vaccines. The EWG heard that a higher proportion of reactogenicity events had been reported in younger recipients of the vaccine.

7.2 The EWG heard that a comparison of the data collected from the Yellow Cards for the flu vaccine from 2011 up to the present day was compared against the data collected and reported for the Pfizer/BioNTech and the AZ COVID-19 vaccines. Analysis of the data was made using reports which were flagged as serious. Serious events were defined as causing disability and incapacitation, being life-threatening, causing hospitalisation, death or other (which includes definitions such as the inability to carry out daily activities).

7.3 The EWG heard that from the data collected, the cases flagged as serious (serious as defined within the categories mentioned above) were 42% for AZ vaccine and 34% from the Pfizer/BioNTech data and 48% for the flu vaccine. Within those figures, the proportion of each type of event was similar between the AZ and Pfizer/BioNTech, and slightly higher for the flu vaccines. For example, disability and incapacitation was observed in 6.5%, 6% and 9% of AZ, Pfizer and flu vaccine recipients, respectively.

7.4 The EWG heard that the frequency of serious reports flagged for the AZ vaccine was slightly higher than that for the Pfizer/BioNTech vaccine; however this figure was similar to the figure reported for the flu vaccine. The types of serious events observed with the vaccine were also comparable with those observed with the flu vaccine, typically reactogenicity (e.g. headache, myalgia, pyrexia).

7.5 It was also noted that the proportion reporting serious events was much higher amongst the under 65 age group versus over 65 age group. Similarly, for the type of serious event, the frequency of reporting was higher in the under 65 age group than the over 65 age group. For example, of the disability/incapacitation occurring in recipients of the Pfizer vaccine, 82% were under 65, and 84% for recipients of the AZ vaccine, and 55% for the flu vaccine. The potential for higher reporting was assumed to be in part due to more awareness in the younger age group regarding the yellow card scheme (particularly as a lot of these will be healthcare workers) and access to technology. However, further stratification of these events by age group is needed.

7.6 During the clinical trials, reactogenicity events were more frequently reported in the under 65 age group, although serious events in general were reported in the over 65 age group.

7.7 Preliminary information from the Zoe app shows a higher proportion of reactogenicity in those recipients of the Pfizer/BioNTech vaccine that have had previous COVID-19 infection (which was not reflected in the clinical trial data) and also in recipients after the second dose of vaccine. This data is also corroborated by the Yellow Card data. PHE does have a cohort of patients with prior COVID-19 infection confirmed by antibody testing, who could be useful in comparing with these data.

7.8 The increased reactogenicity observed in the under 65 age group is thought to correspond with a stronger immune response in this age group.

7.9 The EWG was informed that so far there has been no indication of a decrease of recipients under 65 refusing any of the vaccines because of the increased occurrence of reactogenicity events. However, it is something that will need careful monitoring and communication to ensure that it does not affect uptake of the vaccines in this age group.

7.10 The EWG noted that further data is being collected in terms of Yellow Card vaccine monitoring, and ongoing collaborations are present with PHE, and data from surveillance applications such as monitoring of the ZOE app. The EWG also noted the potential bias of reporting using Yellow Card towards more severe/serious events.

7.11 The EWG enquired about the current stage of the Yellow Card vaccine monitor, which recruits individuals who have been invited for vaccination. Invitations have been sent out to recipients and it is being considered whether to add questions concerning prior COVID-19 infection, but there is a concern as to how reliable that data will be. Apps have been launched in the US and Germany, which will also provide useful data.

7.12 The EWG raised concerns that there could be an under-reporting of events, especially from healthcare professionals, who may be more reluctant to report on themselves, even with increased familiarity of Yellow Card.

7.13 The EWG concluded that the data was on interest, as part of an ongoing monitoring of events experienced by recipients of the vaccines.

8. Verbal overview of safety data with AZ

8.1 The EWG heard that the AZ vaccine was authorised on 4 January 2021. To date, up to 1.6 million vaccines have been administered. It was noted that up to 25 January 2021, the MHRA has received 68069 ADR reports (~4 Yellow Card reports per 1000 doses). Reactogenicity reports were as expected, including ADRs such as headaches, chills, nausea, and injection site reactions. As had been mentioned previously, these were more prevalent in younger vaccine recipients, who were also predominantly healthcare professionals. A reduction in reactogenicity with the second dose has been observed with the AZ vaccine in clinical trials, but it is not possible to analyse this effect properly at this time. A small overall population of vaccinated recipients have reported reactogenicity symptoms (less than 0.5% of the population reporting as serious events).

8.2 The EWG heard that 36 fatal cases had been reported, most of which affected frail elderly care home residents with end stage diseases. As a result, it was noted that a number of reports were being submitted where an association with vaccination was not necessarily suspected but the reporter considered it good practice to report given the temporality of the fatality with vaccination.

8.3 The EWG heard events of special interest were also being reported; 10 cases reported facial paralysis but not all cases of facial paralysis were consistent with Bell's palsy with some describing facial numbness.

8.4 The EWG heard that one case of transverse myelitis had also been reported. This event was also reported in the clinical trials and is an adverse event of special interest.

8.5 The EWG confirmed further monitoring is taking place for all neurological adverse drug reactions via detailed follow up forms to help understand the exact nature of these adverse drug reactions.

8.6 The EWG noted that at the request of the FDA, AstraZeneca was requested to set up an independent panel to monitor the neurological adverse drug reactions of this vaccine. The panel considered that MHRA and the EWG should also be kept informed of its findings.

8.7 MHRA confirmed that a paper would be submitted to the EWG for next week's meeting.

9. Anaphylaxis data for AstraZeneca

9.1 The EWG heard a brief update on the anaphylaxis data for the AZ vaccine. They heard that although this vaccine does not contain the polyethylene glycol (PEG) component of the mRNA vaccines which can cause severe anaphylaxis, it does however contain a component known as polysorbate which is cross reactive with PEG.

9.2 The EWG heard that unlike PEG, polysorbate has been used as an excipient in other biological medicines as well vaccines used in the routine immunisation schedule (e.g. Fluad), Fluad has been part of the UK's annual influenza vaccination campaign for the past three years and millions of doses have been administered and no signal of anaphylaxis has been detected to date.

9.3 The EWG also heard that no signal for anaphylaxis was seen in clinical trials.

9.4 The EWG heard that a total of 14 cases reporting anaphylactic or anaphylactoid reactions were reported to the MHRA. Only a small proportion of cases reported immediate onset following vaccination (i.e. within 30 minutes of vaccination). Most cases did not appear to have the same level of severity as cases seen with the Pfizer vaccine and a specific waiting time after vaccination, as is in place for the Pfizer vaccine, was not deemed necessary at this point. In addition to this, current evidence on polysorbate as a vaccine excipient does not suggest that we would expect the rate of anaphylaxis to be increased with the AZ vaccine and clinical trial data did not identify any cases of anaphylaxis which were likely related to the vaccine.

9.5 The EWG heard that a number of hypersensitivity reactions were being reported post authorisation. It was noted that this reaction was also seen in the clinical trials.

9.6 The EWG noted that the frequency of anaphylaxis is more frequent in the Pfizer/BioNTech vaccine. The EWG considered that there was no strong basis for the inclusion of anaphylaxis in the product information and the 15 minute onset time noted with the Pfizer vaccine; however, it was agreed that the inclusion of any wording in the product information should be discussed with company. With regards to the inclusion of information for quantifying anaphylaxis in the Information for Healthcare Professionals, the EWG requested a proposal on appropriate wording that would not cause further alarm to the patient. The EWG was concerned to strike the right balance between informing patients and worrying them.

9.7 The EWG agreed a discussion with the company should take place to review cases indicative of hypersensitivity and/or angioedema that have been received in the post-authorisation setting and to determine if updates to the product information are needed.

10. Update on anaphylaxis data for mRNA COVID-19 vaccines

10.1 The EWG heard a brief update to the Yellow Card data reported for the Pfizer/BioNTech vaccine.

10.2 The EWG heard that up to 25 January 2021, the MHRA has received a total of 90 reports with the preferred term (PT) anaphylaxis, 6 with the PT anaphylactoid reaction, and 2 each for anaphylactic shock and anaphylactoid shock following the Pfizer/BioNTech vaccine. A reporting rate of 1.8 cases per 100,000 doses is estimated in the UK based on these cases. Overall, spontaneous reporting in the UK has maintained a similar pattern of events with an onset largely within 15 minutes of vaccine administration and with no particular history of allergic reactions in the cases.

10.3 The EWG heard that although Moderna's COVID-19 vaccine is not yet available in the UK, a review of post marketing data from the US by the CDC provided an estimate of 2.5 cases per million doses of the Moderna vaccine. The CDC has estimated approximately 0.5 cases per 1 million doses with the Pfizer/BioNTech vaccine.

10.4 The EWG heard that this is lower than the estimates of UK rates for the Pfizer/BioNTech vaccine, and agreed, that this was due to the differences in the criteria for determining the rates, with the US analysis excluding a high number of cases by using the Brighton Collaboration criteria, and so any comparison should be treated with caution.

10.5 The EWG noted that anaphylaxis is already listed as an identified risk in the Moderna risk management plan (RMP) and therefore do not propose new safety advice.

10.6 The EWG reiterated that the data presented on anaphylaxis following the Moderna and Pfizer COVID-19 Vaccine does not indicate any new safety concerns with these products and that the current advice on anaphylaxis and allergic reactions are still supported by the available data for both these vaccines.

10.7 The EWG heard that the UK RMP for the Pfizer/BioNTech vaccine does not currently include anaphylaxis as an important identified risk, however this is included in the EU RMP which was authorised after the UK's authorisation of this vaccine.

10.8 The EWG discussed that the UK RMP should be updated to include anaphylaxis as an important identified risk, bringing the information in line with the warnings depicted in the SmPC and further bringing the information in line with the EU RMP.

11. <u>Any Other Business</u>

None.

12. <u>Date and time of next meeting</u>

The next meeting is scheduled to take place on Thursday 4th February 2021 at 10:30.

The Meeting today started at 13:33 and ended at 17:32

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NOT FOR PUBLICATION

COMMISSION ON HUMAN MEDICINES (CHM)

COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Thursday 4th February 2021** at **10:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan[1]
Professor N French
Professor D Goldblatt
Ms S Hunneyball[2]
Professor K Hyrich
Sir M Jacobs[2]
Professor P J Lehner
Dr S Misbah
Professor S Price
Dr A Riordan
Professor C Robertson
Professor P Shah
Professor T Solomon[3]
Dr R Thorpe
Mrs M Wang
Professor C Weir

Apologies

Professor H J Lachmann

Member of the CTBV Expert Advisory Group

Professor B K Park

Members of the CPS Expert Advisory Group

Mr VI G Fenton-May
Professor K M G Taylor (Chair of CPS)
Dr S Walsh

Invited Expert

[redacted][4]

Secretariat

[redacted]

MHRA Observers continued

[redacted] - LD
[redacted] - LD

[1] Joined during item 2
[2] Left after item 5
[3] Left during item 4
[4] Presented item 2 & left after this item

Professional Staff of MHRA Present

Principal Assessors[5]

Dr J Bonnerjea - LD
Dr P Bryan - VRMM

MHRA Presenters supporting specific items[5]

[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - VRMM

MHRA Observers

[redacted] - VRMM
[redacted] - LD
[redacted] - LD
Dr S Branch - VRMM
[redacted] - VRMM
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[redacted] - LD
[redacted] - VRMM
Ms N Rose - MHRA-NIBSC
[redacted] - LD
[redacted] - LD
[redacted] - VRMM
Mr P Tregunno - VRMM
[redacted] - Government Legal Team
[redacted] - MHRA-NIBSC

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[5] supporting specific items

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Dr Riordan - Other relevant interests - Participant in Oxford University's ChAdOx1 nCoV-19 clinical trial –received immunisation 27/8/2020. NPNS - Postgraduate External Examiner for Oxford University (Postgraduate Diploma in Paediatric Infectious Diseases)

Professor Solomon - Other relevant interests – Professor Solomon provides clinical care for patients with Covid-19; chaired the MRC/NIHR committee which awarded funding for development of the Oxford Vaccine.

Mrs Wang – Personal interests arising from being highly sensitive to insect stings, and plant products such as Hyacinth bulbs, which are recorded on Mrs Wang's medical records.

Professor Weir - NPNS - Imperial College and Other relevant interest arising from his department collaborates with Imperial College on a number of clinical trials.

CTBV

Professor Park - NPNS in GSK Research & Development Ltd. and in Janssen as I received a research grant in the past two years. The grant has been handed over to a colleague in 2020 and the grant is due to finish in 2020. Professor Park received no direct payment. In addition, Professor Park have two active IMI grants for Transbioline and Quantitative Systems Toxicology, he is the PI on the TransBioline grant for the University of Liverpool. Both grants are paid directly to the University of Liverpool.

CPS

Mr V'lain Fenton-May – None
Professor Kevin Taylor – None
Dr Susannah Walsh – None

1.4 The Chair welcomed [redacted] from ZOE, Kings College London

2. ZOE App and suspected adverse events

2.1 The EWG heard from [redacted] on the preliminary analysis of the occurrence of adverse effects and reduction of SARS-CoV-2 positivity rate, based on the data provided by contributors to the ZOE/KCL COVID Symptom study. On 4th December 2020, questions on vaccination were made available to users of the app. Most of the ~4.5 million users are located in the UK. 1.5 million log data each week, and many of these have been reporting via the app since April 2020.

2.2 ~300,000 users had logged their vaccine; most were white and BAME populations were underrepresented. A high number of healthcare professionals reported regularly (45,000). Post vaccination PCR tests have been reported from 51,763 contributors while a much smaller proportion had antibody tests (1,654).

2.3 The first analysis focused on data from 40,000 mainly healthcare professionals who had received the Pfizer/BioNTech vaccine - at cut off ~23,000 first dose only (65%), and ~12,000 (35%) first and second dose. Local and systemic adverse effects were studied. Systemic effects were more frequent after the 2nd injection, (~11.1% reported at least one systemic adverse effect after the 1st dose versus ~19.7% same reporting measure after the 2nd dose). Systemic adverse effects were headache, fatigue, chills, shivering, diarrhoea, fever, arthralgia, myalgia, and nausea. The data were fairly consistent with the clinical trial data for the vaccine. Contributors who had COVID in the past were more almost twice as likely to have at least one systemic adverse effect (~33% vs ~19%). Younger users <55 years also reported more systemic effects (~25% vs ~13% in those >55 years), possibly due to a reduced immune response in older people. The most frequent adverse effects are fatigue and headache, and aftereffects tend to resolve after 2-5 days, although ~2% continued for longer.

2.4 Local adverse effects were pain that is localised, swelling, tenderness, redness, itch, warmth, proximal lymphadenopathy; these effects were short lasting (most lasting 3 days or less) and highly similar in both rate and type to those reported in the clinical trial. Local effects were more common after the 2nd dose. It should be noted that check box lists of adverse events were displayed to users, and the list was developed in collaboration with virologists and the Pfizer BioNTech clinical trial investigators. A free text box was also included under the category of other, to enable reporting of effects outside of the predefined list. Female contributors reported more adverse effects (both local and systemic).

2.5 The re-infection rates post Pfizer/BioNTech vaccination increased during the period 5-12 days after vaccination. The increase was suspected to be due to the window where there is no protection as the immune response has not had time to develop combined with a potentially higher risk of exposure, on travelling en route to and from vaccination centres / clinics, and possibly increased socialisation due to a false perception of immediate protection. After 12 days and adjusted for the background decrease in cases, an approximate reduction in infections in the vaccinated group of contributors of approximately 50% was observed.

2.6 Future analyses are planned to investigate similar parameters for the AstraZeneca vaccine and compare these to the Pfizer/BioNTech data. Questions to be explored included if past COVID may remove the need for a 2nd dose, the biological vaccine response in long COVID and responses in BAME vaccine recipients, to work with the MHRA to enhance reporting of rare side effects, and to explore the duration of protection through natural exposure and vaccine-based protection. In the invited experts closing remarks, attention was drawn to the limited NHS promotion of the app, for example at vaccination centres and other NHS platforms, despite Chief Medical Officer (CMO) support.

2.7 Questions and Answers

2.7.1 The Commission heard it will be explored if there is a relationship between the time interval from natural infection to vaccination, and if this affects the likelihood of developing systemic side effects. There is a hypothesis that vaccine recipients with a longer interval between natural infection and vaccination may experience reduced vaccination side effects, which may be attributed to waning immunity.

2.7.2 The Commission heard the vast majority of healthcare workers tested for COVID-19 post vaccination were symptomatic according to the app's symptom criteria which includes a greater list of symptoms compared with that used by Public Health England (PHE). The Commission noted that the post vaccination infection rate was similar to that observed in vaccine effect studies conducted in Scotland, and Professor Tim Spector requested access to any other relevant epidemiological data sets.

2.7.3 The Commission noted it may be beneficial on a precautionary basis, to calculate the number contributors that reported (resolved) infection prior to vaccination as a positive control when analysing the 5-12 day post vaccination infection data. If the proportion who had prior infection is high, there would be expected to be a degree of immunity, this could help to eliminate social factors and other routes of elevated exposure as causes.

2.7.4 The Commission heard messaging at the point of vaccination seems to focus on managing of common aftereffects, and perhaps, neglects to reinforce the message that no additional protection against infection will be acquired until at least 12 days after vaccination.

2.7.5 The Commission heard the Zoe app currently does not request information on use of analgesics including paracetamol by contributors to manage vaccine aftereffects, but this could be potentially added.

2.7.6 The Commission asked if any contributors have reported anaphylaxis or severe systemic reactions. No events have been seen so far, although the review of the other column is still incomplete. There is also another limitation that contributors may be unlikely to report severe systemic reactions due to their condition and perhaps due to the knowledge that the healthcare professional should report via the Yellow Card Scheme. Contributors might also report once they have recovered, so there could be a time lag. Data on localised allergic reactions is being collected and can be provided in due course. Professor Tim Spector was also keen for the MHRA to highlight any potential side of effects of special interest or rare side effects that could be investigated further using the app's data sets. Data from the CDC and MHRA indicate rates of anaphylaxis to be ~1 in 100,000 for PfizerBioNTech vaccine recipients.

2.7.7 The vaccinated cohort appear well motivated and drop-out rates from the app are low, users consistently and frequently engage with the app, and other materials on the affiliated website, e.g. a webinar with 100,000 attendees; frequent feedback also helps retain contributors. Complete data is preferred and generally contributors that drop-out are not included in the analyses.

2.7.8 The app includes a system to permit reporting on behalf of elderly relatives: ~300,000 users are in this group. The median age of contributors is ~55 years so the coverage of the JCVI priority list is relatively good, although a full proportional analysis is needed. The Commission heard that symptoms and severity of symptoms could be further defined / sub-divided in the app's checklist, where the MHRA feels it may be useful, e.g. in line with emerging signals to improve granularity of the data. The need to gather more detailed information needs to be balanced against the risk of dissuading users / lowering compliance if reporting takes too long, for example if symptom lists are too exhaustive. An alternative option would be to email all contributors reporting a specific symptom and ask them to provide a detailed narrative.

2.7.9 MHRA and [redacted] agreed that continued liaison between the VRMM and the King's College team is beneficial and should be continued, including to discuss data linkage.

2.7.10 The MHRA was asked to assist with facilitating promotion of the app through the NHS.

2.7.11 The Chair gave thanks [redacted] for the valuable contributions Kings College and ZOE are making to increase data collection and analysis to help further understanding of COVID-19.

3. Bell's palsy and myocarditis rapid cycle analysis and observed vs expected

3.1 The EWG discussed a paper which presented summaries of the most recent epidemiological analyses of the incidence of Bell's palsy and myocarditis or pericarditis following COVID-19 vaccination. The EWG heard updates on the observed vs expected analyses of Yellow Card reports and the rapid cycle analysis being conducted in the Clinical Practice Research Datalink (CPRD).

3.2 The analyses specific to Bell's Palsy were described and the EWG discussed the inconsistent results. In particular, they discussed the finding within the rapid cycle analysis which suggested a higher observed number of cases of Bell's Palsy in the 42 days following the first dose of the Pfizer/BioNTech vaccine than expected based on age-specific background risks of Bell's Palsy calculated in the CPRD primary care data.

3.3 The EWG agreed that there were limitations to the analyses and as such they did not provide evidence of an increased risk of Bell's Palsy and should be treated with caution. However, they were broadly supportive of the initiation of a more robust epidemiological study to further explore the issue. They noted that such a study would allow for more careful case definition and identification and advised that sensitivity analyses should be conducted around the risk window. The EWG agreed that monitoring of Bell's Palsy should also continue with further consideration of incidence rates following the second dose of the vaccine.

3.4 The analyses specific to myocarditis/pericarditis were also described and the EWG discussed the statistical signal of an increased incidence in the 42 days following the first dose of the Pfizer/BioNTech vaccine in the rapid cycle analyses. It was noted that this was based on a small number of cases.

3.5 It was agreed that this was likely to be a chance finding given the body of evidence but that monitoring of myocarditis should continue given the overlap with multisystem inflammatory syndrome seen predominantly in paediatric patients with COVID-19 infection.

4. Trends in reactogenic adverse reactions with the Pfizer and AZ vaccines

4.1 The EWG was presented with a summary of Yellow Card data for the Pfizer/BioNTech and AstraZeneca COVID-19 vaccines focusing on cases capturing one of the relevant serious criteria available; hospitalised, life threatening, fatal, disability/incapacitation and "other" medically significant such as affecting everyday activities. The meeting commented on how subjective these categories can be for recording the severity of reactions.

4.2 The meeting heard that a higher proportion of cases reporting any serous criteria was identified for the AstraZeneca COVID-19 vaccine compared to the Pfizer/BioNTech vaccine, and that this difference was largely related to the more moderate "other" serious criteria. The types of events most commonly reported for both of the COVID-19 vaccine related to reactogenicity side effects known to be associated with the vaccines. It was noted that a higher proportion of cases are reported in females compared to males, and the meeting commented that this has been seen with other vaccines too and the potential biases behind this were discussed.

4.3 Compared with Yellow Card data available on the flu vaccine for the past 10 years, there is higher proportion of serious reports for the flu vaccine compared to the COVID-19 vaccine. The nature of the events reported in the serious categories was similar between the flu vaccine and the COVID-19 vaccines. The frequency and nature of events reported for the Pfizer/BioNTech COVID-19 vaccine was also similar to data provided by the ZOE COVID Symptom Study and US data published by the CDC.

4.4 The meeting was presented with the reporting rates broken down by age groups based on usage data of both COVID-19 vaccines, which showed a higher proportion of serious events reported in younger age groups, particularly in the "other criteria" and largely representing reactogenicity events. Similarly, clinical trial data for both vaccines showed a higher proportion of reactogenicity events being reported in the younger age groups. In comparison with the flu vaccine data, there is not such a pronounced difference in younger age groups. The meeting discussed which reporting biases may be contributing to this difference.

4.5 The meeting was also presented with Yellow Card data suggestive of a higher proportion of serious events reported following the second dose of the Pfizer/BioNTech vaccine compared to that reported with any dose. This is similar to data from the clinical trials and that reported from the ZOE COVID Symptom Study and US data published by the CDC. There is limited data to conduct a similar analysis with the AstraZeneca vaccine; a higher frequency of events with the second was not observed in the clinical trials.

4.6 The meeting discussed the available data on use in those with prior-COVID-19 infection and it was noted by the meeting that the MHRA were engaged with PHE on how best to gather further data on this topic. The meeting also considered the need for a second dose of the COVID-19 vaccines in those with prior-COVID infection and that further data was needed before any conclusions could be drawn.

4.7 The meeting agreed with the conclusions presented in the paper and that the data did not indicate any new safety concern for either of the COVID-19 vaccines currently in use.

5. General safety update for the AZ vaccine

5.1 The meeting heard an overview of the safety of the AstraZeneca Covid-19 vaccine as described by Yellow Card reports. The meeting heard that up to the end of 31st January 2021, an estimated 3,098,605 doses of COVID-19 Vaccine AstraZeneca have been given

in the UK. Up to 28th January 2021, the MHRA has received a total of 9681 reports of suspected ADRs in association with COVID-19 Vaccine AstraZeneca.

5.2 The reactions reported most frequently are common reactogenicity reactions seen with all vaccines as well as in the AstraZeneca clinical trials. These terms, or associated umbrella terms are labelled in the product information.

5.3 63 fatal cases were received, with most occurring in patients aged 80+ and with underlying comorbidities.

5.4 The meeting heard that cases of Bell's Palsy and transverse myelitis, which are adverse events of special interest, had been received. These are being monitored closely and Observed vs Expected and Rapid Cycle analyses are also being performed.

5.5 Overall, the ADR data was broadly in line with the safety profile seen in clinical trials. Review of the cumulative data does not identify any new safety signals.

5.6 The EWG found the safety data reassuring.

5.7 The EWG commented regarding anaphylaxis that a recent case had been identified of a patient who experienced anaphylaxis with a biological medicine and had a strong reaction upon skin testing to both polysorbate and PEG.

5.8 Regarding transverse myelitis, the meeting commented that we may not see all cases of transverse myelitis reported via the Yellow Card Scheme and that these may be seen in hospital. Observed vs Expected and Rapid Cycle analyses will also be important to pick up additional cases, but hospital admission and discharge data could be important in identifying cases.

5.9 The meeting suggested that use of prophylactic paracetamol could be proposed to reduce the number of adverse events experienced. However, it was recalled that the data regarding use of prophylactic paracetamol in clinical trials was limited and this was only recorded in a small number of participants. This data therefore could not be used to recommend prophylactic use.

6. Verbal update on Yellow Card Vaccine Monitor

6.1 The EWG was provided with an update on enrolment of individuals to the Yellow Card Vaccine Monitor (YCVM), part of the MHRA pharmacovigilance surveillance strategy for the COVID-19 vaccines.

6.2 The EWG heard that individuals are recruited through the national call-recall process for vaccinations and receive a letter following the national call inviting them for vaccination. The EWG heard that many individuals also receive invitations through local call-recall processes that the MHRA is considering linking into.

6.3 The EWG heard to date approximately 120,000 invites to register with the YCVM platform have been posted with the aim of enrolling 10,000 individuals in total.

6.4 The EWG heard that approximately 8,000 individuals have registered with the YCVM platform to date. The EWG also heard that an equal proportion of men and women have registered and 92% are aged 70 years and over. The EWG noted the proportion of younger people registered should increase once the priority groups have been vaccinated.

6.5 The EWG heard that around 92% of individuals registered were of white British or white Irish ethnicity and that consideration is being given to increasing the representation of other ethnic groups.

6.6 The EWG heard that of the 8,000 individuals registered, approximately 4,000 have entered details regarding their first vaccine dose and that an equal proportion have received the Pfizer-BioNTech or Oxford AstraZeneca vaccines as their first dose.

6.7 The EWG heard that a small proportion of immunocompromised individuals have registered, and it is anticipated this number will increase as this group is called in for vaccination.

6.8 The EWG considered the importance of this data collection and promotion of the YCVM platform could occur at the point of vaccination and continue throughout the vaccination programme to maximise numbers contributing to the platform.

6.9 The EWG noted that epidemiological studies and rapid cycle analyses form will enable linkage to hospital admission data with the YCVM data important as an additional data source providing long-term follow-up.

7. Verbal update on Janssen Vaccine Quality issues

7.1 The Commission heard two rolling review cycles have been undertaken in order to review the data on the Janssen vaccine provided so far. The data reviewed was of high quality, and no unresolvable issues are currently envisaged by the quality assessment team. Certificates of Analysis for small commercial-scale process performance qualification (PPQ) batches are not expected until after the 22nd February 2021. The February data package is also expected to include details of manufacturing scale-up. Comprehensive comparability data for scaled-up supply is not expected until early March and is intended to be assessed by variation to the conditional marketing authorisation, if given. There are no concerns presently in relation to the finished product stability data, and preliminary data showed that the product is stable to at least 6 weeks at room temperature.

7.2 In terms, of resolvable issues, an out-of-date GMP certificate dated 2017 has been provided for the drug substance manufacturing site, likely due to COVID related delays to the next planned inspection. Some key release potency acceptance criteria are also wider than those specified for the clinical trial material, and therefore an in-depth clinical justification of the wider limits will be required. The company have requested that no questions are to be sent by the MHRA, until the MHRA have been sent the questions/assessment reports from the European Medicines Agency (EMA).

7.3 The Chair conveyed to members that data package would likely be available to be seen by the EWG by late February/early March 2021, depending on when the data have been submitted and assessed (and potentially when the EMA's assessment has been received).

8. Any Other Business

8.1 None.

9. Date and time of next meeting

The next meeting is scheduled to take place on Monday 15th February 2021 at 10:30.

The Meeting today started at 10:34 and ended at 12:51

[redacted]

19th July 2021

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NOT FOR PUBLICATION

COMMISSION ON HUMAN MEDICINES (CHM)

COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Monday 15th February 2021** at **10:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer[1]
Professor G Dougan
Professor N French[1]
Professor D Goldblatt[2]
Ms S Hunneyball
Professor K Hyrich
Sir M Jacobs
Professor H J Lachmann[2]
Professor P J Lehner
Dr S Misbah
Professor S Price
Dr A Riordan
Professor C Robertson[2]
Professor P Shah
Dr R Thorpe
Mrs M Wang
Professor C Weir

Apologies

Professor T Solomon

Member of the CTBV Expert Advisory Group

Professor B K Park
Professor M Turner

Members of the CPS Expert Advisory Group

Mr VI G Fenton-May
Mr R Lowe
Professor Y Perrie
Professor K M G Taylor (Chair of CPS)
Dr S Walsh[1]

Invited Expert

[redacted][3]

Observers

[redacted]

Secretariat

[redacted]

[1] Left during item 9
[2] Left during item 8 & [3] supporting specific items

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD

MHRA Presenters supporting specific items[3]

[redacted] - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - MHRA-NIBSC
[redacted] - LD

MHRA Observers

[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - LD
Dr S Branch - VRMM
[redacted] - LD
[redacted] - MHRA-NIBSC
[redacted] - VRMM
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[redacted] - MHRA-Policy
[redacted] - LD
Mr K McDonald - LD
Ms T Moore - IE&S
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - MHRA-NIBSC
Ms N Rose - MHRA-NIBSC
[redacted] - LD
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[redacted] - LD

Key

LD = Licensing Division
NIBSC = National Institute for Biological Standards & Control
VRMM = Vigilance & Risk Management of Medicines
CTBV = Clinical Trials, Biologicals & Vaccines EAG
CPS = Chemistry, Pharmacy & Standards EAG
IE&S = Inspection, Enforcement & Standards

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Professor Lachmann – Other relevant interest as a volunteer participant in the Oxford vaccine study and no other involvement in the study.

Professor Lehner - Other relevant interest – Professor Lehner previously held a DPAC (Discovery Partnership with Academia) agreement with GSK, but this has been completed. Professor Lehner's participation in his local hospital D and T governance committee deliberations would form the normal activity and professional responsibility in his post and does not interfere with the EWG considerations (Sept 2020).

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CTBV

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Professor Turner – NPNS interest. Professor Turner is a Non Executive Director (non-remunerated) on the Board of the Cell and Gene Therapy Catapult (CGT) until the end of March. CGT have been tasked by UK Government with re-purposing a factory in Braintree to manufacture either a vaccine or a therapeutic mAb. No decision has been made as to whether or what product CGT Braintree may be asked to manufacture and that decision will be made by UK Government. Professor Turner does not believe that CGT Board will have any material input into the decision as to what product may be manufactured. Rentschler have signed a contract with the Cell and Gene Therapy Catapult (CGT) to rent

one of the manufacturing clean room suites at the Stevenage Centre. Professor Turner understands that this will be for contract AAV manufacture.

CPS

Mr V'lain Fenton-May – None

Mr Robert Lowe – None

Professor Yvonne Perrie - NPNS in Pfizer & AstraZeneca arising from a contract for a grant (March 2018), which includes contributions from these companies to the University of Strathclyde, Janssen in writing a grant for a PhD (now funded), GSK – arising from an EU grant to University of Strathclyde (Jan 2019-Dec 2019).

Professor Kevin Taylor – None

Dr Susannah Walsh – None

1.4 Apologies were received from Professor Solomon for the meeting today.

1.5 The Chair welcomed [redacted] from PHE as an Invited expert for Item 2 - Update on Impact Surveillance. [redacted] left the meeting after his presentation.

1.6 The Chair also welcomed [redacted] of HSCNI and [redacted] of Public Health Wales as Observers for Items 4 & 5. The Observers left after item 5.

2. Update on Impact Surveillance

2.1 The EWG viewed slides and heard a presentation from Public Health England (PHE) on an update on Impact Surveillance. A presentation three weeks earlier consisted of analysis on Pillar 1 and Pillar 2 routine testing data. This update concerns data analyses from Pillar 1 and Pillar 2 data, SIREN (Sarscov2 Immunity and REinfection EvaluatioN) study data, the Severe Acute Respiratory Infection (SARI)-Watch surveillance system and the Royal College of GP (RCGP) Database.

2.2 Pillar 1 and Pillar 2 update

2.2.1 The EWG heard an update on the analysis of available Pillar 1 and Pillar 2 data; the data is linked to the National Immunisation Management Service (NIMS) database. The focus of the analysis was vaccine effectiveness (VE) for Pfizer and AstraZeneca (AZ) vaccines, rather than any impact analyses data.

2.2.2 The EWG heard that the Pillar update includes new data for AZ, the over 70s cohort population, analysis of cohorts with repeat testing and care home analysis.

2.2.3 In summary, PHE reported that VE against symptomatic diseases reaches 60-65% in the over 70s and ≤ 65 HSCW (health and social care workers) after the first Pfizer dose. There is a continued apparent reduction from day 35, but continued monitoring is required to discount any possible bias. After the second Pfizer dose, VE reaches approximately 85% in the over 70s and approximately 90% in < 65 HSCW. The VE of the AZ dose against symptomatic disease was shown to increase from 21 days.

2.2.4 EWG also heard that interim analysis of the data showed (i) preliminary evidence of VE against infection from Pfizer vaccine in HSCW (stronger evidence provided in the Siren data,

see below) and care home residents (ii) preliminary evidence of VE against infection from AZ in HSCW but not yet in care home residents (iii) Evidence of reduced mortality in vaccinated cases (Pfizer).

2.3 SIREN update

2.3.1 EWG heard that for this update the vaccination data sources were National Immunisation Management Service (NIMS) dataset and self-reporting via Siren questionnaires.

2.3.2 EWG heard that participants were assigned to cohort based on baseline antibody status (at 07 December 2020); positive cohort participants - antibody positive or evidence of infection and negative cohort – antibody negative and no previous positive test. The outcome for analysis was infection (positive Polymerase chain reduction test; PCR+) in the negative cohort.

2.3.3 EWG heard that this study had better defined cohorts of under 65 HSCW than that found in the Pillar cohorts.

2.3.4 The EWG heard that the Siren interim data showed vaccine effectiveness of 60-74% against infection at 21 days after a single dose of Pfizer vaccine in the negative cohort. The invited PHE expert indicated that future analyses may include symptomatic infection and hospitalisation.

2.4 Cohort analysis within the Royal College of General Practitioners (RCGP) Database

2.4.1 EWG heard that PHE conducted an analysis within the RCGP database, which is a General Practitioner (GP) cohort dataset. This database allows adjustment for more variables than is possible with the Pillar data, while still using the PCR-positive data that arise from the Pillar data. Initial analyses included the 80+ population, over the period 07/12/2020 – 24/01/2020 who tested PCR-positive and had a GP consultation with symptoms/clinical illness consistent with COVID-19 around the time the test was taken. This was compared against a Test-Negative Case Control (TNCC) data set.

2.4.2 PHE concluded that the results from analysis were broadly consistent with routine testing data. VE after one dose was 60-65% and 50% for the TNCC cohort. After two doses, vaccine effectiveness was 85% and 70-75% for the TNCC cohort.

2.4.3 The invited PHE expert indicated that future analyses would focus on VE within clinical risk groups.

2.5 SARI-Watch surveillance system

2.5.1 EWG heard that the Severe Acute Respiratory Infections (SARI)-Watch is the surveillance system for new Covid 19 hospitalisations.

2.5.2 EWG heard that analysis was restricted to elderly with Covid with symptoms. Hospitalisations were matched against the National Immunisation Management Service (for vaccination status with the Pfizer vaccine), age, sex, geographic region and period. The data was not adjusted for care home residents.

2.5.3 PHE reported that preliminary evidence shows that Pfizer vaccine is effective at preventing hospitalisation in patients in the 80+ age group (75%-80% reduction), compared to those that had not been vaccinated. It should be noted that the low number of hospitalisations seen immediately after vaccination is likely related to the deferral effect, where patients testing positive for Covid-19 or showing symptoms have their vaccinations deferred.

2.5.4 The invited PHE expert concluded overall that the preliminary evidence showed that the Pfizer vaccine was effective in preventing hospitalisations and that evidence through the Pillar 2 mortality analysis showed a lower risk of death in recipients of the Pfizer vaccine.

2.5.5 The PHE expert commented on the potential biases that cause the differences between real world data and trial data.

2.6 EWG discussion/comments

2.6.1 EWG asked whether the invited expert was able to link the efficacy data to variants. PHE stated that early data reflect the older variants and the majority of the data now emerging is against the newer variants. EWG heard that PHE does receive some data from the Lighthouse labs that would allow split along the lines of efficacy against older and newer variants. However, this sub-set of the data shows the same effect, but with wider confidence intervals.

2.6.2 EWG asked the PHE expert whether analysis of the Royal College of General Practitioners (RGCP) data was possible to look at effects on recipients of the vaccine who are on immunosuppressants. The invited expert indicated that this analysis would be conducted alongside other collaborators and result were expected soon.

2.6.3 EWG were interested in possible data to show whether protection is seen a few days after vaccination, which could be related to an adjuvant effect and could be very important to patients who are immunocompromised. The PHE expert thought that there is potential for a lot of bias in the day 0 to 3 data, but that interesting data regarding the severity of symptoms could be shown.

2.6.4 EWG asked for further information on the relationship between immunogenicity and the efficacy of the vaccines, given that some data show that immunogenicity (antibody levels) is lower in the over 65s. The PHE expert stated that they would like to see more antibody data in the over 65s before coming to any conclusions. However, the PHE expert stated that their efficacy results in the over 65s were higher than those seen in the Real-time Assessment of Community Transmission (REACT) study results.

2.6.5 EWG commented that it will be interesting to see the data for the end of February/start of March, i.e., when recipients who received their first dose at vaccine rollout will reach 12 weeks and receive their second dose.

2.6.6 EWG commented on parallel analyses conducted in Scotland and England, where the dataset reliably identified subjects that were known HSCW at time of test. Within this subset, the response was consistent with that presented by PHE over the interval 21 days- 6 weeks. As they have a fifth of the population, the dosing interval is wider in Scotland; however, the pattern is similar.

2.6.7 EWG stated that they looked forward to the next update.

3. Proposed statement on "flu like illness" for Pfizer/BioNTech and AstraZeneca COVID 19 vaccines – Verbal update

3.1 The meeting heard that flu like illness is a recognised side effect of the vaccines, and the EWG had previously discussed and agreed that further communication on this side effect was required to better inform patients on how this might present in patients. The EWG were presented with proposed wording to further characterise "flu like illness" in the information

for UK recipients and healthcare providers for the Pfizer/BioNTech and AstraZeneca COVID-19 vaccines, and for a similar statement to be included in the ADR data publication.

3.2 The EWG supported the inclusion of this statement and the EWG noted that it was important the information was worded in way that would be reassuring to recipients and that the advice is consistent with information provided in other patient leaflets on COVID-19 vaccination produced by the UK healthcare agencies. The EWG considered that the event of heart palpitations required further characterisation before it should be included in the product information for the vaccines.

4. Safety update on Pfizer/BioNTech COVID-19 vaccine

4.1 The EWG was presented with a second safety update for the Pfizer COVID-19 vaccine. The EWG was informed that the ADRs being reported for the vaccine were broadly in line with the known safety profile for the vaccine and that seen in the clinical trials. The EWG also heard that the signal of Bell's palsy has persisted in the observed/expected analysis and that the planned formal epidemiological study was progressing. The EWG were informed that the possible signal of myo/pericarditis which had been detected in the Rapid Cycle Analysis has continued to diminish and was likely a chance finding. The meeting discussed that there was a slightly lower reporting rate in the past month compared to previously and was reassured that promotion of the scheme was ongoing.

4.2 The meeting was presented with a summary of the anaphylaxis reports received through the Yellow Card scheme and related international data, and that the nature and frequency of events is similar to that reported previously for the Pfizer/BioNTech. The meeting discussed concerns from healthcare professionals and the JCVI COVID-19 subcommittee on the risk of transmission related to the 15-minute observation period which was introduced following initial reports of anaphylaxis with the Pfizer/BioNTech COVID-19 vaccine. The EWG acknowledged the practical constraints of the observation time and representatives from HSCNI and PHW noted that there was no direct evidence of increased COVID-19 transmission due to the waiting time. The EWG highlighted that there was limited data on the risk of anaphylaxis with the second dose. The meeting concluded that the 15-minute wait should remain in place until more data is available to support its removal.

4.3 The meeting concluded that of the data presented overall in the safety update that no new safety signal has been identified.

5. Review of fatal reports for the AstraZeneca and Pfizer/BioNTech COVID-19 vaccines

5.1 The EWG was presented with a paper which gave an overview of fatal reports received by MHRA to date. The paper presented cumulative vaccine exposure, broken down by age and discussed the analysis MHRA has performed on fatal reports, as well as international data available. The EWG noted that observed/expected analysis did not indicate an excess of deaths; however, it was acknowledged that these analyses are used with caution to assess mortality.

5.2 The meeting broadly found the data reassuring. It was noted that there was significant under reporting of fatalities to the Yellow Card Scheme and that there can be difficulty in interpreting the data where reports are sparse. The EWG discussed whether Hospital Episode Statistics data could be used to support Yellow Card data but noted that there is a 3 month lag to this data.

5.3 The EWG agreed with the conclusion that there was not a signal indicating an increased risk of death following vaccination.

6. Regulatory approach to new variants – feedback from international regulators' meeting

6.1 The EWG were informed about recent discussions held with other international regulators. While there is broad agreement about a more tailored approach to regulating SARS-Cov2 vaccine variants, it was highlighted that the draft MHRA guidance document required more discussion in its non-clinical and clinical sections. For the non-clinical section, experts emphasized the novelty of the coronavirus and the need, in principle, for a sufficiently large non-clinical database overall. It was appreciated, however, that the extent would depend on the knowledge already gained and the particular format of a given vaccine, and therefore agreed on an approach where absence of non-clinical data, including immunogenicity, will have to be justified by the Applicant. It was agreed that generation of non-clinical data should not delay the development and introduction of updated coronavirus vaccines. It was highlighted that SARS-Cov2 variants which are adapting to humans may be less pathogenic in animals, rendering animal challenge studies less straight-forward.

6.2 For the clinical part, the Expert Group noted that MHRA does not propose to ask for head-to-head non-inferiority studies on neutralising antibodies, but rather asks for studying humoral and cellular immune response (including neutralising antibodies) with the new variant, comparing with a panel of convalescent sera. Experts broadly agreed with this approach, in absence of knowledge of a meaningful non-inferiority margin.

7. Supply of AZ vaccine from SII

7.1 The EWG viewed slides and heard a presentation from MHRA concerning a paper assessment of an application under Regulation 174 (R174) to approve three named batches of ChAdOx1 nCov-19 vaccine from the Serum Institute of India (SII), a major facility in India, for use in the UK national vaccination programme. The assessment has been expedited to approve before the shelf-life expiry is reached.

7.1.1 The EWG heard that Covishield was developed in collaboration with Oxford University and AstraZeneca (AZ). The technology to manufacture this vaccine along with virus seed and cell banks were received from Oxford/AstraZeneca. The product has been approved in 10 countries and 34.5 million doses have been distributed worldwide by the end of January 2021.

7.1.2 The EWG heard that SII has provided MHRA with full Modules 1, 3 and 5 of the dossier, and some additional batch release data for the three named batches. The full-scale 2000 litre batches will be manufactured on two different lines in the SII facility.

7.1.3 The EWG also heard that AstraZeneca has transferred manufacturing process and key analytical methods for Covid-19 ChAdOx1 vaccine to SII. There have been some changes to manufacturing, however with no material effect to the product.

7.1.4 The EWG heard that manufacturing and testing of the seeds/banks appear largely acceptable, but some questions are raised re methods validation/missing reports. Questions have also been raised concerning testing for adventitious agents.

7.1.5 The EWG heard that the specifications for drug substance and drug product are almost identical to AZD1222. Data submitted confirm R174 batches conform to AZ R174 specifications (SII has provided a commitment to adhere to the AZ specifications previously approved as per R174). Analytical methods/validation were also assessed as generally acceptable.

7.1.6 The EWG heard that satisfactory stability data for 4 weeks at 2-8°C have been presented for the drug substance and inspection feedback confirms acceptable on-site procedures for storage and transportation within the facility. Currently limited stability data is available for the drug product; further stability data has been requested. The proposed shelf life is 6 months at 2-8°C The regulation 174 batches were manufactured in October 2020, and therefore, MHRA would require additional assurance over stability before these batches can be accepted with a > 6 -month shelf-life. The in-use shelf-life of 6 hours stored at 2 to 25°C is acceptable.

7.1.7 Concerning the dossier, MHRA concluded that subject to satisfactorily resolving the requests for further information (RFIs) the product demonstrates sufficient comparability to the Oxford/AZ vaccine, the manufacturing process is reproducible, and in control and the dossier provide sufficient data concerning safety of the product. However, additional stability data is required before an increased drug product shelf life can be assigned. Further, safety of the batches with regards to adventitious agents needs to be assured. The MHRA considered that if all RFIs are resolved (some immediately, some as a commitment), these R174 batches could be approved and could be labelled as AZ batches.

7.1.8 The EWG heard that SII is making/planning future changes to the manufacturing process, mainly related to changes in fermentation parameters (SII Process IV) and will make it more similar to the AZ Process IV. The process is currently undergoing validation with tentative completion late February 2021.

7.1.9 The EWG also heard the MHRA assessment of the interim report of the immunogenicity and safety bridging study performed in India (Interim CSR) submitted to support the application. EWG heard that safety data has been provided from 1600 subjects who received at least one vaccination with either Covishield (1200), placebo (300) or AZD1222 (100) in the immunogenicity and safety study. Reactogenicity was assessed in the same subpopulation as immunogenicity. The immunogenicity results indicate that Covishield can be considered noninferior to AZD1222 vaccine. In summary, there are no concerns about the safety of Covishield and its reactogenicity is broadly comparable to that of AZD1222.

7.1.10 MHRA requested whether EWG agrees that (i) the three named batches to be approved under R174, if RFIs are resolved and appropriate conditions are imposed (e.g. independent batch release, etc), (ii) that MHRA approves individual SII batches on the basis that they have consistent quality and production with the batch data obtained for the R174 batches, (iii) assuming the committee agrees to point (ii) would the committee wish to re-discuss regarding individual batches produced by the updated SII process (SII Process IV) before MHRA approved them.

7.2 EWG comments/discussion

7.2.1 The EWG asked the MHRA for an update concerning inspection of the facility. EWG heard that the MHRA-GMP inspection has been conducted and is to be concluded with the company imminently. No critical deficiencies had been raised and the conditions for supply would follow normal Marketing Authorisation Application routes (importation testing would be required and independent batch release by NIBSC would be specified in the conditions).

7.2.2 The EWG also requested an update from NIBSC regarding batch testing. EWG heard that NISBC had received samples of the R174 batches, and these were currently on test. NISBC assured the EWG that the same suite of testing as performed on the AZ vaccine would be applied to the R174 batches and the batches would also be tested against the AZ specifications (with respect to product appearance, the identity and the infectivity). Test results are expected later this week.

7.2.3 The EWG asked why these batches have become available, seeing that these batches are coming out of a geographical area which would be expected to have great need for these vaccines (India). The EWG was informed by MHRA-LD that the R174 batches were coming towards the end of their shelf life and run the risk of going out of date; it was considered that the UK, more so than others, have the logistics to deploy them quickly. NIBSC further commented that the MHRA had experience testing product from SII and results had been reassuring.

7.2.4 The EWG discussed the issue concerning the remaining shelf life on the product and concluded that the issue of deployment was outside the remit of the MHRA.

7.2.5 Concerning the quality data provided, EWG considered that overall, the quality aspects of the three discussed batches were acceptable once a small number of issues related to pathogen safety were satisfactorily resolved. These must be resolved before the batches are approved. The remaining concerns can be resolved as commitments. EWG was reassured, for the present time, that the clinical, immunogenicity and safety data is generally equivalent to the AZ vaccine.

7.2.6 The EWG endorsed the MHRA recommendations concerning approval of the R174 batches; once relevant quality issues are satisfactorily resolved EWG endorses the application being forwarded for CHM consideration for approval under R174. Further, EWG confirmed that there was no need for EWG to re-discuss individual batches produced by SII Process III or IV before MHRA approve them.

8. Updated efficacy analysis of AZD1222 vaccine and updated UK information for HCPs

8.1 The EWG was presented with an updated efficacy analysis based on the 07-12-2020 data cut off and which included all four studies (Cov001, -002, -003, and -005). This analysis will be presented in the updated UK Public Assessment Report (UKPAR) and updated Information for Healthcare Professionals (HCPs). The primary endpoint of vaccine efficacy was 66.7% (95%Confidence Interval [CI] 57.4, 74.0) with no severe cases/hospitalisations in the vaccinated participants. The efficacy with a dosing interval ≥ 12 weeks was 80.0% (95%CI 65.2, 88.5). Analyses incorporating both asymptomatic positive and symptomatic positive cases in the UK COV002 trial were further explained to show that the vaccine is reducing not only the proportion of symptomatic cases, but also the overall proportion of PCR-positive cases. This shows that the vaccine is reducing the transmission rate.

8.2 Apart from updated efficacy and immunogenicity data in the UK Information for HCPs, there will be changes to the safety data presented with the addition of anaphylaxis and diarrhoea in the list of Adverse Drug Reactions (ADRs) and corrections of frequency in a few reactogenicity ADRs. Slight differences in the safety sections with the EU-approved SmPC were highlighted, the main one being that in Section 4.4, the EU SmPC recommendation of close observation for at least 15 minutes following vaccination, in line with the other approved vaccines in the EU.

8.3 EWG comments/discussion

8.3.1 The EWG asked whether updated data was available from all studies on the median duration of follow-up following administration of the two vaccine doses. MHRA indicated that this information was currently awaited, as confirmation of the median duration of follow up had already been requested from AstraZeneca.

8.3.2 The EWG also raised concerns that the control arm of the study would have a diminishing number of subjects with time, as they are vaccinated in line with their national vaccination schemes. MHRA has confirmed that this is the case. The EWG asked for confirmation from

AZ of what they would be doing with their control arm in the future. MHRA confirmed that a protocol amendment to the UK studies had been approved to that effect.

8.3.3 One EWG member commented that anecdotal feedback received from patients would indicate that information being provided by health professionals to patients at the time of vaccination is inconsistent with scientifically established information, e.g. patients have reported being informed that vaccine effectiveness post vaccination is 2 weeks rather than 3 weeks. EWG recommended that MHRA liaise with the public health bodies to ensure clearer, consistent, unequivocal information is provided to patient concerning vaccination and vaccine effectiveness.

8.3.4 Overall, it was agreed that the UKPAR and the HCPs should be updated with the new information.

9. Analysis of ADZ1222 vaccine against new variants

9.1 The EWG was presented with recent results (submitted for publication) of AZD1222 vaccine against SARS-CoV-2 variants.

9.2 The first paper relates to the UK variant B.1.1.7. Vaccine recipients had neutralisation titres 9-fold lower against the B.1.1.7 lineage than against the Victoria lineage. However, the UK COV002 study showed an efficacy of 75% against the B.1.1.7 variant compared to 84% against the other variants to prevent symptomatic disease and an efficacy of 67% compared to 81%, respectively, to prevent any SARS-CoV-2 infection. An evaluation of viral load in the nasal swabs showed lower viral load in vaccinated participants compared to controls and in asymptomatic subjects compared to symptomatic subjects. Likewise, the duration of positivity of nasal swabs was shorter in vaccinated participants compared to controls and in asymptomatic subjects compared to symptomatic subjects. It was not different between the B.1.1.7 and non-B.1.1.7 variant cases.

9.3 The second paper relates to the South-African variant B.1.351. A [redacted] assay performed in 19 seronegative vaccinees showed that, out of 18 participants with neutralisation activity against B.1.1, 10 (56%) had undetectable neutralisation activity against the B.1.351 variant and the remaining eight showed a 2.5 to 31.5-fold relative reduction in neutralisation. The South-African COV005 study showed an overall efficacy of 22% whereas most cases (39/42) were due to the B.1.351 variant. In contrast, the efficacy after the first dose until 31.10.2020 (i.e., before circulation of the SA variant), a proxy for non-B.1.351 variant infection, was 75%, in line with the UK results.

9.4 EWG discussion/comments

9.4.1 The EWG considered that the data relating to the UK variant was reassuring. The EWG noted that whilst the data regarding the SA variant was more concerning, it is unknown yet whether the vaccine could still protect against severe disease. Given the age of the participants (median of 31 years), the SA trial is unlikely to address this question. The EWG also discussed the current thinking in relation to the role of T cells in the response to SARS-CoV-2, and in particular, that T cells may be more important in protection against severe disease. It has been proposed that T cell response may be preserved against variants due to cross-reactivity of T cell epitopes although what this means clinically is not yet known.

10. <u>Any Other Business</u>

10.1 None.

11. Date and time of next meeting

The next meeting is scheduled to take place on Thursday 25th February 2021 at 12:30.

The Meeting today started at 10:33 and ended at 14:08

[redacted]

19th July 2021

Members are reminded that the content of papers and proceeding of the meetings are to be treated as 'Official – sensitive commercial'. Members are also reminded that, in accordance with the Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members must also declare any other matter which could reasonably be perceived as affecting their impartiality. Detailed guidance is set out in the Code of Practice

COMMISSION ON HUMAN MEDICINES (CHM)

COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Thursday 25th February 2021** at **12:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan
Professor N French
Professor D Goldblatt[1]
Ms S Hunneyball
Professor K Hyrich
Sir M Jacobs
Professor H J Lachmann
Professor P J Lehner
Dr S Misbah
Professor S Price
Dr A Riordan[2]
Professor C Robertson
Professor T Solomon[2]
Dr R Thorpe[1]
Mrs M Wang
Professor C Weir

Apologies

Professor P Shah

Member of the CTBV Expert Advisory Group

Professor B K Park
Professor M Turner

Members of the CPS Expert Advisory Group

Mr VI G Fenton-May
Mr R Lowe
Professor Y Perrie[3]
Professor K M G Taylor (Chair of CPS)
Dr S Walsh

Invited Expert

[redacted][4]

Secretariat

[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD

Presenters supporting specific items[4]

[redacted] - PHE
[redacted] - VRMM
[redacted] - LD
Dr P Bryan - VRMM
[redacted] - MHRA-NIBSC

MHRA Observers

[redacted] - VRMM
[redacted] - LD
Dr S Branch - VRMM
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Ms N Rose - MHRA-NIBSC
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Mr P Tregunno - VRMM
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[redacted] - LD

Key
LD = Licensing Division
NIBSC = National Institute for Biological Standards & Control
VRMM = Vigilance & Risk Management of Medicines
CTBV = Clinical Trials, Biologicals & Vaccines EAG
CPS = Chemistry, Pharmacy & Standards EAG
PHE = Public Health England

[1] Left during item 3
[2] Joined during item 4
[3] Joined during item 3
[4] supporting specific items

1. Introduction and Announcement

1.1 The Chair reminded Members and invited Experts that the content of papers and proceeding of the meeting are strictly confidential and should be treated as 'Official – sensitive commercial' and should not be disclosed. There is no consent for members / participants to record the meeting, take screenshots or photographs of presentations. The meeting was recorded by the MHRA Secretariat for minute taking purposes only. The Chair & Members including all participants gave full consent to the recording prior to the start of the meeting.

1.2 Conflict of Interest Policy (Annex I to the minutes)

The Chair reminded members and participants that, in accordance with the CHM Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members were also reminded to declare any other matter which could reasonably be perceived as affecting their impartiality.

1.3 The following members declared interests and other relevant interests for this meeting:

Professor Sir Munir Pirmohamed - NPNS AstraZeneca - Research grant to UOL to support PhD in drug interactions.
Other relevant interests in Pfizer, Janssen, Sanofi – Sir Munir is part of an EU-funded IMI consortium on gene therapy, and these companies are partners in the project. The University of Liverpool will get funding from the EU (but not from the partners), this IMI project commences on 3rd November 2020.
AGILE – this is a Liverpool early phase trial platform (between University of Liverpool and Liverpool School of Tropical Medicine). It is funded by the Wellcome Trust and UKRI/DHSC/NIHR. It is NOT evaluating vaccines, but only drugs to treat COVID-19. Sir Munir is not on the trial management group, and he is not directly involved in choosing the compounds for the study. Sir Munir has no involvement with any of the developers of the compounds to be studied (academic or industrial).
Sir Munir is a member of the UK COVID Therapeutics Advisory Panel (UK-CTAP), which is advising the CMO on which compounds need to be prioritised for the RECOVERY+ trial (RECOVERY is funded via NIHR/DHSC).

Professor Breuer – NPNS – Professor Breuer is on the data safety monitoring committee, DSMB, a study looking at combining vaccines being run by Matthew Snape in Oxford. There does not appear to be any involvement of the vaccine manufacturers and is for already licensed vaccines. The study is funded by the NIHR (Dec 2020).

Professor French - Other relevant interest **-** Provides clinical care when in covering the acute medical wards where patients with COVID-19 are cared. NPNS in GSK - In September 2020 a sub-contract was signed with the Liverpool School of Tropical Medicine to undertake work evaluating the safety and effectiveness of GSK's RTS's malaria vaccine in Malawi. GSK are the primary funders to the LSTM.

Ms Hunneyball - Other relevant interest – writes articles published in the Chemist and Druggist magazine, a trade magazine for pharmacists, but receives no payment for these articles. The information referred to in the articles is in the public domain. Ms Hunneyball makes it clear that these are her personal views and reflections and references all sources of information used.

Professor Hyrich – NPNS - Professor Hyrich was co-I on an investigator-initiated research grant exploring predictors of outcome in rheumatoid arthritis. NPNS Pfizer- she is a Co-I on a grant exploring adherence to JAK inhibitors in rheumatoid arthritis. NPNS in Abbvie, Professor Hyrich gave some lectures at an education conference on effectiveness of treatment for rheumatoid arthritis.

Sir Michael Jacobs - Other relevant interest - As part of the academic role at the Liverpool School of Tropical Medicine, Sir Michael is a member of the Study Management Team and antiviral drug prioritisation group for the AGILE proof of concept (phase I/II) platform study. Sir Michael is also part of the team that submits new antiviral compounds against SARS-CoV2 for consideration by NIHR for testing on this platform. No commercial or financial interest in the trial or any of the compounds, or any pharmaceutical or biotechnology company.

Professor Lachmann – Other relevant interest as a volunteer participant in the Oxford vaccine study and no other involvement in the study.

Professor Lehner - Other relevant interest – Professor Lehner previously held a DPAC (Discovery Partnership with Academia) agreement with GSK, but this has been completed. Professor Lehner's participation in his local hospital D and T governance committee deliberations would form the normal activity and professional responsibility in his post and does not interfere with the EWG considerations (Sept 2020).

Dr Misbah - NPNS - Holds honorary Senior Lectureship with University of Oxford & Oxford University Hospitals NHS Foundation Trust.

Professor Price - NPNS in GSK and AstraZeneca – which relates to donations provided by both companies to the British Toxicology Society (BTS) to support their Annual Congress and Education and Training of which Professor Price is currently President of the Society (2020-2022).

Dr Riordan - Other relevant interests - Participant in Oxford University's ChAdOx1 nCoV-19 clinical trial –received immunisation 27/8/2020. NPNS - Postgraduate External Examiner for Oxford University (Postgraduate Diploma in Paediatric Infectious Diseases).

Professor Solomon - Other relevant interests – Professor Solomon provides clinical care for patients with Covid-19; chaired the MRC/NIHR committee which awarded funding for development of the Oxford Vaccine.

Professor Weir - NPNS - Imperial College and Other relevant interest arising from his department collaborates with Imperial College on a number of clinical trials.

CTBV

Professor Park - NPNS in GSK Research & Development Ltd. and in Janssen as I received a research grant in the past two years. The grant has been handed over to a colleague in 2020 and the grant is due to finish in 2020. Professor Park received no direct payment. In addition, Professor Park have two active IMI grants for Transbioline and Quantitative Systems Toxicology, he is the PI on the TransBioline grant for the University of Liverpool. Both grants are paid directly to the University of Liverpool.

Professor Turner – NPNS interest. Professor Turner is a Non Executive Director (non-remunerated) on the Board of the Cell and Gene Therapy Catapult (CGT) until the end of March. CGT have been tasked by UK Government with re-purposing a factory in Braintree

to manufacture either a vaccine or a therapeutic mAb. No decision has been made as to whether or what product CGT Braintree may be asked to manufacture and that decision will be made by UK Government. Professor Turner does not believe that CGT Board will have any material input into the decision as to what product may be manufactured. Rentschler have signed a contract with the Cell and Gene Therapy Catapult (CGT) to rent one of the manufacturing clean room suites at the Stevenage Centre. Professor Turner understands that this will be for contract AAV manufacture.

CPS

Mr V'lain Fenton-May – None

Mr Robert Lowe – None

Professor Yvonne Perrie - NPNS in Pfizer & AstraZeneca arising from a contract for a grant (March 2018), which includes contributions from these companies to the University of Strathclyde, Janssen in writing a grant for a PhD (now funded), GSK – arising from an EU grant to University of Strathclyde (Jan 2019-Dec 2019).

Professor Kevin Taylor – None

Dr Susannah Walsh – None

Invited Experts for this meeting

[redacted] – Other relevant interest – The Immunisation Dept at PHE does sell surveillance reports on Meningococcal and Pneumococcal vaccination and disease on cost recovery basis to GSK and Pfizer. [redacted] does not have any personal conflicts of interest.

[redacted] – None

1.4 Apologies were received from Dr Riordan for the meeting today.

1.5 The Chair welcomed [redacted] from PHE as an Invited expert for Item 2 - Update from PHE. [redacted] left the meeting after his presentation.

1.6 The Chair also welcomed [redacted], Consultant Haematologist and Professor of Lymphoma Biology, Kings College Hospital as an Invited expert for Item 4 - COVID-19 Vaccines and risk of immune thrombocytopenia. [redacted] participated for this item only.

2. Update from PHE on the effectiveness of vaccines (Pfizer and AZ)

2.1 The EWG heard an update from [redacted] of Public Health England on vaccine effectiveness data gathered following deployment of Pfizer/BioNTech and AstraZeneca vaccines. The facets of the presentation covered data collected from the following sources: routine testing, SIREN study, General Practitioner cohort study (from Royal College of GPs), hospitalisations, SARI watch, and vaccine impact data.

2.2 In summary, Pfizer vaccine effectiveness against symptomatic disease in older adults shows dose 1 reaches 60-70%, dose 2 reaches 85-90%. AZ vaccine effectiveness against symptomatic disease in older adults shows dose 1 reaches 60-75% and this has not yet

plateaued. The national data provide suggestive evidence of population level impact on hospitalisations and deaths.

2.3 The Chair noted it is reassuring that the results from England, Scotland and Israel on vaccine effectiveness show a great degree of consistency. The Chair also noted that extended interval data on the Pfizer vaccine from Scotland was an exception in that a decline in vaccine effectiveness with an increased interval between first and second doses was present in the data. The EWG noted the analysis plan for the dataset from Scotland will be honed to study the result. The present assumption that the result is not representative of a true effect, but rather an error due to the smaller sample size. The invited expert noted that the longer follow-up data (post 60 days second dose) shows that the Pfizer vaccine takes longer to generate effectiveness in the older subjects, and the uptrend in cases with a longer interval is too minor to produce any concerns. The Chair noted the recent data from the Real-time Assessment of Community Transmission (REACT-2) study show antibody levels are sustained after the first dose of the Pfizer vaccine to at least 36 days, further supportive of that vaccine efficacy reflects a sustained immune response, with no indication that protection is declining.

2.4 The EWG noted that outside of specific studies, systematic sequencing of samples from hospitalised cases in pillar 1 is not being undertaken. The EWG noted the measures to track potential escape variants in the UK datasets was currently limited. The EWG discussed the importance of enriching the sampling (viral genome sequencing) of vaccinated individuals admitted to hospital ("breakthrough cases"), in particular those with symptom onset beyond the date where protection from the vaccine is estimated to occur. Enrichment of sampling in this manner would likely serve to track potential vaccine escape variants of clinical concern more effectively. The invited expert agreed to refer the suggestion to PHE and noted that targeting severe populations (for example hospitalised individuals) would indeed, likely offer over advantages over the random sampling approach.

3. Marketing Authorisation requirements for new COVID-19 vaccines

3.1 Existing guidance on the development of new vaccines when effective vaccines are available and approved was presented. Three situations are possible. 1) There is an established correlate of protection. In that case, no comparative study to an approved vaccine is required. 2) A specific immune response is reasonably likely to predict protection. In that case, a comparative immunogenicity trial may be acceptable. The design of a non-inferiority immunogenicity trial was detailed, including its endpoints (neutralising/binding antibodies, T-cell response), its parameters (geometric mean titre, seroconversion rate), its non-inferiority margin. In addition, safety data (at least 3000 subjects) and post-approval effectiveness studies would be required. However, it was questioned whether this strategy is possible across different manufacturing platforms. 3) There is no approved vaccine of a similar platform. In that case, if a placebo-controlled trial is not feasible, a comparative efficacy trial is required (superiority or non-inferiority). It was questioned whether it might still be possible to justify an immunogenicity comparison between vaccines of "similar" platforms, e.g., inactivated vaccine vs subunit vaccine, and finally whether animal studies or human challenge studies might help support the choice of a comparator.

3.2 The EWG noted that new approaches to define correlates of protection are available which study more than a single antibody level, but comparison between trials is hindered by a lack of standardisation. Ratios of neutralising or binding antibodies to convalescent sera antibodies are being calculated to aid comparative analyses across trials. The EWG noted that the MHRA will most likely need to collaborate with international bodies to facilitate a broader understanding of, and to gather the information required to reliably define the correlates of protection.

3.3 The EWG noted correlates of protection are difficult to establish across different vaccine platforms. For viral vector and mRNA vaccines, in addition to inducing antibody responses these COVID-19 vaccines also provoke fairly potent T-cell responses, whereas theory suggests sub-unit vaccines may trigger lower levels of T-cell responses. The challenge will be to qualify the implications of such differences for immunity in vaccinated subjects and this may be an unrealistic goal.

3.4 The EWG noted standardised assays on variants could promptly be launched at NIBSC, and potentially could be used to assess immunity across vaccine platforms. The EWG heard that NIBSC are exploring using the international standard to compare neutralising assays across various platforms when challenged with different viral variants, but this work is presently hindered by the absence of normalisation of variants in the assays. Therefore, it cannot be ruled out that the intrinsic behaviour of the variant is responsible for any difference in the titres. One of the members of the EWG, offered to assist NIBSC to identify groups that could share provide relevant expertise on variant assays.

3.5 The MHRA informed the EWG that in the absence of correlates of protection, companies are seeking scientific advice from the MHRA with regard to their trial designs. The Chair signposted the trial design proposed by Valneva SE. The company are proposing an immunogenicity and safety trial of 4000 participants, 600 of which will have immunogenicity data collected, with efficacy as a secondary endpoint.

3.6 The EWG noted a method to evaluate a vaccine would be to study equivalent responses in convalescent sera. To benchmark vaccine efficacy, the vaccine should perform better in the same assay / assays when compared to sera of patients that have recovered from natural COVID-19 infection. The EWG noted neutralisation is only one component of the immune response but that T-cell responses are also likely to be important, and as such should also be evaluated. A member raised the data on variants from neutralisation activity compared to efficacy data from clinical trials, the correlation between the two appears clear. The expert also noted the currently emerging consensus is that T-cell responses are unlikely to contribute to protection in the immediate post-vaccination period but will be key for longer-term protection and potentially also in lowering the likelihood of progression to severe disease or death.

3.7 The EWG noted in the absence of correlates of protection, it is best to measure both antibody and T-cell responses as surrogate measures of efficacy.

3.8 The EWG noted that establishing robust measures of the durability of the immune responses caused by COVID vaccines is critical to understanding vaccine efficacy.

3.9 The Chair informed the panel that the EMA appear to be supportive of companies pursuing a non-inferiority approach to immunogenicity trial designs. The EWG statistical expert noted that ascertaining clinical meaning from a non-inferiority margin of a surrogate scale such as neutralising titres is challenging, however non-inferiority studies of other vaccines such as the flu vaccines could be used as an exemplar to follow. The statistical expert continued that more data would be needed for COVID-19 vaccine candidates and suggested that trial designs factor-in the gathering of data that would likely support the discerning of correlates of protection.

3.10 The EWG noted a potential future perspective is to test vaccine efficacy in human challenge models.

3.11 The MHRA informed the EWG that the rationale for the choice of the AZ vaccine as a comparator in the planned Valneva SE trial is not substantiated. The MHRA had also

considered whether a sub-unit vaccine may represent a better choice of comparator in the absence of any licensed vaccine using the same platform technology as Valneva.

3.12 The MHRA informed the EWG that at minimum a regulatory perspective is required on the choice of comparator ahead of the next scheduled meeting with Valneva. The Chair acknowledged that the company should justify the choice of comparator, the dose interval, and the trial age range / group (as the majority of the older population in the UK are, or will be vaccinated by the recruitment period), the company also need to be informed it will be mandatory to undertake a post-authorisation vaccine effectiveness study.

3.13 The MHRA informed the EWG that there are limited countries where placebo-controlled studies would be possible due to the varied national vaccination campaigns in progress.

3.14 The EWG were invited to consider the choice of comparator. The EWG noted that assessing the advantages and disadvantages of using comparators that utilise different platform technologies (from sub-unit vaccines, whole inactivated vaccines, mRNA, to vector vaccines) is problematic as none seem ideal, including sub-unit vaccines, and substituting comparators would not solve the issue. The EWG noted a paper comprising the views of regulators and scientists on non-inferiority challenges in different settings is expected to be published shortly. The Chair acknowledged that regulatory alignment on the global stage will be important in the near future, and it would be beneficial to promptly commence discussions with other regulatory bodies. In the immediacy, Valneva should justify their choice of comparator, including that it is a different platform technology and the proposed dosing interval.

4. COVID-19 Vaccines and risk of immune thrombocytopenia

4.1 The EWG heard reports of immune thrombocytopenia (ITP) for the Pfizer/BioNTech vaccine, AZ vaccine and the international data on the same topic for the Moderna vaccine which is not currently used in the UK. The reports were heard in the context of vaccination coverage in the UK, which at the time of the meeting, it was estimated that over 10 million doses of the Pfizer/BioNTech vaccine have been administered in the UK as of 21 February 2021 and over 8.4 million doses of the AstraZeneca COVID-19 vaccine have been administered in the UK as of 21 February 2021.

4.2 Pfizer/BioNTech have also reviewed events of immune thrombocytopenia in the context of observed vs expected analyses for international usage of their vaccine and did not identify an increased rate in excess of that expected. The meeting also heard that a review by the US Centre for Disease Control (CDC) covered data to 27th of January 2021 and also did not identify a signal of ITP.

4.3 The EWG focused on two key questions a) if the vaccine is causally related to de novo cases of ITP, and b) If there is a signal to suggest the vaccine could exacerbate pre-existing ITP.

4.4 The EWG noted that diagnosis of ITP requires a thorough clinical assessment; however the details within the reports are varied in terms of the level of assessment of the patient as undertaken by the healthcare professionals. The EWG discussed the limited influence that one particular case should have on the considerations, because this patient's low haemoglobin was suggestive of other haematological disease. This case aside, overall the number of plausible ITP cases appears sufficient to justify continued monitoring.

4.5 The EWG discussed the biological plausibility of the potential signal. The EWG noted that vaccines used in other diseases have been causally linked with cases of thrombocytopenia (TP); in some of these instances the adjuvant has been theorised to be responsible, but the identification of TP cases across different vaccine preparations and technologies somewhat

challenges this view. The EWG also noted that COVID-19 infection can also cause thrombocytopenia not only by means of increased platelet turnover, but direct platelet infection by SARS-CoV-2. Therefore, concomitant COVID-19 infection needs to be thoroughly evaluated as potential confounding factor. It was confirmed that the majority of the reports state 'negative' for concomitant COVID-19. In summarising remarks, the EWG noted it was plausible that ITP could potentially be associated with each of the three vaccines discussed.

4.6 The EWG noted the number of ITP cases likely represents a borderline signal with the Pfizer/BioNTech and the Moderna vaccine, and perhaps a more likely signal for the AZ vaccine. Further details of individual cases are required, and any new reports need to be carefully evaluated and incorporated to on-going analyses. Mechanistic data could also be used to interrogate the likelihood of a causal relationship. At present, the EWG noted that the level of information and the proportionately low number of cases of TP preclude making any robust judgements on causality.

4.7 On the topic of exacerbation of pre-existing ITP as potential side effect triggered by the vaccine, the EWG considered that viral infections can lead to flare ups in patients with ITP. Mixed outcomes are also reported with other vaccines in the literature, with some studies suggesting a causal link to the vaccine and others not. It was also considered by the EWG that unvaccinated patients who have a sub-clinical IPT may advance to clinically diagnosable IPT more rapidly following vaccination. The EWG noted a proposed mechanism involved the downstream processes of inflammation in response to vaccination, leading to up-regulation of pre-existing types of autoantibodies. The EWG determined that it was plausible that the time of onset to ITP could potentially be accelerated due to use of COVID-19 vaccines but that an association with the vaccines could not currently be established.

4.8 The EWG noted the detailed narrative regarding the case of fatal cerebral venous sinus thrombosis (CVST) in a 32 year old patient, and that there was no evidence of confounding. The EWG noted thrombotic events or bleeding is rare in cases of ITP, but bleeding can occur in cases of wet ITP. Further information on this case, and any other similar cases, should be obtained as follow-up.

4.9 The EWG noted a number of reports of ITP and thrombocytopenia do not appear to include any confounding factors and which decreased the likelihood these reports represent a chance finding.

4.10 The EWG considered the proposed follow up forms to gather additional information on these cases, and systemic lupus should be added to the list of other potential causes of TP.

4.11 The EWG discussed whether vulnerable patient groups, in particular patients with auto-immune disease, would be more susceptible to ITP. The meeting considered that this could be plausible but there is no evidence to suggest that this is the case at the moment. Monitoring platelet counts in the period prior to vaccination in patients with auto-immune disease was not recommended by the EWG, as there is presently only a potential signal, and also because results would be difficult to interpret especially when considering that some immune conditions can cause low-platelets, e.g. lupus. The EWG agreed the topic of vulnerable patients including those with auto-immune diseases, should be revisited in the near future /when further data may have become available. The EWG discussed ITP in the paediatric population and confirmed that if the vaccination schedule is broadened to include children, there will be a need to rapidly monitor and review potential haematological signals in children, particularly as 40% of ITP cases occur in children mostly under the age of 10 years.

4.12 The EWG noted the need to conduct very in-depth assessments of individual cases that include no apparent confounding factors and communicate with other international regulators to gain further insights, and establish a basis for a coordinated regulatory response.

4.13 The EWG noted future studies should explore platelet activation in vaccinated patients, and although initiating these studies falls outside of the MHRA's purview, the EWG could form a recommendation to researchers.

4.14 The EWG considered that initiation of risk minimisation for ITP would be premature at this stage and the addition of warnings on ITP in the product information for the vaccines would be (currently) unfounded and may only unnecessarily contribute to vaccine hesitancy.

4.15 The EWG concluded that cases of immune and non-immune thrombocytopenia should continue to be monitored.

5. Update on COVID-19 vaccine AstraZeneca safety

5.1 The EWG heard an update on safety data for the AstraZeneca vaccine up to 19th February 2021. 41,157 reports of suspected ADRs in association with COVID-19 Vaccine AstraZeneca had been received in the context of roughly 8 million doses given. The most frequently reported reactions were consistent with expected reactogenicity reactions and were present in the product information. 227 fatal cases had been received, the majority of which were in patients aged over 80 years. An update of cases received for adverse events of interest Bell's palsy and transverse myelitis was provided. Analysis of individual cases as well as epidemiological analysis did not indicate a signal.

5.2 The EWG discussed cases reporting transverse myelitis and the plausibility of cases where patients reporting the condition with very quick recovery, without input from a healthcare professional. The EWG considered these cases to be less plausible to be true transverse myelitis than those where medical review and treatment have been sought.

5.3 The EWG discussed the importance of acquiring more information on the reported cases to allow further assessment of cases although the difficulties in obtaining this with established follow up measures were acknowledged.

5.4 The EWG advised that no regulatory action was required currently but further information for assessment was required.

6. Review of potential risk of encephalitis with Pfizer/BioNTech and AstraZeneca COVID-19 vaccines

6.1 The EWG heard an overview of an ongoing report regarding a recipient of the AstraZeneca Covid-19 vaccine who experienced encephalopathy, multi-organ failure and paralysis with an onset between 24-48hours post vaccination. The patient had a complex medical history, significant for reactions to viral and bacterial infections as well as a previous reaction to a vaccine.

6.2 A review of cases of encephalopathy and encephalitis and related terms reported to the Yellow Card database was presented, to a data lock point of 15th February 2021 and from clinical trials with the Astra Zeneca and Pfizer vaccines.

6.3 The EWG noted that as per the product information, a previous reaction to a vaccine (other than a prior COVID-19 vaccine) does not contraindicate use of any COVID-19 vaccine. A

search of the Yellow Card database for other cases mentioning previous reactions to vaccines found only reports of reactogenicity type reactions to the COVID-19 vaccines.

6.4 The EWG discussed the most recent information regarding the index case and commented on the complexity of the patient's medical history.

6.5 The EWG commented on previous reports of fatal reactions to the use of adenoviral vectors used therapeutically (rather than as a vaccine) and stated that it was important to be clear that these events are not similar to the events being discussed currently and that the adenovirus vectors used in these therapies were live adenovirus vectors, rather than a replication-deficient adenovirus vector, as used in COVID-19 vaccine AstraZeneca.

6.6 The EWG concluded that more information was needed on this case, however it was not possible to establish causality with vaccination for this patient and that there wasn't wider evidence of similar reactions currently. The EWG considered there is no need for any updates to the product information or communications at this time.

7. Core Risk Management Plan for COVID-19 vaccines – requirements for update following strain

7.1 The EWG heard MHRA proposal to principles and requirements of an updated pharmacovigilance system and core Risk Management Plan for COVID-19 vaccines strain variations and agreed of the principles laid down in the proposal.

7.2 Update on the Guideline

7.2.1 MHRA-NIBSC updated the EWG on recent revisions of the guideline that were made in consultation with stakeholders and other regulators. Experts approved all proposals made and strongly encouraged timely publication.

8. <u>Any Other Business</u>

8.1 None.

9. <u>Date and time of next meeting</u>

The next meeting is scheduled to take place on Tuesday 2nd March 2021 at 11:30.

The Meeting today started at 12:32 and ended at 15:00.

[redacted]

19th July 2021

Members are reminded that the content of papers and proceeding of the meetings are to be treated as 'Official – sensitive commercial'. Members are also reminded that, in accordance with the Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members must also declare any other matter which could reasonably be perceived as affecting their impartiality. Detailed guidance is set out in the Code of Practice

COMMISSION ON HUMAN MEDICINES (CHM)

COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Tuesday 2nd March 2021** at **12:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan[1]
Professor N French
Professor D Goldblatt
Ms S Hunneyball
Professor K Hyrich
Sir M Jacobs
Professor H J Lachmann
Professor P J Lehner
Dr S Misbah
Dr A Riordan
Professor C Robertson
Professor P Shah
Professor T Solomon
Dr R Thorpe
Mrs M Wang
Professor C Weir

Apologies

Professor S Price
Professor B K Park (Member of CTBV EAG)

Member of the CTBV Expert Advisory Group

Professor M Turner

Members of the CPS Expert Advisory Group

Mr VI G Fenton-May
Mr R Lowe
Professor Y Perrie
Professor K M G Taylor (Chair of CPS)
Dr S Walsh

Invited Experts presented Item 2[2]

[redacted]

Invited Experts for Items 2 & 5

[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted] - LD (& for CHM)

Presenters supporting specific items[3]

[redacted] - LD
[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD

MHRA Observers

[redacted] – VRMM
[redacted] - VRMM
[redacted] - LD
Dr S Branch - VRMM
[redacted] - LD
[redacted] - VRMM
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[redacted] – VRMM
[redacted] - Devices
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - MHRA-NIBSC
Ms N Rose - MHRA-NIBSC
[redacted] - MHRA-NIBSC
[redacted] - LD
[redacted] - VRMM
[redacted] – Government Legal Team
[redacted] - MHRA-NIBSC
[redacted] - LD
[redacted] - LD
Dr K Wydenbach - LD

Observers

[redacted] (also participated in item 5)

[redacted]

Secretariat

[redacted]

23rd July 2021

[1] Joined during item 5
[2] Left after this item
[3] supporting specific items

Key
LD = Licensing Division
NIBSC = National Institute for Biological Standards & Control
VRMM = Vigilance & Risk Management of Medicines
CTBV = Clinical Trials, Biologicals & Vaccines EAG
CPS = Chemistry, Pharmacy & Standards EAG

1. Introduction and Announcement

1.1 The Chair reminded Members and invited Experts that the content of papers and proceeding of the meeting are strictly confidential and should be treated as 'Official – sensitive commercial' and should not be disclosed. There is no consent for members / participants to record the meeting, take screenshots or photographs of presentations. The meeting was recorded by the MHRA Secretariat for minute taking purposes only. The Chair & Members including all participants gave full consent to the recording prior to the start of the meeting.

1.2 Conflict of Interest Policy (Annex I to the minutes)

The Chair reminded members and participants that, in accordance with the CHM Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members were also reminded to declare any other matter which could reasonably be perceived as affecting their impartiality.

1.3 Participants declared interests and other relevant interests for this meeting listed at **Annex II** to the minutes.

1.4 Apologies were received from Professor Price and Professor Park for the meeting today.

1.5 The Chair welcomed the following invited experts who presented item 2 - Analyses from REACT 2 study on vaccines. The experts left after the presentation of this item:

[redacted]

1.6 The Chair welcomed the following invited experts who participated for item 5 - Vaccination during Pregnancy & Breastfeeding.

[redacted], MD PRCOG

[redacted]

[redacted] **(also observed item 2)**
[redacted]

[redacted] **(also observed item 2)**
[redacted]

1.7 The Chair welcomed the following Observers who observed the meeting today and will be observing future meetings on the safety items:

[redacted]
Locum Consultant in Health Protection
Public Health Agency

[redacted] OBE - **Apologised**
[redacted]

[redacted]
Public Health Scotland

[redacted]

[redacted] MB ChB. FRCGP. FIMC (RCSEd), DUMC
[redacted]

2. Analyses from REACT 2 study on vaccines

2.1 The EWG viewed slides and heard a presentation by Imperial College London experts on the results of real-time assessment of community transmission 2 (REACT-2) programme, round 5, carried out on 26 January - 8 February 2021. REACT 2 is a community survey of adults in England that measures the prevalence of antibodies using the self-administered lateral flow immunoassay (LFIA) test. The survey comprised 172,099 participants, with valid immunoglobulin G (IgG) results from 154,417. The survey questionnaires collected demographic details, as well as clinical and COVID-19 vaccination histories.

2.2 The EWG heard a report on the overall prevalence of positivity for SARS-CoV-2 IgG antibodies in the community in vaccinated and unvaccinated individuals, the impact of vaccination on antibody status, and confidence in vaccination across the population. The EWG heard that antibody responses were detected after vaccination with Pfizer/BioNTech or AstraZeneca vaccines. However, the analysis was limited to those who received the Pfizer/BioNTech vaccine due to insufficient data for comparison with the AstraZeneca vaccine.

2.3 The EWG heard that antibodies to SARS-CoV-2 spike (anti S) protein and neutralisation were detected using the [redacted] (threshold value for positivity AU/ml). The results demonstrated the detection of antibodies on the LFIA correlated well with the threshold for neutralisation of live virus in in-vitro assays.

2.4 The EWG noted that the findings from REACT 2 study indicated higher prevalence of antibodies (37.9%) in the vaccinated population compared to the unvaccinated population (9.8%), which resulted from natural infections. The EWG heard that high level antibody positivity was seen following two doses of Pfizer/BioNTech vaccine across all age groups, with slightly higher levels in the younger population. It was also noted following a single dose of Pfizer/BioNTech vaccine high levels of antibody positivity were detected in those with previous infections compared to those with no history of COVID-19. The EWG heard that following a single dose of Pfizer/BioNTech vaccine lower antibody positivity was seen with increasing age. A high response was noted in those with previous or suspected COVID-19 across all age groups. The results on post vaccination indicated that the antibody response peaks around 30 days for all age groups.

2.5 The EWG heard that the uptake of vaccination by age was the highest in those aged 80 years and over (93.9%), followed by those aged 75-79 (64.9%). The data analysed also reported that 68.9% of healthcare workers and 59.7% of care home workers had received the vaccination. Further data was also received on 17,000 people who had reported having received one or two doses of the vaccine.

2.6 The EWG heard that confidence in the vaccine program was high with 92% of people being vaccinated or agreed to accept the offer. It was reported that vaccine confidence varied with age and ethnicity, with lower confidence in the higher prevalence groups (young people and those of Black or Asian ethnicity). It was noted that the reasons behind vaccine hesitancy were mainly related to the safety of the vaccine. Particular concerns were also identified around pregnancy, fertility, and allergies in all age groups.

2.7 The EWG heard the status and details of future plans, these included analysis of ongoing data, further modelling and comprehensive review of data, continuing to analyse digital images of completed LFIA tests, and conclusion of the pending rounds of REACT and linking the antibody results to cases, hospitalisations and mortality. The group are also awaiting confirmation that the blood testing services of [redacted] can be used to mount a larger scale analysis of the older cohort using [redacted] with the aim of subsequently linking results to clinical and hospital data.

2.8 The EWG asked whether qualitative or further quantitative assessments are being performed on the images. The EWG heard that the images are being read and checked by multiple individuals. However, a new method for automated reading is being developed and will be available in the future.

2.9 The EWG enquired if the apparent lower antibody response with age, may instead be due to an inadequate sensitivity or levels beyond the limit of quantification of the assay. The EWG heard that this was highly unlikely, because when using the same assay in older participants, post second dose, a far higher level of antibody was noted.

2.10 The EWG also heard that use of the [redacted] intends to focus on the older cohort and the assay should be capable of better characterisation of antibody responses when used in conjunction with a standard laboratory rush assay.

2.11 The EWG asked the invited experts about the binding kinetics of antibodies that have been afucosylated. The invited experts expressed a need to review the data on this topic before a response can be given.

2.12 The EWG enquired whether the WHO international standard will be used to calibrate the assay to an international unit to allow comparisons across other data sets. The external experts commented that calibration of assay quantification was based on previous inhouse

assays and information from published papers, and this was then aligned to [redacted]

2.13 The EWG asked the external experts whether people had reported of COVID-19 after receiving the vaccine and if this could be linked to the lateral flow positivity threshold. The expert stated that there are more data from previous study (REACT 1) which is under investigation. Further data are also being collected to link to the subsequent post vaccination hospitalisation, data on positivity and mortality.

3. COVID-19 Vaccine Moderna post authorisation study protocols: Post Authorisation Safety in the US and Observational Pregnancy Outcome Study

3.1 The EWG heard that Moderna had submitted protocols for a post authorisation safety surveillance (PASS) study to be conducted in the US, and for a pregnancy registry, to be conducted in centres in the US and in certain EU countries. The EWG heard that the US PASS proposes to further characterise the safety concerns of long-term safety and anaphylaxis with their COVID-19 vaccine, as included in the Risk Management Plan. The EWG noted that neither of the studies were proposed to be conducted in the UK, and that the protocols would be subject to approval by other regulators such as the US FDA and the EMA.

3.2 The EWG noted that the study design was a retrospective observational cohort study which will be conducted using a large US healthcare database. The EWG also heard that the study objectives were to estimate background rates for adverse events of special interest (AESI) prior to and during the pandemic, and since introduction of COVID vaccines, assess observed versus expected rates for AESIs and to estimate the relative risk for AESIs which meet prespecified evaluation threshold using a self-controlled risk interval (SCRI) analysis. The EWG noted that the proposed study timelines may be subject to change depending on protocol approval by various regulators, although interim updates are proposed every three months.

3.3 The EWG were informed that the MHRA intended to send some questions to the company for consideration, in relation to the power of the study to identify or exclude levels of risk for any AESI studied; also the design of the SCRI analyses will need to be AESI-specific and that use information on the UK deployment of the Moderna vaccine should be used to inform useful stratifications of data in the UK to understand the safety profile in the UK vaccinated cohort.

3.4 The EWG heard that a prospective, observational pregnancy exposure registry is proposed to collect primary data in the US and several EU countries from pregnant women who have received Moderna COVID-19 vaccine, and their healthcare providers. The EWG noted that the study proposes to estimate the proportion of major congenital malformations in the infants of women exposed to Moderna's vaccine and compare the proportion of major congenital malformations with the prevalence of birth defects in the general population in the EU and US (using European Surveillance of Congenital Anomalies [EUROCAT] and Metropolitan Atlanta Congenital Defects Program [MACDP], respectively. The EWG also noted the study also proposes to evaluate other adverse outcomes of pregnancy, and infant outcomes such as minor malformations.

3.5 The EWG agreed with the MHRA's assessment of the protocols and the proposed list of questions for the company. The EWG also recommended asking for some more specific details on other criteria for performing the SCRI analysis in the US PASS. Regarding the pregnancy registry, the EWG proposed asking the company to discuss the representativeness of the data collected in the pregnancy registry, and also whether the

choice of external comparators for the US and EU may introduce bias due to variations in the way that outcome data are collected.

4. COVID-19 Vaccine Moderna post authorisation study protocol: Safety and Immunogenicity of Moderna in Immunocompromised Patients

4.1 The EWG heard that a draft protocol for post authorisation study to characterise the use of SARS-CoV-2 mRNA-1273 vaccine in the subgroup of immunocompromised patients was submitted by Moderna. The protocol concerns a phase III, open-label, clinical trial comparing the safety and immunogenicity of the vaccine in uncomplicated solid organ transplant patients and healthy controls, aiming to monitor participants for 12 months after vaccination. The primary objectives are to evaluate safety and reactogenicity and to evaluate serum neutralising antibody response 28 days after first and second doses. Secondary objectives include evaluation of immune response persistence for a year and describing the incidence of COVID-19 in solid organ transplant (SOT) patients compared to healthy participants.

4.2 The EWG noted that the safety endpoints were assessed by clinical review of relevant parameters including adverse events (AEs), serious adverse events (SAEs), medically attended AEs (MAAEs), any reported adverse events of special interest (AESIs), and a biopsy-proven organ rejection.

4.3 The EWG heard the proposed humoral and cellular immunogenicity response endpoints and safety analyses are acceptable.

4.4 The MHRA has requested clarification from the company on the statistical comparison of the antibody responses of the transplant patients and the healthy participants, and on the method of selecting the antibody threshold from pivotal study mRNA-1273-P301.

4.5 The EWG heard that a request has been made for the company to confirm whether the subset of participants for exploratory cellular immunogenicity responses include both SOT recipients and healthy participants, to enable comparison. Justification was also requested to establish whether the sample size is large enough to achieve the aims of the study.

4.6 The EWG discussed further questions the MHRA will potentially raise with the company. The EWG noted that the immunocompromised subjects proposed in the study are uncomplicated SOT patients. The EWG was asked to comment whether the study population reflects the broader immunosuppressed population, if not, to comment on further suggestions for which other subgroups may be recruited and any potential recruitment sources.

4.7 The EWG agreed with the MHRA assessor that the patient population is very restrictive and is not representative of the wider immunosuppressed population. The EWG advised that the company's post authorisation study should include patient groups with both primary and secondary antibody deficiency, bone marrow transplant recipients, patients on immunosuppressant therapy, and patients with autoimmune disease or inflammatory disease. The EWG also recommended that an adequate sample for each of these groups can be obtained from the relevant scientific, or professional societies. The EWG also recommended having a broad spectrum of patients in these groups, including patients with combined secondary defects in terms of T-cell defects as well as antibody deficiency.

4.8 The EWG also heard about the company's proposal to measure cellular immunogenicity endpoints relating to B-cells and T-cells in a subset of participants at 7 days post second dose. Advice was sought from EWG whether the timing for sample collection is optimal.

4.9 The EWG noted in the phase I study conducted by Moderna, sample collection occurred at 14 days after the second dose, to align with the period for generation of T-cell response. At a minimum, it would be beneficial for the company to include a 14-day time point to allow comparison between the phase I immunogenicity data and the forthcoming post authorisation study data.

4.10 The EWG confirmed that the proposal for evaluation of more general safety endpoints as well as transplant rejection was generally acceptable. The EWG advised the MHRA to encourage the company to consider new data emerging and work closely with academic groups to produce a better-informed study protocol.

4.11 The EWG endorsed the list of questions to the company.

5. Vaccination during Pregnancy & Breastfeeding

5.1 The EWG heard that current COVID-19 vaccine trials within the UK do not allow inclusion of pregnant women but that there are plans from several companies to address this. Pfizer have announced a trial in pregnant women to compare the data to that from their pivotal trial, but as yet this will not involve the UK. Janssen have been in communication with the Clinical Trials Unit (CTU) and submitted an updated protocol for review for their planned phase II trial. The trial will evaluate women in the 2nd and 3rd trimester for safety and immunogenicity as well as parameters in the neonates. The CTU has also heard about a possible trial evaluating the deployed vaccines in pregnant women at 13 to 24 weeks gestation. The design will be similar to another ongoing trial of deployed vaccines but focusing on the doses and prime-boost regimen.

6. Any Other Business

6.1 None.

7. Date and time of next meeting

The next meeting is scheduled to take place on Tuesday 9th March 2021 at 15:30.

The Meeting today started at 11:31 and ended at 13:56.

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Annex I

Conflict of Interest Policy for CHM COVID-19 Vaccine Benefit Risk EWG

Chair and Members

- May not hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
- May not currently be or have previously been involved in the development of COVID-19 vaccines

Invited to all meetings, receives all papers and presentations and is permitted full participation in discussion, including drawing up conclusions and recommendations

Invited experts

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May be invited to all relevant meetings, receives all papers and presentations and is permitted to participate in discussions when invited by the Chair. Does not contribute to conclusions and recommendations

Observers

Are invited to attend all meetings. Will not participate in drawing up conclusions and recommendations.

Annex II

The following participants declared interests and other relevant interests at the meeting today:

Apologies were received from Professor Price and Professor Park for this meeting.

Professor Sir Munir Pirmohamed - NPNS AstraZeneca - Research grant to UOL to support PhD in drug interactions.
Other relevant interests in Pfizer, Janssen, Sanofi – Sir Munir is part of an EU-funded IMI consortium on gene therapy, and these companies are partners in the project. The University of Liverpool will get funding from the EU (but not from the partners), this IMI project commences on 3rd November 2020.
AGILE – this is a Liverpool early phase trial platform (between University of Liverpool and Liverpool School of Tropical Medicine). It is funded by the Wellcome Trust and UKRI/DHSC/NIHR. It is NOT evaluating vaccines, but only drugs to treat COVID-19. Sir Munir is not on the trial management group, and he is not directly involved in choosing the compounds for the study. Sir Munir has no involvement with any of the developers of the compounds to be studied (academic or industrial).
Sir Munir is a member of the UK COVID Therapeutics Advisory Panel (UK-CTAP), which is advising the CMO on which compounds need to be prioritised for the RECOVERY+ trial (RECOVERY is funded via NIHR/DHSC).

Professor Breuer – NPNS – Professor Breuer is on the data safety monitoring committee, DSMB, a study looking at combining vaccines being run by Matthew Snape in Oxford. There does not appear to be any involvement of the vaccine manufacturers and is for already licensed vaccines. The study is funded by the NIHR (Dec 2020).

Professor French - Other relevant interest **-** Provides clinical care when in covering the acute medical wards where patients with COVID-19 are cared. NPNS in GSK - In September 2020 a sub-contract was signed with the Liverpool School of Tropical Medicine to undertake work evaluating the safety and effectiveness of GSK's RTS's malaria vaccine in Malawi. GSK are the primary funders to the LSTM.

Ms Hunneyball - Other relevant interest – writes articles published in the Chemist and Druggist magazine, a trade magazine for pharmacists, but receives no payment for these articles. The information referred to in the articles is in the public domain. Ms Hunneyball makes it clear that these are her personal views and reflections and references all sources of information used.

Professor Hyrich – NPNS - Professor Hyrich was co-I on an investigator-initiated research grant exploring predictors of outcome in rheumatoid arthritis. NPNS Pfizer- she is a Co-I on a grant exploring adherence to JAK inhibitors in rheumatoid arthritis. NPNS in Abbvie, Professor Hyrich gave some lectures at an education conference on effectiveness of treatment for rheumatoid arthritis.

Sir Michael Jacobs - Other relevant interest - As part of the academic role at the Liverpool School of Tropical Medicine, Sir Michael is a member of the Study Management Team and antiviral drug prioritisation group for the AGILE proof of concept (phase I/II) platform study. Sir Michael is also part of the team that submits new antiviral compounds against SARS-CoV2 for consideration by NIHR for testing on this platform. No commercial or financial interest in the trial or any of the compounds, or any pharmaceutical or biotechnology company.

Professor Lachmann – Other relevant interest as a volunteer participant in the Oxford vaccine study and no other involvement in the study.

Professor Lehner - Other relevant interest – Professor Lehner previously held a DPAC (Discovery Partnership with Academia) agreement with GSK, but this has been completed. Professor Lehner's participation in his local hospital D and T governance committee deliberations would form the normal activity and professional responsibility in his post and does not interfere with the EWG considerations (Sept 2020).

Dr Misbah - NPNS - Holds honorary Senior Lectureship with University of Oxford & Oxford University Hospitals NHS Foundation Trust.

Dr Riordan - Other relevant interests - Participant in Oxford University's ChAdOx1 nCoV-19 clinical trial –received immunisation 27/8/2020. NPNS - Postgraduate External Examiner for Oxford University (Postgraduate Diploma in Paediatric Infectious Diseases).

Professor Solomon - Other relevant interests – Professor Solomon provides clinical care for patients with Covid-19; chaired the MRC/NIHR committee which awarded funding for development of the Oxford Vaccine.

Mrs Wang – Personal interests arising from being highly sensitive to insect stings, and plant products such as Hyacinth bulbs, which are recorded on Mrs Wang's medical records.

Professor Weir - NPNS - Imperial College and Other relevant interest arising from his department collaborates with Imperial College on a number of clinical trials.

CTBV

Professor Turner – NPNS interest. Professor Turner is a Non Executive Director (non-remunerated) on the Board of the Cell and Gene Therapy Catapult (CGT) until the end of March. CGT have been tasked by UK Government with re-purposing a factory in Braintree to manufacture either a vaccine or a therapeutic mAb. No decision has been made as to whether or what product CGT Braintree may be asked to manufacture and that decision will be made by UK Government. Professor Turner does not believe that CGT Board will have any material input into the decision as to what product may be manufactured. Rentschler have signed a contract with the Cell and Gene Therapy Catapult (CGT) to rent one of the manufacturing clean room suites at the Stevenage Centre. Professor Turner understands that this will be for contract AAV manufacture.

CPS

Mr V'lain Fenton-May – None

Mr Robert Lowe – None

Professor Yvonne Perrie - NPNS in Pfizer & AstraZeneca arising from a contract for a grant (March 2018), which includes contributions from these companies to the University of Strathclyde, Janssen in writing a grant for a PhD (now funded), GSK – arising from an EU grant to University of Strathclyde (Jan 2019-Dec 2019).

Professor Kevin Taylor – None

Dr Susannah Walsh – None

Observers for this meeting

[redacted]

COMMISSION ON HUMAN MEDICINES (CHM)
COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Tuesday 9th March 2021** at **15:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan
Professor N French
Professor D Goldblatt
Ms S Hunneyball
Professor K Hyrich
Sir M Jacobs
Professor H J Lachmann
Professor P J Lehner
Dr S Misbah
Professor S Price
Dr A Riordan
Professor T Solomon
Dr R Thorpe
Mrs M Wang
Professor C Weir

Apologies

Mr R Lowe
Professor C Robertson
Professor P Shah

Member of the CTBV Expert Advisory Group

Professor M Turner

Members of the CPS Expert Advisory Group

Mr VI G Fenton-May
Professor Y Perrie
Professor K M G Taylor (Chair of CPS)
Dr S Walsh

Observers

[redacted]

Secretariat

[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted] - LD (& for CHM)

Presenters supporting specific items

[redacted]

MHRA Observers

[redacted]
Dr S Branch - VRMM
[redacted]
Dr P Bryan - VRMM
[redacted]
Dr S P Lam - LD
[redacted]
Ms N Rose - MHRA-NIBSC
[redacted]
Mr P Tregunno - VRMM
[redacted]
Dr K Wydenbach - LD

Key
LD = Licensing Division
NIBSC = National Institute for Biological Standards & Control
VRMM = Vigilance & Risk Management of Medicines
CTBV = Clinical Trials, Biologicals & Vaccines EAG
CPS = Chemistry, Pharmacy & Standards EAG

[redacted]

13th April 2022

1. Introduction and Announcement

1.1 The Chair reminded Members and invited Experts that the content of papers and proceeding of the meeting are strictly confidential and should be treated as 'Official – sensitive commercial' and should not be disclosed. There is no consent for members / participants to record the meeting, take screenshots or photographs of presentations. The meeting was recorded by the MHRA Secretariat for minute taking purposes only. The Chair & Members including all participants gave full consent to the recording prior to the start of the meeting.

1.2 Conflict of Interest Policy (Annex I to the minutes)

The Chair reminded members and participants that, in accordance with the CHM Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members were also reminded to declare any other matter which could reasonably be perceived as affecting their impartiality.

1.3 Participants declared interests and other relevant interests for this meeting listed at **Annex II** to the minutes.

1.4 Apologies were received from Professors Robertson, Shah and Mr Lowe for the meeting today.

1.5 The Chair welcomed the following observers invited to observe the safety items discussed at the meeting today:

[redacted]

[redacted]
Public Health Scotland

[redacted] Public Health Wales

[redacted]

2. Moderna dosing interval

2.1 The EWG heard the Moderna COVID-19 vaccine was authorised under Regulation 174 of the HMRs 2012 on 08 January 2021. On 31 December 2020, in response to a DHSC request for specific guidance on an extended dosing interval, EWG and CHM advised that the recommended dosing interval should be at least 28 days. But, in subsequent discussions the manufacturer did not agree, and the product information for HCPs states that it is recommended to administer the second dose 28 days after the first dose and refers to

section 5.1 which provides an outline of the data on efficacy after the first dose and information about the dosing interval in the trial which was up to 42 days.

The EWG was reminded of the efficacy seen after 1 dose of Moderna and after 1 dose of Pfizer-BioNTech, as they are both mRNA vaccines with similar results in their clinical trials. Effectiveness data after one dose were presented mainly for the Pfizer-BioNTech vaccine.

2.2 The EWG were asked to consider, if a dosing interval of 'at least 28 days' for the Moderna vaccine could still be recommended, based on the currently available data.

2.3 The EWG noted recent discussions on the topic of vaccine dosing interval in the medical literature. The EWG noted an interval of 'at least 28 days' would be consistent with the outcome of the previous EWG discussion on the 31 Dec 2021, and the decision to make the specific recommendation of 'up to 12 weeks' is within JCVI's purview. The evidence on mRNA vaccine efficacy post first dose is reassuringly high ~80-90%. The real-world vaccine effectiveness data from Scotland, and Canada is also very encouraging, although the recent rate of infection in Canada has been lower. The EWG also noted the need to be consistent with the dosing interval between the two mRNA vaccines, or to be able to factually describe the basis for any inconsistencies, given the platforms are very similar.

2.4 The EWG noted that the most recent evidence available strengthens rather than undermines the rationale for an interval of at least 28 days. The EWG noted there is a reasonable basis to support extending the dose interval to at least 28 days. The precise implementation of the interval e.g. possibly to 12 weeks, in order to optimise population coverage falls within JCVI's purview.

2.5 The EWG noted the Pfizer and Moderna platforms use very similar but not identical technologies, and therefore, any comparison needs to be precisely constructed / grounded in science. Another caveat is that the landscape may change depending on the emergence of variants and as the present understanding of the disease matures.

2.6 The EWG noted it was of great benefit that high levels of efficacy have been shown against the primary virus, but as mentioned previously variants remain a potential concern. The scientific rationale that led to the extension of the AZ vaccine interval was based on fairly limited data, but this rationale was shown to be correct when cross-referring to real-world data. Therefore, applying the same thought process to the Moderna vaccine would not be unreasonable, but would need to be supported by immunogenicity data / other trial data such as the Oxford Vaccine Group heterologous prime-boost COVID-19 vaccination trial (Com-COV).

2.7 The EWG noted there is a need for more comparative immunogenicity data, but data emerging on the correlates of protection is promising for both for binding antibody to spike and viral neutralisation. The identical testing platforms are being used to test sera from cohorts of Moderna vaccine recipients and Pfizer vaccine recipients. The early comparative results show immunogenicity three weeks after one dose to be similar. The EWG noted that the recommended dosage of Moderna dose is larger than that of Pfizer/BioNTech.

2.8 The EWG asked about the process to handle the potential amendment to return the vaccine interval to that originally endorsed by the EWG. The Chair explained that the present meeting represents the first stage, the collation of the views of the expert committee, which will be followed by a CHM meeting, where a recommendation may be given. The recommendation will enable the MHRA to approach DHSC with the position of the CHM, and a discussion with the manufacturer will follow to reconcile the product information with an extended dosing

interval. A dosing interval of at least 28 days should permit the JCVI greater flexibility to facilitate wider Moderna first dose vaccine coverage.

2.9 The EWG requested information on the approach taken by the Canadian regulatory authority. The EWG heard a form of emergency-use authorisation has been granted and currently reflects the 28-day interval, reflecting an off-label approach that has been taken for the roll-out. The EWG noted that the dose interval of 4 weeks selected in the trials, was not based on exploratory clinical data.

2.10 The Chair concluded that the EWG share the perspective that the available data continue to support a dosing interval of at least 28 days for the Moderna vaccine, and that dosing interval recommendations should be consistent across both mRNA vaccines (Moderna and Pfizer/BioNTech).

3. Covid-19 Vaccines – Risk of Seizures

3.1 The EWG was informed of a cluster of 4 cases of seizures in patients with epilepsy who developed pyrexia and seizures within a few hours of receiving the AstraZeneca COVID-19 vaccine. The EWG noted that seizures/convulsions are included in the list of adverse events of special interest (AESI) for all COVID-19 vaccines and as such are closely monitored by the MHRA and the vaccines' authorisation holders. The EWG heard that although vaccines in general are not known to be causally associated with seizures in adults, seizures are included as an AESI as a precaution, because of the known but uncommon risk of febrile seizures in children following some immunisations.

3.2 The EWG considered an assessment of clinical trial data and individual case reports of seizure-related events reported via the UK Yellow Card Scheme for the Pfizer-BioNTech and AstraZeneca COVID-19 vaccines. For the Moderna vaccine, only clinical trial data and data from non-UK cases reported to the MHRA by the vaccine authorisation holder were considered; UK specific post-marketing data are not currently available as this vaccine has not yet been deployed in the UK.

3.3 The EWG agreed that the currently available data do not provide any evidence of a causal association between the COVID-19 vaccines and onset of seizure events in people without a prior history of seizure.

3.4 The EWG also agreed that the currently available data do not suggest a direct vaccine-specific increased risk of seizure and the COVID-19 vaccines in people with epilepsy or history of seizure.

3.5 The EWG discussed the small number of cases of seizure in people with a prior history of seizure reported alongside other known side effects of the COVID-19 vaccines. The EWG noted that intercurrent illness, feeling generally unwell, fever and fatigue can be triggers for seizures in some people with epilepsy and that some people do experience flu-like symptoms within 1-2 days of COVID-19 (and other) vaccinations. The EWG heard that the International League Against Epilepsy currently advises that fever developing after a COVID-19 vaccination could lower the seizure threshold in some people and that antipyretics, such as paracetamol, taken regularly after vaccination will minimise this risk.

3.6 The EWG noted that the UK information for the COVID-19 vaccines includes advice that, if required, paracetamol may be used after vaccination to provide symptomatic relief from post-vaccination adverse reactions and that advice about the use of paracetamol is also provided in the Green Book. The EWG agreed that there was no evidence available on whether

prophylactic paracetamol would reduce the risk of seizures in people with epilepsy following COVID-19 vaccination.

3.7 The EWG advised that based on the data currently available no updates to the product information for the COVID-19 vaccines are required, but that the risk of seizures should continue to be kept under close review.

4. Potential risk of Guillain-Barré syndrome GBS with Pfizer/BioNTech and AstraZeneca COVID-19 vaccines

4.1 The EWG was provided with an overview of Yellow Card reports of Guillain-Barré syndrome (GBS), an Adverse Event of Special Interest, up to and including 3 March 2021 with the Pfizer, AstraZeneca and Moderna vaccines. Clinical trial data and company data from Summary Monthly Safety Reviews were also provided.

4.2 The EWG heard epidemiological analysis which involved ecological, observed vs expected and rapid cycle analyses.

4.3 The EWG commented on the importance of following up GBS reports to gain sufficient detail to understand whether the cases meet the Brighton Collaboration Criteria for true Guillain-Barré syndrome.

4.4 The EWG and invited observers discussed ways to encourage healthcare professionals to provide more detail in Yellow Card reports and respond to follow up requests, including communicating with royal colleges and similar bodies, as well as medical directors of trusts.

4.5 The EWG noted that it was important to promote thorough reporting for all adverse events, rather than specific ones in order to avoid stimulating reporting and creating biases within the Yellow Card database.

4.6 The EWG stated that there was the potential of an increased signal of GBS, particularly with the AstraZeneca vaccine and that reports of GBS should be closely monitored but that a formal epidemiological study was not yet indicated at this stage.

5. Review of safety data for use of COVID-19 vaccines in patients with neuromuscular disorders

5.1 The EWG heard background information about a case of a patient with a neuromuscular disorder who had died shortly after receiving the AstraZeneca vaccine, as well as reports of patients with neuromuscular disorders experiencing more severe myalgia and creatinine kinase increases after vaccination with the Pfizer and AstraZeneca vaccines.

5.2 The EWG was provided with an overview of clinical trial data, Yellow Card reports and international reports regarding patients with underlying neuromuscular disorders who reported an aggravation of the underlying disease or renal damage, as well as reports of severe muscle damage in recipients regardless of their underlying disease status.

5.3 The EWG noted that the effects reported were broad but that no clear signal of vaccine association could be seen in the data.

The EWG requested that where possible, further details should be obtained for the most serious cases.

The EWG commented that creatinine kinase increases were difficult to interpret without knowing what the patient's baseline levels are.

5.4 The EWG concluded that these types of report should be kept under close monitoring but that no regulatory action was required at this stage.

6. Yellow Card Vaccine Monitor: Verbal Update

6.1 The EWG was provided with an update on enrolment of individuals to the Yellow Card Vaccine Monitor (YCVM), part of the MHRA pharmacovigilance surveillance strategy for the COVID-19 vaccines.

6.2 The EWG were reminded that individuals are recruited through the national call-recall process for vaccinations and receive a letter following the national call inviting them for vaccination.

6.3 The EWG heard that approximately 17,000 individuals have registered with the YCVM platform to date. Around 13,500 individuals have submitted data on their vaccination, of which around 5,700 individuals have submitted adverse reactions amounting to 11,500 adverse drug reactions reported to the YCVM.

6.4 The EWG also heard that a slightly higher proportion of women have registered compared to men, and women were also more likely to report an ADR.

6.5 The EWG heard that around 90% of individuals registered were of white British or white Irish ethnicity. The EWG considered the need to increase ethnic diversity and heard that engagement with the national call-recall process could increase ethnic diversity in specific areas.

6.6 The EWG heard that the top ten ADRs reported by vaccine type were consistent with the known short-term reactogenic effects of the COVID-19 vaccines.

6.7 The EWG considered that the presentation of data from the YCVM could be amended with stratification based on patient characteristics as opposed to the vaccine type in future updates to the EWG.

7. Any Other Business

7.1 None.

8. Date and time of next meeting

The next meeting is scheduled to take place on Thursday 18th March 2021 at 10:30.

The Meeting today started at 15:33 and ended at 17:24.

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Sir Munir is a member of the UK COVID Therapeutics Advisory Panel (UK-CTAP), which is advising the CMO on which compounds need to be prioritised for the RECOVERY+ trial (RECOVERY is funded via NIHR/DHSC).

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Professor French - Other relevant interest **-** Provides clinical care when in covering the acute medical wards where patients with COVID-19 are cared. NPNS in GSK - In September 2020 a sub-contract was signed with the Liverpool School of Tropical Medicine to undertake work evaluating the safety and effectiveness of GSK's RTS's malaria vaccine in Malawi. GSK are the primary funders to the LSTM.

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Dr Misbah - NPNS - Holds honorary Senior Lectureship with University of Oxford & Oxford University Hospitals NHS Foundation Trust.

Professor Price - NPNS in GSK and AstraZeneca – which relates to donations provided by both companies to the British Toxicology Society (BTS) to support their Annual Congress and Education and Training of which Professor Price is currently President of the Society (2020-2022).

Dr Riordan - Other relevant interests - Participant in Oxford University's ChAdOx1 nCoV-19 clinical trial –received immunisation 27/8/2020. NPNS - Postgraduate External Examiner for Oxford University (Postgraduate Diploma in Paediatric Infectious Diseases).

Professor Solomon - Other relevant interests – Professor Solomon provides clinical care for patients with Covid-19; chaired the MRC/NIHR committee which awarded funding for development of the Oxford Vaccine.

Mrs Wang – Other relevant interest arising from family with several rare diseases and conditions, some of which result in epileptic fits as a consequence.

Professor Weir - NPNS - Imperial College and Other relevant interest arising from his department collaborates with Imperial College on a number of clinical trials.

CTBV

Professor Turner – NPNS interest. Professor Turner is a Non Executive Director (non-remunerated) on the Board of the Cell and Gene Therapy Catapult (CGT) until the end of March. CGT have been tasked by UK Government with re-purposing a factory in Braintree to manufacture either a vaccine or a therapeutic mAb. No decision has been made as to whether or what product CGT Braintree may be asked to manufacture and that decision will be made by UK Government. Professor Turner does not believe that CGT Board will have any material input into the decision as to what product may be manufactured. Rentschler have signed a contract with the Cell and Gene Therapy Catapult (CGT) to rent one of the manufacturing clean room suites at the Stevenage Centre. Professor Turner understands that this will be for contract AAV manufacture.

CPS

Mr V'lain Fenton-May – None

Professor Yvonne Perrie - NPNS in Pfizer & AstraZeneca arising from a contract for a grant (March 2018), which includes contributions from these companies to the University of Strathclyde, Janssen in writing a grant for a PhD (now funded), GSK – arising from an EU grant to University of Strathclyde (Jan 2019-Dec 2019).

Professor Kevin Taylor – None

Dr Susannah Walsh – None

Observers for this meeting

[redacted] – [redacted]

[redacted]

[redacted] – [redacted]

[redacted] – [redacted]

COMMISSION ON HUMAN MEDICINES (CHM)

COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Wednesday 17th March 2021** at **15:00** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan
Mr VI G Fenton-May
Professor N French
Professor D Goldblatt
Ms S Hunneyball
Sir M Jacobs
Professor H J Lachmann
Professor P J Lehner
Mr R Lowe
Dr S Misbah
Professor Y Perrie
Professor S Price
Dr A Riordan
Professor T Solomon
Professor K M G Taylor
Dr R Thorpe
Professor M Turner
Dr S Walsh
Mrs M Wang
Professor C Weir

Apologies

Professor K Hyrich
Professor C Robertson
Professor P Shah

Invited Experts

[redacted]

Observers

[redacted]
Professor W S Lim
[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted] - LD (& for CHM)

Presenters supporting specific items

[redacted] - VRMM
[redacted] - VRMM
[redacted] - VRMM
[redacted] - VRMM

MHRA Observers

Ms R Arrundale - MHRA-Policy
[redacted] - Directorate
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - LD
Dr S Branch - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - MHRA-NIBSC
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - VRMM
[redacted] - MHRA-NIBSC
[redacted] - LD
[redacted] - Medical Writer
[redacted] - Comms
[redacted] - LD
[redacted] - LD
[redacted] - VRMM
[redacted] - LD - Medical Writer
[redacted] - LD
[redacted] - LD
[redacted] - MHRA-NIBSC
[redacted] - LD
Dr J Raine - MHRA CEO
Ms N Rose - MHRA-NIBSC
[redacted] - VRMM
[redacted] - LD
[redacted] LD
[redacted] - VRMM
Mr P Tregunno - VRMM

[redacted]

[redacted] - LD
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - VRMM
Dr K Wydenbach - LD

Secretariat

[redacted]

[redacted]

22nd June 2021

Key
LD = Licensing Division
NIBSC = National Institute for Biological Standards & Control
VRMM = Vigilance & Risk Management of Medicines
Directorate = Director of Operational Transformation
MHRA CEO = Chief Executive

1. Introduction and Announcement

1.1 The Chair reminded Members and invited Experts that the content of papers and proceeding of the meeting are strictly confidential and should be treated as 'Official – sensitive commercial' and should not be disclosed. There is no consent for members / participants to record the meeting, take screenshots or photographs of presentations. The meeting was recorded by the MHRA Secretariat for minute taking purposes only. The Chair & Members including all participants gave full consent to the recording prior to the start of the meeting.

1.2 Conflict of Interest Policy (Annex I to the minutes)

The Chair reminded members and participants that, in accordance with the CHM Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members were also reminded to declare any other matter which could reasonably be perceived as affecting their impartiality.

1.3 Participants declared interests and other relevant interests for this meeting at **Annex II** to the minutes.

1.4 Apologies were received from Professors Hyrich, Robertson and Shah for this meeting.

1.5 The Chair welcomed the following invited experts for the meeting today:

[redacted] Professor of [redacted] University of Oxford

[redacted] Imperial Healthcare College NHS Trust

[redacted] at Oxford University Hospitals

[redacted] at University Hospital Birmingham

[redacted] University College London Hospitals

According to the Conflict of interest Policy invited experts are permitted to participate in discussions and do not contribute to conclusions and recommendations. At the chair's discretion, Professor Scully, Dr Cooper and Dr Lester was permitted to participate by answering specific questions from the chair, but not raise spontaneous comments or questions.

1.6 The Chair welcomed the following Observers for the meeting today:

[redacted] Public Health England

[redacted]
Immunisation, Hepatitis, Blood Safety and Countermeasures Response
National Infection Service
Public health England

[redacted]

[redacted]
Professor of Primary Care and Director of Graduate Studies
[redacted]

[redacted]
Locum Consultant in Health Protection
Public Health Agency

[redacted]
Public Health England

[redacted], NIHR Health Protection Research Unit in Immunisation
London School of Hygiene & Tropical Medicine

[redacted]
Public Health Scotland

Professor Wei Shen Lim
COVID-19 Chair for JCVI

[redacted]
Public Health England

[redacted] Public Health Wales

[redacted]
Clinical Workstream [redacted]
National COVID-19 Vaccination Programme
NHS England and NHS Improvement (National)

[redacted]
Immunisation, Public Health England

2. Review of venous thromboembolism and thrombosis with thrombocytopaenia reported following vaccination with AstraZeneca COVID-19 vaccine

2.1 Introduction

2.1.1 The Chair welcomed the invited experts in haematology to the ad hoc Expert Working Group which had been convened to advise on reports of venous thromboembolism and thrombosis with thrombocytopaenia following vaccination with the AstraZeneca COVID-19 vaccine.

2.1.2 The Chair indicated that there were three questions to consider:

a. Is there an increased risk of peripheral VTE associated with the Pfizer and AZ vaccines?

b. Is there an increased risk of thrombocytopaenia with the Pfizer and AZ vaccines?

c. What is the expert view on cases of thrombosis with thrombocytopaenia associated with the AZ vaccine?

2.2 Peripheral Venous thromboembolism

2.2.1 The meeting heard data presented by MHRA and Public Health England in relation to peripheral venous thromboembolic events. Combined epidemiological evidence from multiple data sources including the MHRA's Yellow Card database, CPRD and the Secondary Uses Service consistently indicate that the incidence of venous thromboembolic events is not at a higher level than expected when compared to historical background rates and when other risk factors such as underlying conditions were taken into account. The Group concluded following discussion that the available data indicate there was no signal of these events occurring with either COVID-19 vaccine currently deployed in UK, Pfizer/BioNTech and AstraZeneca COVID-19 vaccine.

2.3 Immune thrombocytopaenia

2.3.1 Observed/ expected analyses indicate the number of observed spontaneous reports of ITP received through the Yellow Card scheme remains substantially below the expected.

2.4 Thrombosis with thrombocytopaenia

2.4.1 There were no cases noted for the Pfizer vaccines. Case report details were presented for the Astra Zeneca vaccine. The meeting noted a small cluster of 7 thrombotic events (5 CVST and 2 PE) occurring in conjunction with thrombocytopenia predominantly in younger patients (range 19-73, mean 41.7, median 32 years) following vaccination with AstraZeneca COVID-19 vaccine. This was agreed to be a challenging issue to investigate: due to the combination of events, it would extremely be difficult to evaluate this using epidemiological analyses alone, and detailed examination of the clinical characteristics of the cases would be needed.

2.4.2 The meeting heard evidence relating to a signal of thromboembolic events occurring with thrombocytopaenia that had been raised by the EMA following suspension of the AstraZeneca vaccine in several EU member states including Ireland, Norway, Iceland, Austria, Estonia, Lithuania, Luxembourg, Italy, Latvia, and most recently, France, Spain and Germany. There appeared to be a pattern of Cerebral Venous Thrombosis with thrombocytopaenia. Some cases were apparently confounded, e.g. by concomitant hormonal oral contraceptives. There were 5 cases in Norway (4 CVST plus 1 portal venous

thrombosis, three of whom were on Oral Contraceptives or Nuvaring) and 7 cases in Germany all in young women (three with potential risk factors for thrombosis, oral contraceptives, unspecified genetic disorder and pre-existing thrombophilia with von Willebrand disease type 1, Factor V Leiden mutation and anticardiolipin antibody).

2.4.3 The meeting noted anecdotally that there were likely other similar cases that had not yet been received by the MHRA. Experts agreed there was a need to rapidly gather data on these cases, including previous COVID-19 infection, with clinical input from a panel of clinical experts as the data emerged to keep pace with the dynamic nature of the signal. It would also be helpful to put out a call for reporting via the British Society for Haematology, not only of cases occurring in relation to the vaccine but also those which occur naturally.

2.4.4 Experts noted that the co-existence of a prothrombotic state with thrombocytopaenia is rare. Although this is seen to occur rarely with certain conditions, at present it is unclear if a causal association exists with the vaccine. Nevertheless, given the close temporal association and the rare nature of the event, the meeting concluded this should be promptly evaluated further as a signal.

2.4.5 To date, thrombosis occurring with thrombocytopenia has not been noted with the Pfizer vaccine from UK Yellow Card reports. The Centres for Disease Control's rapid cycle analysis for events of venous thromboembolism, pulmonary embolism and disseminated intravascular coagulation has not identified a statistically significant increased risk for any of these events for the mRNA vaccines in use in the USA (Pfizer and Moderna).

2.4.6 Immune thrombocytopenia can occur with vaccines, for example, it has been noted to be associated with the MMR vaccine at a risk of approximately 1 per 25,000. Further literature analyses of the occurrence of thrombocytopaenia together with thrombosis for any vaccine needs to be undertaken.

2.5 Conclusion

2.5.1 The Group agreed that there was no evidence of an increased risk of peripheral venous thromboembolism. The group also agreed that the evidence did not support an increased risk of thrombocytopaenia alone.

2.5.2 Although the numbers of cases of thrombosis with thrombocytopaenia were small, the Group advised that since this was a very serious condition further information should be rapidly gathered.

2.6 Advice

2.6.1 The meeting advised that the benefit-risk of the vaccine was still positive overall, although it may vary in different age groups and clinical vulnerability. Further data on the risk of COVID-19 stratified by age needs to be evaluated (not only with respect to mortality, but also hospitalisation) to provide a better assessment of benefit-risk in different age groups.

2.6.2 The meeting agreed on the further next steps:

a. To work with expert haematologists on a proforma to rapidly gather more relevant clinical details on cases of thrombosis with thrombocytopaenia

b. To work with a panel of experts to obtain expert review of cases, understand their nature and whether there is a causal association.

c. To work with clinical groups including the British Society for Haematology to encourage pro-active reporting of cases to the Yellow Card scheme in as much

detail as possible. This would include reporting of COVID-19 serology, and also of similar events not associated with vaccination.

d. Along with experts, to carefully establish appropriate risk minimisation strategies to enable patients and non-specialists to be able to detect the occurrence of these events at an early stage.

e. Ongoing review at a rapid pace to be discussed with the Expert Working Group at subsequent meetings.

2.7 Communications

2.7.1 The meeting noted that public messaging around the signal would need to be very carefully handled to maintain public confidence.

3. Any Other Business

None.

4. Date and time of next meeting

The next meeting is scheduled to take place on Thursday 18th March 2021 at 10:30.

The Meeting today started at 15:01 and ended at 17:10.

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Annex I

Conflict of Interest Policy for CHM COVID-19 Vaccine Benefit Risk EWG

Chair and Members

- May not hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
- May not currently be or have previously been involved in the development of COVID-19 vaccines

Invited to all meetings, receives all papers and presentations and is permitted full participation in discussion, including drawing up conclusions and recommendations

Invited experts

- May hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
- May currently be or have previously been involved in the development of COVID-19 vaccines

May be invited to all relevant meetings, receives all papers and presentations and is permitted to participate in discussions when invited by the Chair. Does not contribute to conclusions and recommendations

Observers

Are invited to attend all meetings. Will not participate in drawing up conclusions and recommendations.

Annex II

The following participants declared interests and other relevant interests at the meeting today:

Professor Sir Munir Pirmohamed - NPNS AstraZeneca - Research grant to UOL to support PhD in drug interactions.
Other relevant interests in Pfizer, Janssen, Sanofi – Sir Munir is part of an EU-funded IMI consortium on gene therapy, and these companies are partners in the project. The University of Liverpool will get funding from the EU (but not from the partners), this IMI project commences on 3rd November 2020.
AGILE – this is a Liverpool early phase trial platform (between University of Liverpool and Liverpool School of Tropical Medicine). It is funded by the Wellcome Trust and UKRI/DHSC/NIHR. It is NOT evaluating vaccines, but only drugs to treat COVID-19. Sir Munir is not on the trial management group, and he is not directly involved in choosing the compounds for the study. Sir Munir has no involvement with any of the developers of the compounds to be studied (academic or industrial).
Sir Munir is a member of the UK COVID Therapeutics Advisory Panel (UK-CTAP), which is advising the CMO on which compounds need to be prioritised for the RECOVERY+ trial (RECOVERY is funded via NIHR/DHSC).

Professor Breuer – NPNS – Professor Breuer is on the data safety monitoring committee, DSMB, a study looking at combining vaccines being run by Matthew Snape in Oxford. There does not appear to be any involvement of the vaccine manufacturers and is for already licensed vaccines. The study is funded by the NIHR (Dec 2020).

Professor French - Other relevant interest **-** Provides clinical care when in covering the acute medical wards where patients with COVID-19 are cared. NPNS in GSK - In September 2020 a sub-contract was signed with the Liverpool School of Tropical Medicine to undertake work evaluating the safety and effectiveness of GSK's RTS's malaria vaccine in Malawi. GSK are the primary funders to the LSTM.

Ms Hunneyball - Other relevant interest – writes articles published in the Chemist and Druggist magazine, a trade magazine for pharmacists, but receives no payment for these articles. The information referred to in the articles is in the public domain. Ms Hunneyball makes it clear that these are her personal views and reflections and references all sources of information used.

Sir Michael Jacobs - Other relevant interest - As part of the academic role at the Liverpool School of Tropical Medicine, Sir Michael is a member of the Study Management Team and antiviral drug prioritisation group for the AGILE proof of concept (phase I/II) platform study. Sir Michael is also part of the team that submits new antiviral compounds against SARS-CoV2 for consideration by NIHR for testing on this platform. No commercial or financial interest in the trial or any of the compounds, or any pharmaceutical or biotechnology company.

Professor Lachmann – Other relevant interest as a volunteer participant in the Oxford vaccine study and no other involvement in the study.

Professor Lehner - Other relevant interest – Professor Lehner previously held a DPAC (Discovery Partnership with Academia) agreement with GSK, but this has been completed. Professor Lehner's participation in his local hospital D and T governance committee deliberations would form the normal activity and professional responsibility in his post and does not interfere with the EWG considerations (Sept 2020).

Dr Misbah - NPNS - Holds honorary Senior Lectureship with University of Oxford & Oxford University Hospitals NHS Foundation Trust.

Professor Perrie - NPNS in Pfizer & AstraZeneca arising from a contract for a grant (March 2018), which includes contributions from these companies to the University of Strathclyde, Janssen in writing a grant for a PhD (now funded), GSK – arising from an EU grant to University of Strathclyde (Jan 2019-Dec 2019).

Professor Price - NPNS in GSK and AstraZeneca – which relates to donations provided by both companies to the British Toxicology Society (BTS) to support their Annual Congress and Education and Training of which Professor Price is currently President of the Society (2020-2022).

Dr Riordan - Other relevant interests - Participant in Oxford University's ChAdOx1 nCoV-19 clinical trial –received immunisation 27/8/2020. NPNS - Postgraduate External Examiner for Oxford University (Postgraduate Diploma in Paediatric Infectious Diseases).

Professor Solomon - Other relevant interests – Professor Solomon provides clinical care for patients with Covid-19; chaired the MRC/NIHR committee which awarded funding for development of the Oxford Vaccine.

Professor Turner - NPNS interest. Professor Turner is a Non Executive Director (non-remunerated) on the Board of the Cell and Gene Therapy Catapult (CGT) until the end of March. CGT have been tasked by UK Government with re-purposing a factory in Braintree to manufacture either a vaccine or a therapeutic mAb. No decision has been made as to whether or what product CGT Braintree may be asked to manufacture and that decision will be made by UK Government. Professor Turner does not believe that CGT Board will have any material input into the decision as to what product may be manufactured. Rentschler have signed a contract with the Cell and Gene Therapy Catapult (CGT) to rent one of the manufacturing clean room suites at the Stevenage Centre. Professor Turner understands that this will be for contract AAV manufacture.

Professor Weir - NPNS - Imperial College and Other relevant interest arising from his department collaborates with Imperial College on a number of clinical trials.

Invited Experts for this meeting

[redacted]

Observers for this meeting

[redacted] - None

[redacted] - None

[redacted] - None

[redacted]

[redacted] – None

Professor Lim - NPNS interest as the institution he works for (Nottingham University Hospitals NHS Trust) has received unrestricted investigator-initiated research funding from Pfizer for an unrelated prospective population-based cohort study of pneumococcal pneumonia in which WSL is the Chief Investigator.

[redacted]

[redacted]

[redacted]

[redacted] – None

[redacted] – None

[redacted] – None

COMMISSION ON HUMAN MEDICINES (CHM)
COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Thursday 18th March 2021** at **10:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan
Mr VI G Fenton-May
Professor N French
Professor D Goldblatt
Professor K Hyrich
Sir M Jacobs
Professor P J Lehner
Mr R Lowe
Dr S Misbah
Professor Y Perrie
Professor S Price
Professor C Robertson
Professor P Shah
Professor T Solomon
Professor K M G Taylor
Dr R Thorpe
Professor M Turner
Dr S Walsh
Mrs M Wang
Professor C Weir

Apologies

Ms S Hunneyball
Professor H J Lachmann
Dr A Riordan

Invited Experts – Presenters of Item 2

[redacted]

Observers

[redacted]

Secretariat

[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD

Presenter supporting specific item

[redacted]

MHRA Observers

[redacted] - LD- Medical Writer
[redacted] - LD- Medical Writer
[redacted] - LD
Dr S Branch - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - VRMM
[redacted] - MHRA-NIBSC
[redacted] LD
[redacted] - LD
[redacted] LD
[redacted] - LD
Ms N Rose - MHRA-NIBSC
[redacted] LD
[redacted] - LD
Mr P Tregunno - VRMM
[redacted] - MHRA-NIBSC
[redacted] - LD
[redacted] - LD

[redacted]

19th July 2021

Key
LD = Licensing Division
NIBSC = National Institute for Biological Standards & Control
VRMM = Vigilance & Risk Management of Medicines

1. Introduction and Announcement

1.1 The Chair reminded Members and invited Experts that the content of papers and proceeding of the meeting are strictly confidential and should be treated as 'Official – sensitive commercial' and should not be disclosed. There is no consent for members / participants to record the meeting, take screenshots or photographs of presentations. The meeting was recorded by the MHRA Secretariat for minute taking purposes only. The Chair & Members including all participants gave full consent to the recording prior to the start of the meeting.

1.2 Conflict of Interest Policy (Annex I to the minutes)

The Chair reminded members and participants that, in accordance with the CHM Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members were also reminded to declare any other matter which could reasonably be perceived as affecting their impartiality.

1.3 Participants declared interests and other relevant interests for this meeting at **Annex II** to the minutes.

1.4 Apologies were received from Professor Lachmann, Dr Riordan and Ms Hunneyball for this meeting.

1.5 The Chair welcomed the following invited experts for the meeting today:

Dr [redacted]
Consultant Epidemiologist, Public Health England

Dr [redacted]
Institute of Health Informatics

Dr [redacted]
Public Health Registrar at UCL

1.6 The Chair welcomed the following Observers for the meeting today:

Dr [redacted]
[redacted], Public Health England

Dr [redacted]

Dr [redacted]
HSCNI

Dr [redacted]
Public Health Scotland

Dr [redacted]
Public Health England

Dr [redacted]
[redacted] Public Health Wales

Dr [redacted] MB ChB, FRCGP, FIMC (RCSEd), DUMC
Clinical Workstream – [redacted]
National COVID-19 Vaccination Programme
NHS England and NHS Improvement (National)

2. Vivaldi Project

2.1 The EWG viewed slides and heard a presentation by Birmingham University/University College London (BHU/UCL) experts on the findings of the Vivaldi Project. The Vivaldi project is an ongoing prospective cohort study of staff and residents 65 years and over in care homes in England that analyses vaccine effectiveness against Polymerase Chain Reduction (PCR)-positive SARS-CoV-2 infection.

2.2 The EWG heard that analysis data are sourced from NHS Foundry (Pillar 1 and Pillar 2 for PCR testing data, and the National Immunisation Management Service [NIMS] database for vaccination). The primary outcome was any new PCR-positive SARS-CoV-2 infection, excluding any PCR+ within 90 days of a prior PCR positive (and start of time at risk delayed until 90 days had elapsed). The analysis period was 08 December 2020 to 09 March 2021 (the date of first vaccination in the resident cohort being the start date of analysis). Vaccination status was defined as a time varying exposure extending from unvaccinated, and day intervals up to 48^{+} days.

2.3 The EWG heard that the cohort for analysis was 10,101 residents (with a median age of 86). 88% of the cohort had received their first vaccine (2/3 Oxford/AstraZeneca and 1/3 Pfizer), with 11% of vaccinees having a prior infection. Only 6% had received their second dose; hence this cohort was not considered in this vaccine effect analysis.

2.4 The majority of the PCR testing in the analysis was Pillar 2 testing (99.4%) with only 0.7.% symptomatic at the time of testing. The median PCR results per month (1.6. PCR^{+} results) were predominately from Pillar 2 testing (84.7%), with only 7.6% symptomatic at time of testing. Based on this analysis data, the overall crude infection rate was 21.2/10,000 person day (95% Confidence Interval [CI] 20.1, 22.3). Overall, there was 52% PCR positives, with cycle threshold of less than 25 (Ct <25).

2.5 The EWG heard that analysis based on adjusted hazard ratios shows an early protective effect that may be due to the deferral effect with active outbreak, with a true protective effect likely from Day 28 for both vaccines. It was noted that the early deferral effect was greater with the AstraZeneca vaccine than with Pfizer; the expert explained that it was not clear as to why this was and suggested that it may be linked with the time of deployment of the two vaccines and the type of homes where they were deployed. Based on the results of the analysis of vaccination effect by prior exposure (infection), it is unclear as to whether vaccination is providing any protection beyond that gained from prior infection.

2.6 The EWG heard that future analyses will include sensitivity analyses and further exploration of Ct values data, further analyses of serology data from pre-and post-vaccination samples, vaccine effectiveness against hospitalisation due to COVID-19, vaccine effect after second

dose of vaccine, incorporating estimates of care home seroprevalence prior to vaccination into care home level analyses, and incorporating staff vaccination coverage estimates into future models.

2.7 The EWG asked for clarification as to the reason for the small number of residents (3 residents out of 631; 0.5% of the cohort) having different first and second vaccines. The external expert explained that this was unclear; however, this is as the NIMS records indicate.

2.8 The EWG asked the external experts whether vaccine protection in this cohort was being seen at 28 days, later than in other studies, due to the older population and the slower ability to mount an immune response in this population. The experts stated that the reasons were unclear. However, they explained that mainly Pillar 2 testing was analysed where the subjects were likely asymptomatic, while the outcome in the trials was symptomatic infection, although these trials looked at some asymptomatic cases as well. External experts also commented that the onset of symptomatic disease appears slightly later in the elderly population than the younger age groups, around 21 days versus 14 days. It was agreed with the EWG that this was consistent with data that has already been published.

2.9 The EWG questioned whether the stratification of data by care home should be carried out to reflect the status of other residents in the care home. However, the external experts explained that in the majority of cases the vaccination is carried out too rapidly within a single care home for this effect to be analysed and adjusted for through this type of stratification.

2.10 The EWG asked whether the invited experts could provide an explanation for reported deaths in unvaccinated care home residents only, in terms of survivor bias. The invited experts commented that potential biases (e.g. decisions as to which residents are vaccinated or are hospitalised due to end of life care) make it difficult to analyse the outcomes of hospitalisation and death; however, a sensitivity analysis is planned to exclude those who were never vaccinated, but were at the home at the time vaccination was occurring within the care home.

2.11 The EWG commented that they are looking forward to the analysis on the impact of the second dose. The external expert confirmed that analysis would be conducted on the second dose once the data is available.

3. Pfizer/BioNTech COVID-19 Vaccine – Risk of severe cutaneous adverse reactions (SCAR)

3.1 The EWG was informed of two reports of Toxic Epidermal Necrolysis (TEN) in which the suspected reaction occurred following vaccination with the Pfizer-BioNTech COVID-19 vaccine, one of them fatal, and one case of Stevens-Johnson syndrome (SJS). The EWG noted that SJS and TEN are variants of the same condition distinct from erythema multiforme with an incidence of about 1-2 cases per million population per year. The EWG was reminded of clinical and histopathological features of this condition.

3.2 The EWG considered an assessment of clinical trial data and individual case reports received via the UK Yellow Card Scheme for the Pfizer-BioNTech vaccine concerning Severe Cutaneous Adverse Reactions (SCARs), including cases of SJS/TEN.

3.3 The EWG agreed that the currently available data do not provide evidence of a causal association between Pfizer-BioNTech vaccine and SJS/TEN, and in the fatal case presented concomitant medication could have also triggered the reaction. In all three cases, the onset of symptoms was inconsistent with a vaccine related effect. In addition, the clinical and histopathological features reported in these cases did not meet all the diagnostic criteria for

SJS/TEN with regard to both clinical and histopathological features. The EWG also noted that the number of cases does not exceed the background rate expected for this disease given over 10 million doses of vaccine were administered.

3.4 The EWG agreed that the review of other bullous and erosive skin conditions reported via the Yellow Card scheme did not identify any further possible cases of SJS/TEN and considered no other cases of Severe Cutaneous Adverse Reactions included in the review raised a concern.

3.5 The EWG noted that reviews of less serious skin hypersensitivity reactions (including rash, urticaria, pruritus) and delayed hypersensitivity reactions (including those starting at the injection site) are ongoing in parallel and agreed these should be discussed at the meeting only if a concern emerged.

3.6 The EWG advised that based on the data currently available no update to the product information is required, but that the risk of severe cutaneous adverse reactions should continue to be kept under review.

4. Any Other Business

4.1 None.

5. Date and time of next meeting

The next meeting is scheduled to take place on Wednesday 24th March 2021 at 13:30.

The Meeting today started at 10:31 and ended at 11:28.

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Annex I

Conflict of Interest Policy for CHM COVID-19 Vaccine Benefit Risk EWG

Chair and Members

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Invited experts

- May hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
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Observers

Are invited to attend all meetings. Will not participate in drawing up conclusions and recommendations.

Annex II

The following participants declared interests and other relevant interests at the meeting today:

Professor Sir Munir Pirmohamed - NPNS AstraZeneca - Research grant to UOL to support PhD in drug interactions.
Other relevant interests in Pfizer, Janssen, Sanofi – Sir Munir is part of an EU-funded IMI consortium on gene therapy, and these companies are partners in the project. The University of Liverpool will get funding from the EU (but not from the partners), this IMI project commences on 3rd November 2020.
AGILE – this is a Liverpool early phase trial platform (between University of Liverpool and Liverpool School of Tropical Medicine). It is funded by the Wellcome Trust and UKRI/DHSC/NIHR. It is NOT evaluating vaccines, but only drugs to treat COVID-19. Sir Munir is not on the trial management group, and he is not directly involved in choosing the compounds for the study. Sir Munir has no involvement with any of the developers of the compounds to be studied (academic or industrial).
Sir Munir is a member of the UK COVID Therapeutics Advisory Panel (UK-CTAP), which is advising the CMO on which compounds need to be prioritised for the RECOVERY+ trial (RECOVERY is funded via NIHR/DHSC).

Professor Breuer – NPNS – Professor Breuer is on the data safety monitoring committee, DSMB, a study looking at combining vaccines being run by Matthew Snape in Oxford. There does not appear to be any involvement of the vaccine manufacturers and is for already licensed vaccines. The study is funded by the NIHR (Dec 2020).

Professor French - Other relevant interest **-** Provides clinical care when in covering the acute medical wards where patients with COVID-19 are cared. NPNS in GSK - In September 2020 a sub-contract was signed with the Liverpool School of Tropical Medicine to undertake work evaluating the safety and effectiveness of GSK's RTS's malaria vaccine in Malawi. GSK are the primary funders to the LSTM.

Professor Hyrich – NPNS - Professor Hyrich was co-I on an investigator-initiated research grant exploring predictors of outcome in rheumatoid arthritis. NPNS Pfizer- she is a Co-I on a grant exploring adherence to JAK inhibitors in rheumatoid arthritis. NPNS in Abbvie, Professor Hyrich gave some lectures at an education conference on effectiveness of treatment for rheumatoid arthritis.

Sir Michael Jacobs - Other relevant interest - As part of the academic role at the Liverpool School of Tropical Medicine, Sir Michael is a member of the Study Management Team and antiviral drug prioritisation group for the AGILE proof of concept (phase I/II) platform study. Sir Michael is also part of the team that submits new antiviral compounds against SARS-CoV2 for consideration by NIHR for testing on this platform. No commercial or financial interest in the trial or any of the compounds, or any pharmaceutical or biotechnology company.

Professor Lehner - Other relevant interest – Professor Lehner previously held a DPAC (Discovery Partnership with Academia) agreement with GSK, but this has been completed. Professor Lehner's participation in his local hospital D and T governance committee deliberations would form the normal activity and professional responsibility in his post and does not interfere with the EWG considerations (Sept 2020).

Dr Misbah - NPNS - Holds honorary Senior Lectureship with University of Oxford & Oxford University Hospitals NHS Foundation Trust.

Professor Perrie - NPNS in Pfizer & AstraZeneca arising from a contract for a grant (March 2018), which includes contributions from these companies to the University of Strathclyde, Janssen in writing a grant for a PhD (now funded), GSK – arising from an EU grant to University of Strathclyde (Jan 2019-Dec 2019).

Professor Price - NPNS in GSK and AstraZeneca – which relates to donations provided by both companies to the British Toxicology Society (BTS) to support their Annual Congress and Education and Training of which Professor Price is currently President of the Society (2020-2022).

Professor Solomon - Other relevant interests – Professor Solomon provides clinical care for patients with Covid-19; chaired the MRC/NIHR committee which awarded funding for development of the Oxford Vaccine.

Professor Turner - NPNS interest. Professor Turner is a Non Executive Director (non-remunerated) on the Board of the Cell and Gene Therapy Catapult (CGT) until the end of March. CGT have been tasked by UK Government with re-purposing a factory in Braintree to manufacture either a vaccine or a therapeutic mAb. No decision has been made as to whether or what product CGT Braintree may be asked to manufacture and that decision will be made by UK Government. Professor Turner does not believe that CGT Board will have any material input into the decision as to what product may be manufactured. Rentschler have signed a contract with the Cell and Gene Therapy Catapult (CGT) to rent one of the manufacturing clean room suites at the Stevenage Centre. Professor Turner understands that this will be for contract AAV manufacture.

Mrs Wang - Other relevant interests arising from being highly sensitive to insect stings, and plant products such as Hyacinth bulbs, as recorded on Mrs Wang's medical records. The family of Mrs Wang lives with several rare diseases and conditions, some of which result in epileptic fits.

Professor Weir - NPNS - Imperial College and Other relevant interest arising from his department collaborates with Imperial College on a number of clinical trials.

Observer declared interest for this meeting

Dr [redacted]

COMMISSION ON HUMAN MEDICINES (CHM)
COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Tuesday 23rd March 2021** at **15:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan[1]
Mr VI G Fenton-May
Professor N French
Professor D Goldblatt
Ms S Hunneyball
Professor K Hyrich[2]
Sir M Jacobs
Professor H J Lachmann
Professor P J Lehner
Mr R Lowe
Dr S Misbah
Professor Y Perrie
Professor S Price
Dr A Riordan
Professor C Robertson
Professor T Solomon
Professor K M G Taylor
Dr R Thorpe
Professor M Turner
Dr S Walsh
Mrs M Wang
Professor C Weir

Apologies

Professor P Shah

Invited Experts

[redacted] (presenter of specific item)

[redacted]

Observers

[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD

Presenter supporting specific item

[redacted] - VRMM
[redacted] - VRMM

MHRA Observers

Ms R Arrundale - MHRA-Policy
[redacted] - VRMM
[redacted] - LD
Dr S Branch - VRMM
[redacted] - MHRA-NIBSC
[redacted] - VRMM
[redacted] – MHRA-Policy
[redacted] - VRMM
[redacted] - VRMM
[redacted] - MHRA-NIBSC
[redacted] - COMMS
[redacted] - VRMM
[redacted] - VRMM
[redacted] - VRMM
Dr J Raine - MHRA CEO
Ms N Rose - MHRA-NIBSC
[redacted] - VRMM
[redacted] - VRMM
Mr P Tregunno - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - VRMM

Secretariat

[redacted]

[redacted]

4th February 2022

Professor W S Lim

[redacted]

Professor Van-Tam

Key
LD = Licensing Division
NIBSC = National Institute for Biological Standards & Control
VRMM = Vigilance & Risk Management of Medicines

[1] left during item 8
[2] joined during item 7

1. Introduction and Announcement

1.1 The Chair reminded Members and invited Experts that the content of papers and proceeding of the meeting are strictly confidential and should be treated as 'Official – sensitive commercial' and should not be disclosed. There is no consent for members / participants to record the meeting, take screenshots or photographs of presentations. The meeting was recorded by the MHRA Secretariat for minute taking purposes only. The Chair & Members including all participants gave full consent to the recording prior to the start of the meeting.

1.2 Conflict of Interest Policy (Annex I to the minutes)

The Chair reminded members and participants that, in accordance with the CHM Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members were also reminded to declare any other matter which could reasonably be perceived as affecting their impartiality.

1.3 Participants declared interests and other relevant interests for this meeting listed at **Annex II** to the minutes.

1.4 Apologies were received from Professor Shah for this meeting.

1.5 The Chair welcomed Invited Expert, Dr [redacted], [redacted] of Public Health England who presented item 7 - Vaccine benefit by age group and analysis of risk of events of thrombosis with thrombocytopenia at the meeting today.

1.6 The Chair welcomed the following Invited Haematology Experts for the meeting today:

Dr [redacted] **-** Imperial Healthcare College NHS Trust
Dr [redacted] **-** [redacted]
Dr [redacted] **-** Oxford University Hospitals
Dr [redacted] **-** University Hospital Birmingham
Professor [redacted], University of Oxford
Professor [redacted] **-** University College London Hospitals
Dr [redacted] **–** [redacted]

1.7 The Chair welcomed the following Observers for the meeting today:

Professor Jonathan Van-Tam - Deputy Chief Medical Officer
[redacted] **-** Public Health England **(**Scientific Secretariat to JCVI)
Dr [redacted] **-** Public Health England (Head of JCVI Scientific Secretariat)
Professor [redacted]
Dr [redacted] **-** HSCNI
Dr [redacted] **-** HSCNI
Dr [redacted] **-** LSHTM
Dr [redacted] **ry -** PHS
Professor Wei Shen Lim - COVID-19 Chair for JCVI
Dr [redacted] **-** Public Health England
Dr [redacted] **-** PHW
Dr [redacted] **-** NHS England & NHS Improvement
Dr [redacted]

Ms [redacted] **-** Public Health England
Dr [redacted] Public Health England
Dr [redacted] **-** Imperial College London

2. Minutes of EWG meeting of 17th March 2021

2.1 The minutes were subject to one comment on the reporting rate being addressed. This comment was actioned. The amendment was revisited by the Chair who then approved the minutes as a true and accurate record of the proceedings on 22nd June 2021.

3. Update on communications since 17 March 2021

3.1 MHRA had published a statement on 18 March which communicated the findings of the EWG so far, that the currently available evidence does not suggest that blood clots in veins (venous thromboembolism) are caused by COVID-19 Vaccine AstraZeneca, and that a further, detailed review into a very rare and specific type of blood clot in the cerebral veins (sinus vein thrombosis) occurring together with lowered platelets (thrombocytopenia) is ongoing. The EWG was informed that the MHRA advice remained that the benefits of the vaccines against COVID-19 continue to outweigh any risks and that the public should continue to get their vaccine when invited to do so.

3.2 The meeting heard an update on the PRAC review of thrombocytopenia and thromboses, and subsequent communications from the EMA. The meeting also heard that pending further review, PRAC had recommended introducing warnings in the product information for AstraZeneca COVID-19 vaccine to inform of a potential risk of DIC or CVST with thrombocytopenia. The meeting was given an overview of several media articles reporting on studies performed in Germany and Norway, which discuss potential mechanisms for the reported events. It was highlighted that there was no peer reviewed published evidence to date. It was also commented that a collection of cases may be published in the Lancet shortly. The experts noted that while there was a difference in wording between the communications released by the EMA and MHRA, both had stated in press briefings that no causal association with the AZ vaccine had been confirmed.

4. Update on COVID-19 Vaccine AstraZeneca and risk of thromboembolic events with concurrent thrombocytopenia

4.1 The EWG were presented with a summary of the cases available to date of thromboembolic events with concurrent thrombocytopenia following vaccination with AZ, both from the UK and worldwide. A potential case definition was also presented to the EWG.

4.2 Experts commented that many of the cases lacked important information for assessment but noted that the overall benefit:risk of the vaccine was still considered positive for the entire currently vaccinated population. The age groups reported in the cases were considered, and it was noted that older patients may present with different thromboses (such as PE and cardiac) due to variable risk factors. The experts noted that a number of cases in their records had tests for antibodies against heparin/platelet factor 4 (anti-PF4 antibodies) carried out, and that a number of these were positive. There was a discussion of the potential mechanism, including if it could be related to the spike protein which would not be specific to AZ. The EWG advised caution in assuming a link to the vaccine without establishing a mechanism as this had led to erroneous associations in some past cases.

4.3 The possible case definition was discussed, and it was proposed that this could be graded into three categories of diagnostic certainty in a similar way to Brighton Collaboration criteria: possible cases which report thrombosis alongside thrombocytopenia; probable cases which

also report D-dimer >4000 and confirmed cases which also include identified anti-PF4 antibodies. The experts suggested that platelet functional test should be considered in cases with strong clinical correlation if anti-PF4 testing was ambiguous.

4.4 The meeting considered whether there could be any relation to vaccine storage or delivery issues; the MHRA confirmed that there was no evidence to support this at present and also no evidence of a batch-related issue.

5. Updated proforma for case report collection – for agreement

The EWG were provided an overview of the proforma developed between MHRA and haematology experts to aid in gathering important case details on reports submitted to the MHRA. The EWG agreed that this could be refined and that comments should be provided to the MHRA so a final version could be agreed.

6. Risk management proposals including draft treatment guideline

6.1 The meeting considered what information could be gathered to further define risk factors in cases and potentially determine at risk groups. The MHRA also summarised future plans for a call to reporting of cases of interest and collaboration with PHE on data collection including serological testing. The meeting also heard of considerations for studies which could be conducted to further assist in the investigation of this potential risk.

6.2 The meeting discussed the lack of risk factors in many of the cases and highlighted that cases in older patients may not have raised suspicion to trigger full investigation and reporting of the events.

6.3 It was also considered what advice could be provided to advise patients on when to seek help, particularly around symptoms of headache and bruising. It was considered that advice to professionals on treatment protocols should be co-ordinated with NHSE and devolved administrations and ensure that it reaches key stakeholders in a co-ordinated way, while avoiding causing unnecessary concerns on the use of the vaccine.

7. PHE: vaccine benefit by age group and analysis of risk of events of thrombosis with thrombocytopenia

7.1 The meeting was presented with updated analysis from PHE of the events of interest associated with the AZ and Pfizer vaccine in the UK. The presentation highlighted that there was no indication of a raised risk of thromboembolic events with either of the vaccines and of the new terms included there were small numbers of events identified. There was no increased risk identified with the exception of 'Intracranial and intraspinal phlebitis and thrombophlebitis' for which there was indication of a small increased risk for AZ in the under 65 year age group; it was noted that unadjusted confounding could be present and that the numbers were small.

7.2 PHE also presented an analysis of the benefit of COVID-19 vaccination. It was shown that younger age groups required higher number of vaccinations to reduce deaths, hospitalisation and long-COVID, and that this effect of age was less pronounced for hospitalisation and long-COVID prevention. It was also noted that risk factors within age groups could impact this effect. A risk analysis of MHRA cases of CVST and CVST concurrent with thrombocytopenia was also provided, and showed that if causality was assumed, there would be a lower number of doses of AZ needed in the younger age group for an event of CVST with thrombocytopenia to occur, compared with older age groups.

7.3 The EWG discussed the uncertainties of the risk analysis and that due to the rarity of the events, these estimates would likely have wide confidence intervals. The EWG commented that an accurate number of cases is also unknown. The meeting highlighted that a case definition would assist in investigating this further.

8. AstraZeneca: presentation from company on cases received, potential mechanisms and discussion on studies planned

The Chair welcomed the following representatives from AstraZeneca for the meeting today:

8.1 AstraZeneca presented a summary of the cases they had received to date. The meeting heard that the majority of cases were female and younger age, and where dose was reported, these were all first dose. Many of the cases had important information missing. AstraZeneca provided an overview of potential mechanisms and discussed whether these would be specific to the AstraZeneca vaccine and its vector or common to all COVID-19 vaccines and associated with the spike protein. AstraZeneca commented on the challenges of epidemiological study of the combined event of thromboses with thrombocytopenia and stated that the company was engaged with NHSE to develop a protocol to study the potential association further.

8.2 The EWG discussed whether there would be any differences in the spike protein in the AZ vaccine compared to that produced with other vaccines. The company also confirmed to the meeting that no invitro assays had been conducted at present and that it was in contact with international investigators regarding cases too.

9. Next steps / Recommendation

9.1 The EWG discussed the information presented at the meeting. Members commented that the cases lacked significant information at present, that there was insufficient evidence to establish causality at present, and that the events that have been reported are rare. The EWG highlighted that information needed to be gathered on possible risk factors in cases.

9.2 The meeting also noted that there had been potential cases of thromboembolic events with thrombocytopenia reported with the Pfizer vaccine and that this information was important to consider. The meeting concluded that details on these reports should be obtained and presented for further discussion could be given at the next EWG meeting (24 March 2021).

10. <u>Any Other Business</u>

None.

11. <u>Date and time of next meeting</u>

The next meeting is scheduled to take place on Wednesday 24th March 2021 at 13:30.

The Meeting today started at 15:32 and ended at 19:01.

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Annex I

Conflict of Interest Policy for CHM COVID-19 Vaccine Benefit Risk EWG

Chair and Members

- May not hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
- May not currently be or have previously been involved in the development of COVID-19 vaccines

Invited to all meetings, receives all papers and presentations and is permitted full participation in discussion, including drawing up conclusions and recommendations

Invited experts

- May hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
- May currently be or have previously been involved in the development of COVID-19 vaccines

May be invited to all relevant meetings, receives all papers and presentations and is permitted to participate in discussions when invited by the Chair. Does not contribute to conclusions and recommendations

Observers

Are invited to attend all meetings. Will not participate in drawing up conclusions and recommendations.

Annex II

The following participants declared interests and other relevant interests at the meeting today:

Professor Sir Munir Pirmohamed - NPNS AstraZeneca - Research grant to UOL to support PhD in drug interactions.
Other relevant interests in Pfizer, Janssen, Sanofi – Sir Munir is part of an EU-funded IMI consortium on gene therapy, and these companies are partners in the project. The University of Liverpool will get funding from the EU (but not from the partners), this IMI project commences on 3rd November 2020.
AGILE – this is a Liverpool early phase trial platform (between University of Liverpool and Liverpool School of Tropical Medicine). It is funded by the Wellcome Trust and UKRI/DHSC/NIHR. It is NOT evaluating vaccines, but only drugs to treat COVID-19. Sir Munir is not on the trial management group, and he is not directly involved in choosing the compounds for the study. Sir Munir has no involvement with any of the developers of the compounds to be studied (academic or industrial).
Sir Munir is a member of the UK COVID Therapeutics Advisory Panel (UK-CTAP), which is advising the CMO on which compounds need to be prioritised for the RECOVERY+ trial (RECOVERY is funded via NIHR/DHSC).

Professor Breuer - NPNS – Professor Breuer is on the data safety monitoring committee, DSMB, a study looking at combining vaccines being run by Matthew Snape in Oxford. There does not appear to be any involvement of the vaccine manufacturers and is for already licensed vaccines. The study is funded by the NIHR (Dec 2020).

Professor French - Other relevant interest **-** Provides clinical care when in covering the acute medical wards where patients with COVID-19 are cared. NPNS in GSK - In September 2020 a sub-contract was signed with the Liverpool School of Tropical Medicine to undertake work evaluating the safety and effectiveness of GSK's RTS's malaria vaccine in Malawi. GSK are the primary funders to the LSTM.

Ms Hunneyball - Other relevant interest – writes articles published in the Chemist and Druggist magazine, a trade magazine for pharmacists, but receives no payment for these articles. The information referred to in the articles is in the public domain. Ms Hunneyball makes it clear that these are her personal views and reflections and references all sources of information used.

Professor Hyrich - NPNS - Professor Hyrich was co-I on an investigator-initiated research grant exploring predictors of outcome in rheumatoid arthritis. NPNS Pfizer- she is a Co-I on a grant exploring adherence to JAK inhibitors in rheumatoid arthritis. NPNS in Abbvie, Professor Hyrich gave some lectures at an education conference on effectiveness of treatment for rheumatoid arthritis.

Sir Michael Jacobs - Other relevant interest - As part of the academic role at the Liverpool School of Tropical Medicine, Sir Michael is a member of the Study Management Team and antiviral drug prioritisation group for the AGILE proof of concept (phase I/II) platform study. Sir Michael is also part of the team that submits new antiviral compounds against SARS-CoV2 for consideration by NIHR for testing on this platform. No commercial or financial interest in the trial or any of the compounds, or any pharmaceutical or biotechnology company.

Professor Lachmann - Other relevant interest as a volunteer participant in the Oxford vaccine study and no other involvement in the study.

Professor Lehner - Other relevant interest – Professor Lehner previously held a DPAC (Discovery Partnership with Academia) agreement with GSK, but this has been completed. Professor Lehner's participation in his local hospital D and T governance committee deliberations would form the normal activity and professional responsibility in his post and does not interfere with the EWG considerations (Sept 2020).

Dr Misbah - NPNS - Holds honorary Senior Lectureship with University of Oxford & Oxford University Hospitals NHS Foundation Trust.

Professor Perrie - NPNS in Pfizer & AstraZeneca arising from a contract for a grant (March 2018), which includes contributions from these companies to the University of Strathclyde, Janssen in writing a grant for a PhD (now funded), GSK – arising from an EU grant to University of Strathclyde (Jan 2019-Dec 2019).

Professor Price - NPNS in GSK and AstraZeneca – which relates to donations provided by both companies to the British Toxicology Society (BTS) to support their Annual Congress and Education and Training of which Professor Price is currently President of the Society (2020-2022).

Dr Riordan - Other relevant interests - Participant in Oxford University's ChAdOx1 nCoV-19 clinical trial –received immunisation 27/8/2020. NPNS - Postgraduate External Examiner for Oxford University (Postgraduate Diploma in Paediatric Infectious Diseases).

Professor Solomon - Other relevant interests – Professor Solomon provides clinical care for patients with Covid-19; chaired the MRC/NIHR committee which awarded funding for development of the Oxford Vaccine.

Professor Turner - NPNS interest. Professor Turner is a Non Executive Director (non-remunerated) on the Board of the Cell and Gene Therapy Catapult (CGT) until the end of March. CGT have been tasked by UK Government with re-purposing a factory in Braintree to manufacture either a vaccine or a therapeutic mAb. No decision has been made as to whether or what product CGT Braintree may be asked to manufacture and that decision will be made by UK Government. Professor Turner does not believe that CGT Board will have any material input into the decision as to what product may be manufactured. Rentschler have signed a contract with the Cell and Gene Therapy Catapult (CGT) to rent one of the manufacturing clean room suites at the Stevenage Centre. Professor Turner understands that this will be for contract AAV manufacture.

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Professor Weir - NPNS - Imperial College and Other relevant interest arising from his department collaborates with Imperial College on a number of clinical trials.

Invited Haematology Experts for this meeting

[redacted]

[redacted]

[redacted]

Dr Will Lester - PNS in Pfizer and Sanofi – no interests were declared in relation to vaccines

[redacted]

[redacted]

[redacted]

[redacted] - None

Observers for this meeting

[redacted]

[redacted]

[redacted]

Professor Wei Shen Lim - NPNS arises from the institution (Nottingham University Hospitals NHS Trust) where Professor Lim works has received unrestricted investigator-initiated research funding from Pfizer for an unrelated prospective population-based cohort study of pneumococcal pneumonia in which Professor Lim is the Chief Investigator.

[redacted]

COMMISSION ON HUMAN MEDICINES (CHM)
COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Wednesday 24th March 2021** at **13:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer[1]
Professor G Dougan[1]
Mr VI G Fenton-May
Professor N French
Professor D Goldblatt
Ms S Hunneyball
Professor K Hyrich
Sir M Jacobs
Professor H J Lachmann
Professor P J Lehner
Mr R Lowe
Dr S Misbah
Professor Y Perrie
Professor S Price
Dr A Riordan
Professor T Solomon
Professor K M G Taylor
Dr R Thorpe
Professor M Turner
Dr S Walsh
Mrs M Wang
Professor C Weir

Apologies

Professor C Robertson
Professor P Shah

Secretariat

[redacted]

Key
LD = Licensing Division
NIBSC = National Institute for Biological Standards & Control
VRMM = Vigilance & Risk Management of Medicines
MHRA CEO = Chief Executive
IE&S = Inspection, Enforcement & Standards
Comms = MHRA Communication

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD

Presenter supporting specific item

[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] – LD
[redacted] - LD

MHRA Observers

[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
Dr S Branch - VRMM
[redacted] - LD
[redacted] - MHRA-NIBSC
[redacted] - LD
[redacted] - MHRA-Policy
[redacted] - LD
[redacted] - Comms
Dr SP Lam - LD
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - VRMM
[redacted] - IE&S
[redacted] - LD
Dr J Raine - MHRA CEO
Ms N Rose - MHRA-NIBSC
[redacted] - MHRA-NIBSC
[redacted] - LD
[redacted] - LD
Mr P Tregunno - VRMM
[redacted] - LD
[redacted] - MHRA-NIBSC
[redacted] - LD
Dr K Wydenbach – LD

[redacted]
4 February 2022

[1] left during item 5

1. Introduction and Announcement

1.1 The Chair reminded Members and invited Experts that the content of papers and proceeding of the meeting are strictly confidential and should be treated as 'Official – sensitive commercial' and should not be disclosed. There is no consent for members / participants to record the meeting, take screenshots or photographs of presentations. The meeting was recorded by the MHRA Secretariat for minute taking purposes only. The Chair & Members including all participants gave full consent to the recording prior to the start of the meeting.

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1.3 Participants declared interests and other relevant interests for this meeting listed at **Annex II** to the minutes.

1.4 Apologies were received from Professors Robertson and Shah for this meeting.

2. Minutes

2.1 Minutes of EWG Meeting on Wednesday 13th January 2021

2.1.1 The minutes were approved as a true and accurate record of the proceedings.

2.2 Minutes of EWG Meeting on Monday 18th January 2021

2.2.1 The minutes were approved as a true and accurate record of the proceedings.

3. Update on cases of thromboembolic events with thrombocytopenia occurring with Pfizer and Astra-Zeneca COVID-19 vaccines

3.1 At the meeting on 23 March 2021, the EWG had noted that there had been potential cases of thromboembolic events with thrombocytopenia reported with the Pfizer vaccine. The MHRA confirmed that to date no UK cases of thromboembolic events with thrombocytopenia had been received following Pfizer COVID-19 vaccination but that one non-UK case of cerebral venous sinus thrombosis (CVST) with concurrent thrombocytopenia in association with the Pfizer vaccine had been reported. The EWG heard that the MHRA was seeking urgent clarification from the European Medicines Agency regarding other potential cases of thromboembolic events with thrombocytopenia occurring with the Pfizer vaccine.

3.2 The EWG heard that since their previous meeting on 23 March 2021, the MHRA had received details of cases of thromboembolic events with concurrent thrombocytopenia following vaccination with AstraZeneca COVID-19 vaccines from haematology experts. Following this, the MHRA were now reconciling such cases with Yellow Card reports on the MHRA database, where this was possible given the limited information in some reports. The EWG noted that there were now over 30 cases of thromboembolic events with thrombocytopenia with AstraZeneca, including cases with and without reported possible confounding factors.

3.3 The EWG highlighted that the background rate of thromboembolic events with thrombocytopenia is not known. The EWG discussed possible ways to obtain further information about the background rate including the feasibility of using laboratory, radiological, or the UK Biobank databases. The EWG considered that one approach would be to identify cases with a clinical diagnosis of CVST (and related terms) and then look at platelet counts to identify if any of these cases occurred with concurrent thrombocytopenia.

3.4 The EWG discussed anti-PF4 antibodies which had been reported in some of the cases of thromboembolic events with thrombocytopenia following AstraZeneca COVID-19 vaccination. The EWG considered anti-PF4 antibodies might not be the only identifying factor in such cases and that was important to know the background incidence of anti-PF4 antibodies in general and in people who had received a COVID-19 vaccine.

3.5 The EWG noted that the cases of CVST with thrombocytopenia that had been reported with AstraZeneca COVID-19 vaccine included cases without pre-disposing factors for CVST. The EWG commented that this was unusual in comparison with previously published reports of CVST in which most patients had a predisposing risk factor for this event.

3.6 The EWG noted that the need for any updates to the product information for AstraZeneca COVID-19 vaccine would be considered at a future meeting when more data would be available including further information on any additional cases in association with the Pfizer COVID-19 vaccine.

4. Novavax NC AR Sequence 1

4.1 The EWG heard the Matrix M1 adjuvant proposed for use in this vaccine has not been used in any vaccines authorised in UK or EU, but may be included in a Hepatitis vaccine in the US (yet to be fully confirmed): it has been used in other vaccines the company has in development. The EWG noted the review of the toxicology data for this adjuvant will need to be particularly in-depth, as human use is relatively recent. The EWG noted that the toxicity studies provide sufficient pharmacological and immunological data to support use of the vaccine in principle, notwithstanding the need for a comprehensive characterisation of the Matrix M1 adjuvant. The EWG also noted the available literature on the Matrix M1 adjuvant does not cover all aspects necessary to assure safety, and therefore additional supportive data will be required from the company. The EWG heard a parallel assessment is being undertaken by the EMA. The EWG noted that the company should be asked whether they intend to supply further data on the Matrix M1 adjuvant.

4.2 The EWG noted that glycosylation of antigens in some circumstances can block access to epitopes, [redacted]. The EWG heard the [redacted] The FluBlok vaccine also uses a baculovirus expression system resulting in glycosylated antigens and this product is widely authorised.

4.3 The EWG noted that the Novavax vaccine is clearly immunogenic, and T-cell responses are well balanced if slightly skewed [redacted] The challenge data in macaques showed sub-genomic SARS-CoV-2 RNA to be undetectable in vaccinated animals, a similar result was noted in non-clinical (NC) studies of the Moderna Vaccine. The AstraZeneca vaccine, however, did not completely eliminate virus in the nose. It is not yet known if the Novavax NC challenge data will translate to reduced transmissibility or perhaps superior efficacy in clinical trials.

4.4 The EWG Novavax data package on immunology was comprehensive, but the EWG noted that the previous application data packages for other, since authorised vaccines, additionally included studies of T-cell exhaustion, although, as of yet, this data has not proved useful.

4.5 The Chair explained that the clinical package is expected to be received shortly, and the data on variants will be a key aspect of the assessment process.

4.6 The EWG heard the Phase I/II data is expected within 2 weeks, and the phase III clinical study is expected to be submitted mid-April. The Chair confirmed that the EWG should be approached for advice on a rolling basis, in line with receipt and review of each data package, rather than the EWG advising on the entire clinical dossier.

4.7 The Chair asked about the mechanism underpinning the differential Th responses to alum adjuvant and Matrix M1. The MHRA noted that the means by which alum induces a Th2-favoured response is not known, but it is reliably established that it does.

4.8 The EWG endorsed the proposed list of questions, also seeking to clarify of there is commercial human use of the M1 matrix adjuvant. The MHRA confirmed the questions will be issued to the company with a deadline of four weeks for response. The company have already indicated that they intend to submit additional NC data to MHRA. It is hoped that these two components (responses, new data) can be brought to the EWG at a future meeting, in early May.

5. Novavax Quality Update

5.1 The EWG were provided with an overview of the manufacturing development. The EWG noted the [redacted] may be complicated by the [redacted] The forms need to be appropriately controlled, [redacted]. The EWG also noted the batch of product used in the clinical trial may not show an appropriate level of similarity to the batches created at production scale. The [redacted] issue should be considered a matter of [redacted] The potential for [redacted] to affect clinical outcomes needs to be investigated and understood. The EWG noted the [redacted] will also affect the [redacted] of the product and could impact [redacted]. The EWG noted that the heterogeneous nature of the product may be unavoidable; however, theoretically suitable antibody selection for the potency assay could qualify the product to a level that is satisfactory for authorisation. Ultimately, the company need to demonstrate that [redacted] of their product does not affect function.

5.2 The EWG endorsed the summary on [redacted] as detailed in the paper prepared by the assessment team. On a related topic, the EWG heard the [redacted] is proposed to demonstrate the potency of commercial batches but is intended for use outside of the release specification.

5.3 The EWG noted the revised [redacted] should be qualified for the purposes of release testing and used to replace the [redacted] The release specification limits also need to be configured to include both an upper and lower limit.

5.4 On a separate topic, the EWG noted that the absence of a signal of coagulopathy in the pre-clinical studies was reassuring. However, if cases of coagulopathy were to appear within the clinical trial, it will need to be established if the phospholipid content of the formulation could be a contributory factor. Currently, the literature on anti-phospholipid in humans shows auto-phosphatidylcholine antibodies can be produced by humans, but these do not appear to be pathogenic.

5.5 The MHRA confirmed meetings have recently occurred weekly with the company, the latest update is that PPQ batches are to be expected mid-April – May. The company are also participating in a rolling review (emergency use) application with the FDA.

6. Janssen update on the 'Reliance Procedure

6.1 The EWG heard that the Janssen Covid-19 vaccine is the first application in the UK with a single dose regimen. It received Emergency Use Authorisation (EUA) in the US on 27 February 2021 and the EMA issued a Conditional Marketing Authorisation (CMA) on 11 March 2021. The CMA submission to the MHRA followed later. The EWG were advised that a Regulation 174 request has not been received from DHSC and that this procedure would follow the EU Decision Reliance Procedure (but with an expedited timetable).

6.2 The EWG noted that the assessment for this regulatory route focuses on 'GB specific considerations' with points raised only if they are considered 'decision critical' meaning any concern which, if not addressed satisfactorily, changes the benefit risk from positive to negative.

6.3 The EWG heard that the complete data package is expected for the Reliance procedure shortly, and that this item will be brought back to the EWG once the assessment team has completed their assessment. It was noted by the assessors that, subject to review of the complete submission, no decision critical points are anticipated. The EWG heard that whilst there were no cases of anaphylaxis up to the data cut-off, there was a report of a delayed hypersensitivity reaction in a subject with angioedema and urticaria several days after vaccination. There was also a late breaking case of anaphylaxis that met the Brighton Collaboration Case Definition after the data cut-off. The EWG heard that the EMA have included a recommendation in the product information that individuals are observed for 15-minutes post vaccination to monitor for potential allergic / hypersensitivity reactions. This is in-line with the recommendations for all COVID-19 vaccines approved by the EMA to date.

6.4 The EWG noted the company are undertaking a second pivotal efficacy trial with two doses, whereas the present data package is based on a single dose pivotal trial. The EWG asked what the outcomes for 'the first' CMA would be, if the two-dose trial subsequently shows better efficacy, and/ or increased durability of immune response. The EWG heard when comparing data from single and two-dose studies in hamsters no differential response was seen. The MHRA assessor noted that if a Regulation 174 authorisation were to be conferred for the single dose, and subsequently greater benefit is shown in the two-dose trial, this may complicate aspects of vaccine policy and roll-out. Particularly, the issue how to manage the time interval for those who have had one dose under the initial regulation 174. However, the single dose vaccine meets the regulatory requirements.

6.5 The MHRA assessment team also confirmed that the data currently available show efficacy up to 2 months post dose and persistence of immunogenicity up to 3 months with the single dose. Longer follow-up data will be provided post-approval.

6.6 The MHRA assessor informed the EWG that 95% of subjects developed neutralising antibodies against the adenoviral vector after a single dose. Available data are limited, but presently show little correlation between levels of antibody against SARS-CoV-2 after the second dose and levels of neutralising antibody against the vector after the first dose. The second dose approximately doubles levels of neutralising antibodies against SARS-CoV-2, but this would need to be balanced against risks of development of neutralising antibodies against the adenoviral vector after the first dose.

6.7 The EWG noted the ongoing signal of rare cases of thrombosis with thrombocytopenia with COVID-19 vaccines. The EWG heard that unlike the AZ vaccine, the Spike protein in the

Janssen vaccine is [redacted]. The EWG noted that 2.5 million doses of the Janssen vaccine have been administered in the US and requested that this data is explored for signals of thrombosis with thrombocytopenia. The MHRA assessment team will also confirm whether or not the EMA have requested the company to submit a protocol for a post-authorisation study in relation to coagulopathy.

6.8 The EWG enquired about the justification of non-COVID-19 vaccine controls in forthcoming studies. The MHRA confirmed that in the Janssen one-dose trial, following the EUA in the US, all subjects on placebo will be offered the vaccine and encouraged to remain in the study for follow-up. The Chair noted the regulatory landscape in terms of clinical trials for future COVID vaccines will likely be adapted to our increased understanding of COVID-19 vaccines, and immunogenicity studies will likely be used to replace trials once a high coverage of the population has been reached.

7. Any Other Business

None.

8. Date and time of next meeting

The next meeting is scheduled to take place on Wednesday 31st March 2021 at 11:30.

The Meeting today started at 13:32 and ended at 15:47.

Members are reminded that the content of papers and proceeding of the meetings are to be treated as 'Official – sensitive commercial'. Members are also reminded that, in accordance with the Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members must also declare any other matter which could reasonably be perceived as affecting their impartiality. Detailed guidance is set out in the Code of Practice

Annex I

Conflict of Interest Policy for CHM COVID-19 Vaccine Benefit Risk EWG

Chair and Members

- May not hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
- May not currently be or have previously been involved in the development of COVID-19 vaccines

Invited to all meetings, receives all papers and presentations and is permitted full participation in discussion, including drawing up conclusions and recommendations

Invited experts

- May hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
- May currently be or have previously been involved in the development of COVID-19 vaccines

May be invited to all relevant meetings, receives all papers and presentations and is permitted to participate in discussions when invited by the Chair. Does not contribute to conclusions and recommendations

Observers

Are invited to attend all meetings. Will not participate in drawing up conclusions and recommendations.

Annex II

The following participants declared interests and other relevant interests at the meeting today:

Professor Sir Munir Pirmohamed - NPNS AstraZeneca - Research grant to UOL to support PhD in drug interactions.
Other relevant interests in Pfizer, Janssen, Sanofi – Sir Munir is part of an EU-funded IMI consortium on gene therapy, and these companies are partners in the project. The University of Liverpool will get funding from the EU (but not from the partners), this IMI project commences on 3rd November 2020.
AGILE – this is a Liverpool early phase trial platform (between University of Liverpool and Liverpool School of Tropical Medicine). It is funded by the Wellcome Trust and UKRI/DHSC/NIHR. It is NOT evaluating vaccines, but only drugs to treat COVID-19. Sir Munir is not on the trial management group, and he is not directly involved in choosing the compounds for the study. Sir Munir has no involvement with any of the developers of the compounds to be studied (academic or industrial).
Sir Munir is a member of the UK COVID Therapeutics Advisory Panel (UK-CTAP), which is advising the CMO on which compounds need to be prioritised for the RECOVERY+ trial (RECOVERY is funded via NIHR/DHSC).

Professor Breuer – NPNS – Professor Breuer is on the data safety monitoring committee, DSMB, a study looking at combining vaccines being run by Matthew Snape in Oxford. There does not appear to be any involvement of the vaccine manufacturers and is for already licensed vaccines. The study is funded by the NIHR (Dec 2020).

Professor French - Other relevant interest **-** Provides clinical care when in covering the acute medical wards where patients with COVID-19 are cared. NPNS in GSK - In September 2020 a sub-contract was signed with the Liverpool School of Tropical Medicine to undertake work evaluating the safety and effectiveness of GSK's RTS's malaria vaccine in Malawi. GSK are the primary funders to the LSTM.

Ms Hunneyball - Other relevant interest – writes articles published in the Chemist and Druggist magazine, a trade magazine for pharmacists, but receives no payment for these articles. The information referred to in the articles is in the public domain. Ms Hunneyball makes it clear that these are her personal views and reflections and references all sources of information used.

Professor Hyrich – NPNS - Professor Hyrich was co-I on an investigator-initiated research grant exploring predictors of outcome in rheumatoid arthritis. NPNS Pfizer- she is a Co-I on a grant exploring adherence to JAK inhibitors in rheumatoid arthritis. NPNS in Abbvie, Professor Hyrich gave some lectures at an education conference on effectiveness of treatment for rheumatoid arthritis.

Sir Michael Jacobs - Other relevant interest - As part of the academic role at the Liverpool School of Tropical Medicine, Sir Michael is a member of the Study Management Team and antiviral drug prioritisation group for the AGILE proof of concept (phase I/II) platform study. Sir Michael is also part of the team that submits new antiviral compounds against SARS-CoV2 for consideration by NIHR for testing on this platform. No commercial or financial interest in the trial or any of the compounds, or any pharmaceutical or biotechnology company.

Professor Lachmann – Other relevant interest as a volunteer participant in the Oxford vaccine study and no other involvement in the study.

Professor Lehner - Other relevant interest – Professor Lehner previously held a DPAC (Discovery Partnership with Academia) agreement with GSK, but this has been completed. Professor Lehner's participation in his local hospital D and T governance committee deliberations would form the normal activity and professional responsibility in his post and does not interfere with the EWG considerations (Sept 2020).

Dr Misbah - NPNS - Holds honorary Senior Lectureship with University of Oxford & Oxford University Hospitals NHS Foundation Trust.

Professor Perrie - NPNS in Pfizer & AstraZeneca arising from a contract for a grant (March 2018), which includes contributions from these companies to the University of Strathclyde, Janssen in writing a grant for a PhD (now funded), GSK – arising from an EU grant to University of Strathclyde (Jan 2019-Dec 2019).

Professor Price - NPNS in GSK and AstraZeneca – which relates to donations provided by both companies to the British Toxicology Society (BTS) to support their Annual Congress and Education and Training of which Professor Price is currently President of the Society (2020-2022).

Dr Riordan - Other relevant interests - Participant in Oxford University's ChAdOx1 nCoV-19 clinical trial –received immunisation 27/8/2020. NPNS - Postgraduate External Examiner for Oxford University (Postgraduate Diploma in Paediatric Infectious Diseases).

Professor Solomon - Other relevant interests – Professor Solomon provides clinical care for patients with Covid-19; chaired the MRC/NIHR committee which awarded funding for development of the Oxford Vaccine.

Professor Turner - NPNS interest. Professor Turner is a Non Executive Director (non-remunerated) on the Board of the Cell and Gene Therapy Catapult (CGT) until the end of March. CGT have been tasked by UK Government with re-purposing a factory in Braintree to manufacture either a vaccine or a therapeutic mAb. No decision has been made as to whether or what product CGT Braintree may be asked to manufacture and that decision will be made by UK Government. Professor Turner does not believe that CGT Board will have any material input into the decision as to what product may be manufactured. Rentschler have signed a contract with the Cell and Gene Therapy Catapult (CGT) to rent one of the manufacturing clean room suites at the Stevenage Centre. Professor Turner understands that this will be for contract AAV manufacture.

Mrs Wang – Other relevant interests arising from being highly sensitive to insect stings, and plant products such as Hyacinth bulbs, as recorded on Mrs Wang's medical records. The family of Mrs Wang lives with several rare diseases and conditions, some of which result in epileptic fits.

Professor Weir - NPNS - Imperial College and Other relevant interest arising from his department collaborates with Imperial College on a number of clinical trials.

COMMISSION ON HUMAN MEDICINES (CHM)
COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Wednesday 31st March 2021** at **11:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan[1]
Mr VI G Fenton-May
Professor N French[2]
Professor D Goldblatt
Ms S Hunneyball[3]
Professor K Hyrich
Sir M Jacobs
Professor H J Lachmann
Professor P J Lehner
Mr R Lowe
Dr S Misbah
Professor Y Perrie
Professor S Price
Dr A Riordan
Professor C Robertson
Professor T Solomon
Professor K M G Taylor
Dr R Thorpe
Professor M Turner
Dr S Walsh
Mrs M Wang
Professor C Weir

Apologies

Professor P Shah

Invited Experts

[redacted]

Observers

[redacted]

Professor W S Lim

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD

Presenter supporting specific item

[redacted]

MHRA Observers

[redacted]
Dr S Branch - VRMM
[redacted]
Dr J Raine - MHRA CEO
Ms N Rose - MHRA-NIBSC
[redacted] - MHRA-NIBSC
[redacted]
Mr P Tregunno - VRMM

Secretariat

[redacted]

Key
LD = Licensing Division
NIBSC = National Institute for Biological Standards & Control
VRMM = Vigilance & Risk Management of Medicines
MHRA CEO = Chief Executive
Comms = MHRA Communications

[redacted]

[1] joined during item 3
[2] joined during item 2
[3] joined during item 5

4th February 2022

1. Introduction and Announcement

1.1 The Chair reminded Members, invited Experts and observers that the content of papers and proceeding of the meeting are strictly confidential and should be treated as 'Official – sensitive commercial' and should not be disclosed. There is no consent for members / participants to record the meeting, take screenshots or photographs of presentations. The meeting was recorded by the MHRA Secretariat for minute taking purposes only. The Chair & Members including all participants gave full consent to the recording prior to the start of the meeting.

1.2 Conflict of Interest Policy (Annex I to the minutes)

The Chair reminded members and participants that, in accordance with the CHM Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members were also reminded to declare any other matter which could reasonably be perceived as affecting their impartiality.

1.3 Participants declared interests and other relevant interests for this meeting listed at **Annex II** to the minutes.

1.4 Apologies were received from Professor Shah for this meeting.

1.5 The Chair welcomed Invited Experts, Professor [redacted], Professor of [redacted] who presented item 2 and left after this item. Dr [redacted] Public Health England joined and presented item 6.

1.6 The Chair welcomed the following observers:

[redacted] – NHS England
[redacted] PHS
[redacted] – PHW
[redacted] Miller – PHE
[redacted] – NHS England
[redacted] – PHE
[redacted] – PHE
Professor Wei Shen Lim – JCVI

2. Vaccine Safety Study

2.1 The EWG viewed slides and heard a presentation by researchers at the University of Edinburgh on the studies conducted in Scotland using a nationwide platform called EAVE (early assessment of antivirals and vaccine effectiveness) II. EAVE II was originally created to respond to the N1H1 (swine flu) pandemic, and is used to link data to monitor, understand and mitigate the effects of a pandemic. The aim of EAVE II is to create a national, real-time prospective cohort, using Scotland's health data infrastructure to investigate the effectiveness and safety of vaccines and treatments.

2.2 The EWG heard that the objectives were i) to investigate the impact of the first dose of vaccine on COVID-19 hospitalisations, ii) to estimate the frequency and characterise severe COVID-19 events i.e.COVID-19 hospitalisations and deaths after 14 days post first dose, and iii) to investigate the association between first doses of vaccines and vascular adverse

events, specifically venous thromboembolic disease and cerebral sinus venous thrombosis (CSVT), haemorrhage, and thrombocytopenia and idiopathic thrombocytopenia (ITP).

2.3 The EWG heard that a prospective cohort study was conducted using the EAVE II database comprised of linked vaccination, primary care, real-time polymerase chain reaction (RT-PCR) testing, hospitalisation and mortality records of 5.4 million people in Scotland. A time-dependent Cox model and Poisson regression models were fitted to estimate effectiveness against COVID-19 related hospitalisation (defined as 1-adjusted Hazard Ratio) following the first dose of the Pfizer/BioNTech and AstraZeneca vaccines.

2.4 The EWG noted that the overall vaccine effect in relation to risk of hospitalisation was assessed across all age groups. The findings of the study for both vaccines showed reduced risk of hospitalisation amongst the vaccinated (with a vaccine effect of 70% at 21-34 days post-vaccination) compared to the unvaccinated individuals. It was noted that limited data was analysed for the AstraZeneca vaccine beyond 28 days post-vaccination, but the data showed some effect of a comparable order of magnitude to the clinical trials. The EWG also heard that the results of the vaccine effect were similar in those aged 80 years and over with a vaccine effect of 60-90%.

2.5 The EWG heard that the national data demonstrated correlation between a single dose of the Pfizer/BioNTech and AstraZeneca vaccines and reductions in the risk of COVID-19 related hospitalisations in Scotland.

2.6 The EWG heard the details of a second ongoing prospective cohort study which investigated the effect of Pfizer/BioNTech and AstraZeneca vaccines 14 days after the first dose to second dose or end of study. The analysis period was between 08 December 2020 to 08 March 2021.

2.7 The EWG heard that the results showed that out of 1,679,756 individuals that were given the first dose of either vaccines, 481 were hospitalised and 260 died of COVID-19. The EWG heard based on the data from distribution of incidents, the majority of deaths occurred with the Pfizer/BioNTech vaccine which was targeted to people in care homes, whereas the AstraZeneca vaccine was given to over 80 year olds who were largely living in the community.

2.8 The EWG heard the interim analysis based on adjusted rate ratios shows higher risk of severe outcomes (hospitalisation or death) in males (with 33% increase) and in the older population aged 80 and over. It was also noted that other characteristics such as presence of comorbidity, higher deprivation, smoking status and no previous COVID-19 infection also influenced the risk ratio of both vaccines.

2.9 The EWG was also presented with details of a third ongoing study to investigate the association between first doses of vaccines and vascular adverse events. The EWG noted that an incident case-control study nested within the prospective cohort study was undertaken on data from consultations requested during a period from 8 December 2020 to 14 March 2021. The EWG heard that very few CSVT events (16 cases) were reported, with less than 5 events amongst individuals vaccinated with the Pfizer/BioNTech or AstraZeneca vaccines. It was reported that most of the events were in unvaccinated individuals. The EWG noted that further analysis will be performed once more data is collected.

2.10 The EWG heard that a seasonal pattern was not associated with the number of consultations; however, an increase in the number of consultations for ITP was observed in 2021.

2.11 The EWG heard that the observed and expected number of events, post vaccination, in the incident case-control study showed no evidence of an increased risk of venous thromoboembolic disease (excluding CSVT), haemorrhage and thrombocytopenia. However, the observed number of ITP events in those vaccinated with AstraZeneca vaccine was higher compared to the expected number of events in those aged 60-79.

2.12 The EWG heard that the preliminary results suggested that there is a signal for ITP with 0.82 cases per 100,000 doses of vaccine. It was also noted that due to the lag of discharge of data, analysis may be incomplete as this is reliant only on the GP data. Further analysis will be carried out to investigate whether the ITP is the causal risk with the AstraZeneca vaccine.

2.13 Discussion/Comments

2.13.1 The EWG asked whether the 260 cases that died were confirmed COVID-19 deaths based on death certificate data. The investigator stated that the deaths mainly occurred in elderly patients who tested positive for COVID-19 and died within 28 days of contracting COVID-19. The association of deaths with COVID-19 was also confirmed from the death certificates.

2.13.2 The EWG questioned whether genomic sequencing of virus had been conducted on samples obtained from the 260 who had died and whether this data could be linked to different variants of concern. The investigator stated that work is in progress, whereby a systematic genome sequencing of the positive cases is conducted, and the potential vaccine failures are linked to the genome data in order to identify variants.

2.13.3 The EWG asked whether smoking was independent of the other risk factors such as comorbidity, sex and deprivation. The investigator stated that smoking was an independent factor.

2.13.4 The EWG enquired whether differences were seen in mortality between individuals admitted from care homes versus from the community, and whether an indication of exposure to higher viral load in care homes was seen which had contributed to hospitalisation and death. The EWG heard that initially there were difficulties obtaining the necessary data to explore this question, but recently this has changed, and the relevant research may soon be possible.

2.13.5 The EWG asked whether analysis of data after 21 days, where immunity appears, or 28 days post vaccination will be undertaken. The investigators confirmed that data analysis following 21 and 28 days post vaccination will be undertaken, and the results will be provided to the MHRA.

2.13.6 The EWG inquired if there was a correlation between obesity and death. The investigators confirmed correlation between obesity and death when presented as a single factor, however, obesity is dominated by the other factors when present with comorbidities.

2.13.7 The EWG noted that natural ITP events are more common in those aged 60 and over. However, data analysed confirmed that more events of ITP were observed than expected in those aged 60-79 with the AstraZeneca vaccine. It was not possible to compare the data for those aged 40 and under due to limitations of the dataset.

2.13.8 The EWG asked that if there is a possibility of tracking the ITP patients aged 60-79 years to confirm that the diagnosis was correct and measure the anti-PF4 antibody in those patients. The EWG heard that it is problematic to link data to these patient records as they are anonymised in line with the privacy agreements on GP data.

2.13.9 The EWG noted both ITP and heparin induced thrombocytopenia (HIT) syndrome are both autoimmune conditions affecting the platelets. However, in classic ITP the most commonly elevated antibodies against platelets are glycoprotein IIb-IIIa or Ib-IX, whereas in HIT syndrome antibodies against platelet factor 4 (PF4) are elevated. The EWG noted additional information is needed to understand the pathogenesis of ITP and HIT and to evaluate potential relationships between them. The EWG also noted that ITP is a complex diagnosis that can be difficult to validate.

2.13.10 The EWG asked if there was a possibility of the ITP cases were also previously diagnosed (prior to vaccination) and if the reduction in platelets was exacerbated rather than initiated by the vaccine. The investigators stated that a special permission is required to retrace these patients and perform further analysis. The EWG advised that these issues need further investigation as it is known that ITP can be affected by a precipitant. The possibility that the case reports reflect previously undiagnosed and/or subclinical clinical ITP also needs to be explored.

2.13.11 The EWG were informed by the MHRA that analysis on hospital episode statistics (HES) data were conducted to investigate the ecological analysis of ITP pre-pandemic and during the pandemic. The EWG heard that data from Public health England showed a marked reduction in ITP cases during the pandemic compared to pre-pandemic levels. CPRD continues to conduct sequential monitoring for ITP which identified an excess number of ITP cases with the AstraZeneca vaccine in younger patients. The MHRA noted the source of the large difference in the underlying baseline rate of ITP in previous years versus during the pandemic need to be investigated. The EWG noted it may be useful to undertake a self-control case series analysis of the CPRD data to mitigate against changes in baseline rates.

2.13.12 The EWG suggested that further analysis is required to confirm the ITP signal with the AstraZeneca vaccine.

3. Risk of anaphylaxis with Pfizer/BioNTech COVID-19 vaccine and review of the recommended observation time

3.1 The EWG noted that Pfizer/BioNTech COVID-19 vaccine UK product information (PI) currently advises that those with known hypersensitivity to any of the vaccines ingredients should not receive the vaccine, and that appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction. Close observation for at least 15 minutes is also recommended. This issue has been previously considered twice in January by the EWG when the current wording to the PI was endorsed. The EWG heard that the total number of doses administered for this vaccine to 24th March 2021 is 10.9 million first doses and 2.5 million second doses. The MHRA has received a total of 256 reporting PTs of anaphylaxis or the related terms (reporting rate of 1.9 cases per 100,000 doses) and among them 87 cases were identified as being possibly or probably meeting levels 1-3 diagnostic criteria of the Brighton collaboration criteria (reporting rate of 0.65 cases per 100,000 doses). Around 60% of anaphylaxis cases were reported to occur within 15 minutes after vaccination.

3.2 The EWG agreed that the current PI is appropriate and agreed on the need to keep the recommendation for 15 min observation time. Although better evidence on possible transmission occurring in vaccination centres is welcomed, it is at present difficult to attribute a possible increased risk of contracting Covid19 to the waiting time alone, without also considering all other steps involved in the vaccination process (for example travel to the vaccination centre on public transport). The EWG discussed the need to maintain public confidence in the program and the fact that a change in recommendations could generate confusion in the public and loss of confidence if supervision is withdrawn and an incident occurs.

4. Safety of COVID-19 Vaccines in Pregnancy

4.1 The EWG noted that limited information is available for use of COVID-19 vaccines in pregnancy and so are not currently recommended for use during pregnancy but may be given to front-line healthcare workers and pregnant women with underlying health conditions that place them at greater risk of severe illness.

4.2 Yellow card reports have been received for both the Pfizer-BioNTech and Oxford-AZ vaccines (n=89 and 114 respectively), with most reports related to vaccination occurring early in pregnancy.

4.3 Reports of first trimester miscarriage have been received for both vaccines, both with and without other reactions to the vaccine being reported for the same cases. Based on the number of reports received, the rate of miscarriages for the Oxford-AZ vaccine (23%) is similar to the 25% background rate expected in the UK, whereas the reporting rate for the Pfizer-BioNTech vaccine is currently higher (54%). The EWG noted that data on numbers of vaccinations administered to pregnant women are not yet available to give an accurate estimate of miscarriage rates and that data from the USA for this and the Moderna vaccine has shown a lower miscarriage rate than expected from background.

4.4 A few reports of preterm deliveries following third trimester vaccination have been received but pregnancy outcomes for the majority of 2nd and third trimester vaccines are not yet known.

4.5 The EWG noted that pregnancy carries an elevated risk of blood clots due to hypercoagulability especially in later pregnancy and postpartum. One case of deep vein thrombosis in a leg had been reported following a third trimester vaccination which was being treated according to standard obstetric practice.

4.6 Overall, the EWG considered that the current data are limited but do not raise any particular safety concerns.

4.7 The EWG noted that randomised controlled trials in pregnant women are proposed for the Pfizer-BioNTech vaccine and for the Janssen vaccine (not yet authorised in the UK) whilst an observational cohort study is proposed to investigate safety of the Oxford-AZ vaccine in pregnancy.

5. Discussion on update of thromboembolic events associated with thrombocytopenia reported following COVID-19 vaccination

5.1 The EWG was presented with an update on the issue of thromboembolic events with thrombocytopenia; a review of cases of thromboembolic events associated with thrombocytopenia following vaccination with COVID-19 Vaccine AstraZeneca; a review of cases of thromboembolic events associated with thrombocytopenia following vaccination with other COVID-19 vaccines and a presentation of epidemiological data.

5.2 The EWG heard an updated summary of actions regarding the issue of thromboembolic events and thrombocytopenia, which included:

- temporary suspension of use in people aged less than 55 years in Canada by the Public Health Authority,
- a recommendation by the German Standing Committee on Vaccination (STIKO)

- MHRA's statement on 18th March which communicated the Expert Working Group (EWG) advice that the available evidence currently does not suggest blood clots in veins (venous thromboembolism) are caused by COVID-19 Vaccine AstraZeneca, and that a further, detailed review into a very rare and specific type of blood clot in the cerebral veins (sinus venous thrombosis) occurring together with lowered platelets (thrombocytopenia) is ongoing.
- EMA made a similar statement on 18th March with a decision to update the product information while further investigations were ongoing.

5.3 The EWG was presented with some background information and background rates of thromboembolic events, cerebral venous sinus thrombosis (CVST) specifically, and thrombocytopenia. It was noted that both thrombosis and thrombocytopenia are known to occur in COVID-19 infection - occasionally with mild disease and even after recovery from acute infection. There is also a correlation of these events with severe disease and death.

5.4 The EWG heard that cases reported to MHRA have been evaluated and validated using the WHO-UMC causality assessment system and the case definition which had been established by the EWG and invited haematology experts. The case definition is as follows:

- Confirmed case: Venous/ arterial thrombosis + Platelet count < 150 + D-dimer > 4000 + anti-PF4 antibodies
- Probable: Venous/ arterial thrombosis + Platelet count < 150 + D-dimer > 4000
- Possible case: Venous/ arterial thrombosis + Platelet count < 150
- Unlikely: Criteria met for any of the above BUT alternative diagnosis more likely to explain event.
- Criteria not met: only one or none of the criteria met

A summary of the outcomes of case validation and adjudication was presented, with case details and the validation results provided as an annex in advance of the meeting. Summary details of reported sex and a breakdown of reported ages per classification category were also presented.

5.5 The EWG noted the invited haematology expert's considerations from the adjudication of cases and the difficulties in evaluating the data due to insufficient information in some reports such as the sequence of events (and therefore ability to discern whether cases were predominantly thrombotic or haemorrhagic). The EWG noted the expert's comment that some cases were atypical in that they reported CVST with haemorrhages (which was uncommon), and also that haemorrhage would be unusual if the events are due to a HITT-like mechanism. However, neurologists felt that haemorrhage does occur in patients with CVST even in the absence of thrombocytopenia.

5.6 The EWG discussed the case definition and concluded that it was appropriate and is currently broad enough to capture possible cases and that it can be narrowed and refined as we learn more. The EWG commented that both venous and arterial thromboembolic events should be included in the case definition and that there was not a need to specify a time to onset until a proposed mechanism is better understood.

5.7 The EWG commented that a better understanding of the rate of PF4 antibody positivity in the vaccinated population in general and in people who had had a COVID-19 infection would be valuable. Public Health England informed the EWG of plans underway to gather data on background presence of antibodies to PF4 using samples from older vaccine recipients, unvaccinated individuals and convalescent samples.

5.8 The EWG noted recent literature which quoted the background rate of CVST as 15 per million per year, with 5% mortality. The number of cases and those that were fatal were therefore of significance. The EWG considered that there may be more reporting of such events in younger age groups as they may be less recognised, diagnosed and investigated in older people. In the elderly, symptoms may be ascribed to an ischaemic stroke without undertaking a CT venogram potentially underestimating the incidence of CVST in the elderly. The EWG also considered that differences in the deployment strategies between the AstraZeneca and Pfizer vaccines may affect reporting of potential cases, as elderly people in care homes mostly received the Pfizer vaccine.

5.9 The EWG heard that work was ongoing with collaboration between neurologists and haematologists to establish background rates using neurology and radiology centre data on CVST events and linking it to records of the patients' platelet counts.

5.10 The EWG discussed possible mechanisms for the events reported. A HITT-like mechanism has been proposed by international research groups, due to the presence of anti-PF4 antibodies in some affected patients. It was noted that PF4 can be stimulated by inflammatory responses and that there were likely many conditions that can stimulate PF4, with tuberculosis being one example. The EWG commented that it could be associated with the PF4 antibodies plus a currently unknown other factor(s). Nevertheless, the EWG noted that it could take a long time to identify a mechanism.

5.11 The EWG considered that the onset times of the reports showed a temporal association with vaccination. However, they noted that the pattern seen in onset times could be due to a healthy vaccinee effect following vaccination and then fewer cases with longer onset times due to a lack of longer follow-up time after vaccination and a detection bias in cases with longer onset times.

5.12 The EWG concluded that while there was a temporal association between vaccination and the reported events, the mechanism had not been confirmed and thus a causal association with the AstraZeneca vaccine could not be established. The EWG considered that useful information could be gleaned from data from 2nd doses; however, there currently was not sufficient 2nd dose data to analyse any potential risks.

5.13 The EWG heard that no UK cases of thromboembolic events with thrombocytopenia had been reported for the Pfizer vaccine. However, one case had been reported in Italy (of cerebral venous thrombosis with thrombocytopenia), as well as a Slovenian report of M2 branch thrombus with a low platelet count and an Italian case of pulmonary embolism with thrombocytopenia. Non-UK cases were also validated with the criteria described above. MHRA highlighted a US publication of a series of cases reporting thrombocytopenia within 2 weeks of vaccine with mRNA COVID-19 vaccines. Two cases reported thrombotic events with thrombocytopenia following Pfizer vaccine. MHRA also reported on 1 case from clinical trials and another from post-marketing use of the Janssen vaccine in the US.

5.14 The EWG was presented with statistics on the cumulative exposure to the AstraZeneca and Pfizer vaccines, broken down by age, followed by estimates of the incidence rates of CVST with thrombocytopenia and as well as for all thromboembolic events with thrombocytopenia, broken down by age and gender.

6. An updated epidemiological analysis of the risks of thromboembolic events and potential further study

6.1 The EWG heard the MHRA review of an analysis from PHE of the events of interest associated with the AZ and Pfizer vaccine from hospital admissions data in the UK. The presentation highlighted that there was no indication of a raised risk of thromboembolic

events with either of the vaccines. There was no increased risk identified with the exception of 'Intracranial and intraspinal phlebitis and thrombophlebitis' for which there was indication of a small increased risk for AZ in the under 65 years age group; it was noted that unadjusted confounding could be present and that the numbers were small. The EWG was also informed about an analysis of the benefit of COVID-19 vaccination based on a PHE review. The number of cases of hospitalisation, death and long-COVID prevented per 1 million vaccinations per age group was presented, along with the number of cases and fatal cases of thromboembolic events expected to be reported per 1 million doses.

6.2 The EWG were also presented with opportunities for further epidemiological analysis.

6.3 When discussing the benefit risk in different age groups, the EWG again commented that there could be under reporting of events in elderly people due to a less thorough investigation of neurological symptoms. That being said, the EWG noted that the age distribution seen is typical for CVST events in the non-vaccinated population.

6.4 The EWG discussed whether risk mitigation was needed due to the presence of an alternative vaccine where these events are not seen at the same level, however it was agreed that risk benefit evaluations should be made without consideration of other vaccines.

6.5 The EWG considered that the overall risk of thrombosis with thrombocytopenia remains low but there is concern of significant harm for individual patients. In younger age groups, the risk of COVID-19 and associated complications might not be as high and so the benefit risk from the vaccine in these groups may be different to older groups. It was however noted that while Long COVID is still not well understood, this is an important risk in young people and a potential decrease in this risk would be an additional benefit of vaccination.

6.6 The EWG was not able to identify any specific risk factors but did note that cases with confounding factors should be further investigated to determine if there are any specific populations at risk.

6.7 The EWG concluded that based on current data it not possible to establish an age group where the benefit risk was negative but recognised that irrespective of causality, early identification of such events and correct treatment were needed.

6.8 The EWG commented that the gender bias usually seen with CVST has not been established in the reported cases, which could also suggest a causal link. It was agreed that simple and clear messaging on warning signs is needed so that cases could be identified early, reported in detail and managed clinically.

6.9 The EWG was presented with an overview of planned and ongoing pregnancy studies for the Pfizer and AstraZeneca vaccine, as well as initiated paediatric studies.

6.10 The EWG heard that there was clear support from the Paediatric Medicines Expert Advisory Group for vaccine studies in children with careful evaluation of safety in this population. The EWG considered it reasonable to suggest that children will be at lower risk of these events as thromboembolic risk factors are much lower in children and also there were no documented cases of HITT in children.

6.11 The EWG concluded that paediatric and pregnancy trials should not be stopped at this point, but there needs to further evaluation of the pregnancy trials, and pregnancy exposure to date.

6.12 The EWG advised that the benefit/risk is still overwhelmingly positive, however younger age groups may have risk minimisation needs. Further work is needed on case definition and

case ascertainment will be important. Understanding the background rate of these thromboembolic events with concurrent low platelets will be critical as it is not currently clear if or how much higher above background rates these events are currently occurring. Better mechanistic data is needed to establish causality. Currently a temporal association is seen with vaccination, but causality has not been established.

6.13 The EWG considered it important to communicate what is currently understood about these events with clear, simple messaging in order that vaccine recipients can be appropriately informed. The EWG highlighted the two important audiences for communications; the general population and the healthcare professionals in order to minimise misinformation and establish MHRA evidence as the single point of truth.

6.14 The EWG supported the co-ordination with the EMA and WHO, and to consider lessons learnt from previous high-profile vaccine communications.

6.15 Regarding the content of communications, the EWG advised that the benefits of vaccination should be emphasised in order to contextualise this small potential risk. Information about the potential risk should be provided in absolute terms, with the uncertainties stated. The upper estimate of the risk should be presented, compared to the potential risks from COVID-19 infection.

6.16 The EWG advised that communications should avoid segmenting young vs old or by gender as there are currently too many uncertainties. It should be made clear that it remains a dynamic situation which is still under extensive investigation and advice might change as evidence emerging.

7. Any Other Business

7.1 None.

8. Date and time of next meeting

The next meeting is scheduled to take place on Tuesday 6th April 2021 at 12:30.

The Meeting today started at 11:32 and ended at 14:42.

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Annex I

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- May not currently be or have previously been involved in the development of COVID-19 vaccines

Invited to all meetings, receives all papers and presentations and is permitted full participation in discussion, including drawing up conclusions and recommendations

Invited experts

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Observers

Are invited to attend all meetings. Will not participate in drawing up conclusions and recommendations.

Annex II

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Professor Sir Munir Pirmohamed - NPNS AstraZeneca - Research grant to UOL to support PhD in drug interactions.
Other relevant interests in Pfizer, Janssen, Sanofi – Sir Munir is part of an EU-funded IMI consortium on gene therapy, and these companies are partners in the project. The University of Liverpool will get funding from the EU (but not from the partners), this IMI project commences on 3rd November 2020.
AGILE – this is a Liverpool early phase trial platform (between University of Liverpool and Liverpool School of Tropical Medicine). It is funded by the Wellcome Trust and UKRI/DHSC/NIHR. It is NOT evaluating vaccines, but only drugs to treat COVID-19. Sir Munir is not on the trial management group, and he is not directly involved in choosing the compounds for the study. Sir Munir has no involvement with any of the developers of the compounds to be studied (academic or industrial).
Sir Munir is a member of the UK COVID Therapeutics Advisory Panel (UK-CTAP), which is advising the CMO on which compounds need to be prioritised for the RECOVERY+ trial (RECOVERY is funded via NIHR/DHSC).

Professor Breuer - NPNS – Professor Breuer is on the data safety monitoring committee, DSMB, a study looking at combining vaccines being run by Matthew Snape in Oxford. There does not appear to be any involvement of the vaccine manufacturers and is for already licensed vaccines. The study is funded by the NIHR (Dec 2020).

Professor French - Other relevant interest **-** Provides clinical care when in covering the acute medical wards where patients with COVID-19 are cared. NPNS in GSK - In September 2020 a sub-contract was signed with the Liverpool School of Tropical Medicine to undertake work evaluating the safety and effectiveness of GSK's RTS's malaria vaccine in Malawi. GSK are the primary funders to the LSTM.

Ms Hunneyball - Other relevant interest – writes articles published in the Chemist and Druggist magazine, a trade magazine for pharmacists, but receives no payment for these articles. The information referred to in the articles is in the public domain. Ms Hunneyball makes it clear that these are her personal views and reflections and references all sources of information used.

Professor Hyrich - NPNS - Professor Hyrich was co-I on an investigator-initiated research grant exploring predictors of outcome in rheumatoid arthritis. NPNS Pfizer- she is a Co-I on a grant exploring adherence to JAK inhibitors in rheumatoid arthritis. NPNS in Abbvie, Professor Hyrich gave some lectures at an education conference on effectiveness of treatment for rheumatoid arthritis.

Sir Michael Jacobs - Other relevant interest - As part of the academic role at the Liverpool School of Tropical Medicine, Sir Michael is a member of the Study Management Team and antiviral drug prioritisation group for the AGILE proof of concept (phase I/II) platform study. Sir Michael is also part of the team that submits new antiviral compounds against SARS-CoV2 for consideration by NIHR for testing on this platform. No commercial or financial interest in the trial or any of the compounds, or any pharmaceutical or biotechnology company.

Professor Lachmann - Other relevant interest as a volunteer participant in the Oxford vaccine study and no other involvement in the study.

Professor Lehner - Other relevant interest – Professor Lehner previously held a DPAC (Discovery Partnership with Academia) agreement with GSK, but this has been completed. Professor Lehner's participation in his local hospital D and T governance committee deliberations would form the normal activity and professional responsibility in his post and does not interfere with the EWG considerations (Sept 2020).

Dr Misbah - NPNS - Holds honorary Senior Lectureship with University of Oxford & Oxford University Hospitals NHS Foundation Trust.

Professor Perrie - NPNS in Pfizer & AstraZeneca arising from a contract for a grant (March 2018), which includes contributions from these companies to the University of Strathclyde, Janssen in writing a grant for a PhD (now funded), GSK – arising from an EU grant to University of Strathclyde (Jan 2019-Dec 2019).

Professor Price - NPNS in GSK and AstraZeneca – which relates to donations provided by both companies to the British Toxicology Society (BTS) to support their Annual Congress and Education and Training of which Professor Price is currently President of the Society (2020-2022).

Dr Riordan - Other relevant interests - Participant in Oxford University's ChAdOx1 nCoV-19 clinical trial –received immunisation 27/8/2020. NPNS - Postgraduate External Examiner for Oxford University (Postgraduate Diploma in Paediatric Infectious Diseases).

Professor Robertson - Other relevant interest arising from presenting a vaccine safety study alongside Professor Sheikh of Primary Care Research and Development to the EWG on behalf of the EAVE II and DaC-VaP Collaborators.

Professor Solomon - Other relevant interests – Professor Solomon provides clinical care for patients with Covid-19; chaired the MRC/NIHR committee which awarded funding for development of the Oxford Vaccine.

Mrs Wang - Other relevant interests arising from being highly sensitive to insect stings, and plant products such as Hyacinth bulbs, as recorded on Mrs Wang's medical records. The family of Mrs Wang lives with several rare diseases and conditions, some of which result in epileptic fits.

Professor Weir - NPNS - Imperial College and Other relevant interest arising from his department collaborates with Imperial College on a number of clinical trials.

Observers

Dr [redacted] **-** [redacted]

Professor Wei Shen Lim - NPNS arises from the institution (Nottingham University Hospitals NHS Trust) where Professor Lim works has received unrestricted investigator-initiated research funding from Pfizer for an unrelated prospective population-based cohort study of pneumococcal pneumonia in which Professor Lim is the Chief Investigator.

COMMISSION ON HUMAN MEDICINES (CHM)
COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Tuesday 6th April 2021** at **12:00** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan
Mr VI G Fenton-May
Professor N French
Professor D Goldblatt
Ms S Hunneyball
Professor K Hyrich
Sir M Jacobs
Professor H J Lachmann
Professor P J Lehner
Mr R Lowe
Dr S Misbah
Professor Y Perrie
Professor S Price
Dr A Riordan
Professor C Robertson
Professor T Solomon
Professor K M G Taylor
Dr R Thorpe
Professor M Turner
Dr S Walsh
Mrs M Wang
Professor C Weir

Apologies

Professor P Shah

Observers

[redacted]
Professor W S Lim
[redacted]

Secretariat

[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD

Presenter supporting specific item

[redacted]

MHRA Observers

[redacted]
Ms R Arrundale - MHRA-Policy
[redacted]
Dr S Branch - VRMM
[redacted] - Comms
Dr SP Lam - LD
[redacted] - LD
Dr J Raine - MHRA CEO
[redacted] - MHRA-NIBSC
[redacted]

[redacted]

4th February 2022

Key

LD = Licensing Division
NIBSC = National Institute for Biological Standards & Control
VRMM = Vigilance & Risk Management of Medicines
MHRA CEO = Chief Executive
Comms = MHRA Communications

1. Introduction and Announcement

1.1 The Chair reminded Members, invited Experts and observers that the content of papers and proceeding of the meeting are strictly confidential and should be treated as 'Official – sensitive commercial' and should not be disclosed. There is no consent for members / participants to record the meeting, take screenshots or photographs of presentations. The meeting was recorded by the MHRA Secretariat for minute taking purposes only. The Chair & Members including all participants gave full consent to the recording prior to the start of the meeting.

1.2 Conflict of Interest Policy (Annex I to the minutes)

The Chair reminded members and participants that, in accordance with the CHM Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members were also reminded to declare any other matter which could reasonably be perceived as affecting their impartiality.

1.3 Participants declared interests and other relevant interests for this meeting listed at **Annex II** to the minutes.

1.4 Apologies were received from Professor Shah for this meeting.

1.5 The Chair welcomed the following observers:

[redacted] Statistician, Public Health England

[redacted] Joint Committee on Vaccination and Immunisation, Public Health England

[redacted] NHS England [redacted] for COVID-19 Immunisation [redacted]

Professor Wei Shen Lim
Chair of COVID-19 Subcommittee at JCVI

[redacted] Public Health England

[redacted] Public Health Scotland

[redacted] Public Health England

[redacted] Vaccine Preventable Disease Programme at Public Health Wales

[redacted]
National COVID-19 Vaccination Programme

[redacted]
Public Health England

[redacted]
Public Health England

1.6 The Chair welcomed the following representatives from AstraZeneca:

[redacted] Late Respiratory & Immunology

[redacted] Clinical Development, Immunology

[redacted] Clinical lead

[redacted] Medical and Payer Evidence Strategy, Respiratory and Immunology

[redacted]
Professor of Haemostasis and Thrombosis, [redacted]

[redacted] Pharmacovigilance [redacted]

[redacted] Regulatory Affairs

[redacted] Medical Officer

[redacted]
Regulatory Affairs [redacted]

[redacted] Regulatory Science [redacted] Inflammation Autoimmune, Infection & Vaccines

[redacted] Pharmacovigilance [redacted]

[redacted] Patient Safety

2. Presentation from AstraZeneca

2.1 The company gave a presentation on the global reports of thromboses with concurrent thrombocytopenia. The company highlighted that the vast majority of cases had come from the UK and EU, and that there had been a significant rise in reporting following media interest. It was commented that CVST represented a significant number of the cases of thromboembolism reported, and the cases showed a trend towards younger age groups and females. The meeting was informed that a number of the cases had significant missing data which limited assessment.

2.2 The company presented their observed-expected analysis using a large US insurance claims database to calculate the background incidence of CVST, CVST with thrombocytopenia and any large thromboses with thrombocytopenia within a 14-day risk window. ICD10 codes had been selected which were considered to most closely relate to events reported in such cases. It was noted that the use of the US claims database had a number of limitations including a larger representation of the younger population and those who were insured which may not represent the population as a whole. The analysis showed that for thromboses with thrombocytopenia, there was a higher observed rate than expected in the younger age groups and that this imbalance was not seen in the older age groups (50+ years), and this was similar in the UK and EU data. Similarly, for CVST alone, there was a higher reporting rate in the observed cases than expected for those aged less than 60 years, but no increased incidence detected in those over 60 years old. It was noted by the company that confidence intervals were wide, and the number of cases was small.

2.3 The company concluded that the benefit risk balance for the vaccine remained positive. The company stated that they were working on epidemiological analysis alongside investigation into the mechanism of the events in association with the vaccine.

2.4 The EWG agreed that a consistent definition to use globally could be preferable, including which risk window should be considered. The company noted that there is a natural background incidence of anti-PF4 antibodies in the population regardless of heparin exposure and without thrombus associated, at around 3-5%. Analysis of sera from sample study participants was underway by the company to investigate the prevalence of anti-PF4 antibodies. The company confirmed that they were not aware of any cases occurring after the second dose.

2.5 The company confirmed that the study in adolescents had been paused for recruitment following a data monitoring board discussion.

2.6 The EWG commented how unusual it was to have a large usage of the vaccine in India and yet only 2 cases outside of Europe. The company confirmed that they were working with the Serum Institute of India to engage with national reporting work in India.

2.7 AstraZeneca representatives were asked to leave the meeting before the next presentation.

3. Thromboembolic events with thrombocytopenia - update on cases

3.1 The EWG was presented with an update of the Yellow Card data on cases of thromboembolism and thrombocytopenia up to the data lock point of 31 March 2021. It was reported that the majority of cases related to CVST alongside thrombocytopenia, but other thromboembolic events had also been reported, and that a higher proportion of CVST cases were fatal compared to other thromboembolism events. The EWG heard that the quality of cases had greatly improved since the introduction of the Yellow Card proforma with specific questions on tests and investigations.

3.2 Incidence rates of the events by age group were also presented to the meeting, alongside epidemiological data on the vaccine's impact on reducing COVID-19 cases, long COVID, hospitalisations, ICU admissions and deaths. Modelling data was also provided showing the impact of a hypothesised 10% slower roll out of the vaccine on the predicted cases in the UK.

3.3 The EWG discussed the incidence rates by age for both CVST and non-CVST events and fatalities. It was commented that the case numbers were low considering the usage. Differences compared to the company analysis of benefit risk were highlighted and this could be due to different calculations on the expected impact of the vaccines in preventing cases globally. The EWG noted that the data had consistently showed a higher incidence in younger individuals in both the MHRA and company data. The EWG concluded that it was important to communicate on the available evidence in the younger age groups and allow informed consent, but that an age cut off for usage would not be proposed at present from a regulatory perspective.

4. Proposed revisions to product information

4.1 The EWG was presented with proposed product information statements which had been compiled following discussion at CHM. The EWG agreed with the proposed contraindication wording for patients with previous major thrombotic event with thrombocytopenia. The EWG discussed the proposed warnings and description of symptoms. and generally agreed that the information proposed was appropriate. There was discussion on the time frame for the symptoms of concern and it was agreed not to be restrictive on this. The EWG considered a statement on the causal relationship should be maintained with consideration to the wording to reflect current evidence levels.

4.2 Advice on use in pregnancy was also discussed, noting the lack of data in this area and the desire not to restrict options for pregnant women when the risk factors were unclear. The EWG concluded that the current statement should be retained with a linking statement to the information in 4.4 and 4.8.

4.3 The draft statement for section 4.8 was presented and the limitations of the frequency definitions used were discussed as the "very rare" category did not clearly indicate the rarity of the events.

4.4 The EWG was informed that statements for the patient information leaflet would be drafted once the healthcare professional information had been confirmed and that lay members would have the opportunity to input on this.

5. Any Other Business

None.

6. Date and time of next meeting

The next meeting is scheduled to take place on Monday 12th April at 11:00.

The Meeting today started at 12:01 and ended at 14:38.

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Professor Wei Shen Lim - NPNS arises from the institution (Nottingham University Hospitals NHS Trust) where Professor Lim works has received unrestricted investigator-initiated research funding from Pfizer for an unrelated prospective population-based cohort study of pneumococcal pneumonia in which Professor Lim is the Chief Investigator.

[redacted] **-** Lapsed and NPNS - Regarding companies to declare interests for, prior to joining Public Health Scotland, [redacted] worked for a company that provided epidemiological services to the pharmaceutical industry. Whilst working there, [redacted] supported respiratory vaccine development activities at Janssen (Johnson & Johnson). [redacted] has now left that role.

[redacted] - Other relevant interests in Pfizer & GSK- The Immunisation and Countermeasures Division has provided vaccine manufacturers (including Pfizer and GSK) with post-marketing surveillance reports on pneumococcal and meningococcal infection which the companies are required to submit to the UK Licensing authority in compliance with their Risk Management Strategy. A cost recovery charge is made for these reports.

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COMMISSION ON HUMAN MEDICINES (CHM)
COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Monday 12th April 2021** at **11:00** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor G Dougan
Mr VI G Fenton-May
Professor N French
Professor D Goldblatt
Ms S Hunneyball[1]
Professor K Hyrich
Sir M Jacobs
Professor H J Lachmann
Professor P J Lehner
Mr R Lowe
Dr S Misbah
Professor Y Perrie
Professor S Price
Dr A Riordan
Professor C Robertson[2]
Professor T Solomon
Professor K M G Taylor
Dr R Thorpe
Professor M Turner
Dr S Walsh
Mrs M Wang
Professor C Weir

Apologies

Professor J Breuer

Observers

[redacted]

Secretariat

[redacted]

[1] Left for 30 mins and returned during item 2
[2] Joined during item 2

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD

Presenter supporting specific item

[redacted] - VRMM
[redacted] - VRMM
[redacted] - VRMM

MHRA Observers

[redacted] - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - LD
Dr S Branch - VRMM
[redacted] - LD
[redacted] - MHRA-Policy
[redacted] - VRMM
[redacted] - Comms
[redacted] - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - LD
Mr P Tregunno - VRMM
[redacted] - LD

[redacted]

22nd July 2022

Key
LD = Licensing Division
VRMM = Vigilance & Risk Management of Medicines
Comms = MHRA Communications

1. Introduction and Announcement

1.1 The Chair reminded Members, invited Experts and observers that the content of papers and proceeding of the meeting are strictly confidential and should be treated as 'Official – sensitive commercial' and should not be disclosed. There is no consent for members / participants to record the meeting, take screenshots or photographs of presentations. The meeting was recorded by the MHRA Secretariat for minute taking purposes only. The Chair & Members including all participants gave full consent to the recording prior to the start of the meeting.

1.2 Conflict of Interest Policy (Annex I to the minutes)

The Chair reminded members and participants that, in accordance with the CHM Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members were also reminded to declare any other matter which could reasonably be perceived as affecting their impartiality.

1.3 Participants declared interests and other relevant interests for this meeting listed at **Annex II** to the minutes.

1.4 Apologies were received from Professor Breuer for this meeting.

1.5 The Chair welcomed the following observers:

Professor [redacted]

Dr [redacted]

Dr [redacted]
Public Health Scotland

Dr [redacted]
Public Health England

Dr [redacted] Public Health Wales

Dr [redacted] MB ChB, FRCGP, FIMC (RCSEd), DUMC
Clinical Workstream – [redacted]
National COVID-19 Vaccination Programme

2. Update on COVID-19 Vaccines and risk of thromboembolic events with concurrent thrombocytopenia

2.1 The VBR EWG was presented with the latest data on thromboembolic events with thrombocytopenia associated with the COVID-19 Vaccines up to a data lock point of 5 April 2021. A summary of regulatory actions taken by the MHRA and EMA since the last VBR EWG meeting on 6 April 2021 was also presented.

2.2 A summary of the case reports associated with the AstraZeneca COVID-19 Vaccine was presented along with summary tables of co-morbidities and concomitant medication for the 19 confirmed cases with thrombocytopenia associated with CVST or non-CVST events. It was noted that 5 were obese, 4 cases had no reported co-morbidities or concomitant medication, 1 had been treated for hypothyroidism and the majority were Caucasian. No apparent risk factors were identified. The overall fatality rate has decreased to 22% but it was not clear if this reduction reflected reporting of less serious cases or improved patient management. The EWG also noted that a possible pregnancy case has been reported along with a single case following a second dose of the vaccine. Approximately 1 million second doses of the AstraZeneca COVID-19 Vaccine have been administered mainly to older people in the UK to date.

2.3 The UK and foreign cases associated with the Pfizer, Moderna and Janssen COVID-19 vaccines were summarised using the same case definition. It was noted that the Janssen paediatric trial has been suspended because of issues related to reactogenicity and that the initial marketing authorisation for this product is currently under MHRA evaluation via an EE reliance procedure.

2.4 For the AstraZeneca COVID-19 Vaccine, the EWG heard that there had been no significant change to the overall incidence or fatality rates of CVST with thrombocytopenia since the last meeting. An increase in the estimated incidence of CVST+ other site thromboembolic events with thrombocytopenia had been seen since the last data lock point, although the confidence intervals were overlapping. The difference was driven by events in vaccinees aged between 50 and 70, which corresponds with the ages currently being targeted for vaccination. No change was seen in the fatality rate for CVST+ other site thromboembolic events.

2.5 The EWG was presented with an updated evaluation of events of interest after COVID-19 vaccines using first episodes in the SUS database linked to National Immunisation Management System by NHS number. The adjusted risk of CVST in the 15-39 age group was increased, particularly in the defined risk window of 4 to 13 days after immunisation with the AstraZeneca COVID-19 Vaccine. Two cases of disseminated intravascular coagulation have also occurred in the same age group following vaccination with the Pfizer vaccine but this only provides weak evidence of an association. Cases of thrombocytopenia are not reliably identified using this data.

2.6 Three cases of capillary leak syndrome (CLS) associated with the AstraZeneca COVID-19 vaccine were also presented. It was noted that CLS is a very rare, relapsing-remitting disorder of unknown aetiology and that 2 cases had such a prior history, making any causality assessment difficult. The EWG concluded that this signal should be closely monitored.

2.7 The EWG concluded that it was not possible to evaluate individual risk-benefit profiles for sub-populations of healthy people and patients with comorbidities in the age-stratified data presented but the overall benefit-risk balance for the AstraZeneca COVID-19 Vaccine

remained positive. It also advised the MHRA to continue closely monitoring these events associated with COVID-19 vaccines, particularly following second doses.

3. Third update on the Safety Data for the Pfizer/BioNTech COVID-19 Vaccine

3.1 The EWG was provided with a verbal update on the cumulative safety data for the Pfizer/BioNTech COVID-19 Vaccine, up to a data lock point of 6 April 2021. The EWG was informed of the current usage data for first and second doses of the Pfizer/BioNTech COVID-19 vaccine in the UK, up to the 4 April 2021.

The EWG heard that the nature of the Yellow Card reports was similar to that previously presented for the Pfizer/BioNTech vaccine. A slight decrease in the reporting rate was noted which may suggest increased awareness of common side effects experienced after receiving the Pfizer/BioNTech vaccine as the vaccination campaign progresses. The EWG heard that the most frequently reported events were consistent with previous safety updates and those observed in clinical trials, and that the reporting was noted to be largely related to typical reactogenicity events, and that this was true for both first and second doses.

Higher proportions of reports in females and in those under the age of 55 years was noted for both first and second doses; higher reporting in females has previously been discussed at the EWG as potentially caused by underlying reporting biases in spontaneous reporting systems, in combination with a higher proportion of female vaccinees in the health and social care work force population prioritised by the vaccine campaign.

3.2 The EWG heard that caution should be used in interpretation of the UK Yellow Card dose data, as dose number is not a mandatory reporting field and routine collection of these data was introduced from February 2021.

The EWG were also informed of data from international regulators, which included similar reactogenic events after the second vaccine dose, and an increased frequency of events after the second vaccine dose compared to the first dose which is similar to that seen in clinical trials.

3.3 The EWG were also provided with an update of the adverse events of special interest which are currently under review for the Pfizer/BioNTech vaccine. These included fatal cases, anaphylaxis, Bell's palsy, Guillain-Barré syndrome and cardiac adverse event reports including myocarditis and pericarditis.

The EWG were informed of trends in the data from the UK vaccination programme and new data from international regulators. The EWG heard of potential confounding factors were described in the data, such as age, plausibility of time to onset, variable reporting terms, reporter's opinion of causality and significant comorbidities.

The EWG was informed of ongoing epidemiological studies and analysis, including rapid cycle analysis and mortality stratified by frailty index, that seeks to identify any emerging signals and trends in reporting data for the Pfizer/BioNTech vaccine.

3.4 The EWG discussed the data available regarding fatal anaphylactic reactions, Guillain-Barre and Bell's palsy.

The EWG commented that tryptase laboratory test values should be interpreted with caution and requested that further details on the anaphylaxis reports be provided when available.

The EWG discussed the cases of Guillain-Barré and Bell's palsy, including epidemiological evidence that the background population rate of Guillain-Barré during the pandemic has

reduced and that Guillain-Barré has been associated with COVID-19 infection. The EWG recommended that safety data for Bell's palsy in relation to the Pfizer/BioNTech vaccine and Moderna vaccine should continue to be monitored, and suggested sources of safety data from epidemiological studies and the NHS.

The EWG also requested that cases of exposure during breast-feeding be presented in future updates on reproduction issues.

3.5 The EWG concluded that no new safety concerns had been identified and therefore no further regulatory action was required based on the data presented.

4. Any Other Business

None.

5. Date and time of next meeting

The next meeting is scheduled to take place on Friday 23rd April at 14:00.

The Meeting today started at 11:01 and ended at 12:24.

Members are reminded that the content of papers and proceeding of the meetings are to be treated as 'Official – sensitive commercial'. Members are also reminded that, in accordance with the Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members must also declare any other matter which could reasonably be perceived as affecting their impartiality. Detailed guidance is set out in the Code of Practice

Annex I

Conflict of Interest Policy for CHM COVID-19 Vaccine Benefit Risk EWG

Chair and Members

- May not hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
- May not currently be or have previously been involved in the development of COVID-19 vaccines

Invited to all meetings, receives all papers and presentations and is permitted full participation in discussion, including drawing up conclusions and recommendations

Invited experts

- May hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
- May currently be or have previously been involved in the development of COVID-19 vaccines

May be invited to all relevant meetings, receives all papers and presentations and is permitted to participate in discussions when invited by the Chair. Does not contribute to conclusions and recommendations

Observers

Are invited to attend all meetings. Will not participate in drawing up conclusions and recommendations.

Annex II

The following participants declared interests and other relevant interests at the meeting today:

Professor Sir Munir Pirmohamed - NPNS AstraZeneca - Research grant to UOL to support PhD in drug interactions.
Other relevant interests in Pfizer, Janssen, Sanofi – Sir Munir is part of an EU-funded IMI consortium on gene therapy, and these companies are partners in the project. The University of Liverpool will get funding from the EU (but not from the partners), this IMI project commences on 3rd November 2020.
AGILE – this is a Liverpool early phase trial platform (between University of Liverpool and Liverpool School of Tropical Medicine). It is funded by the Wellcome Trust and UKRI/DHSC/NIHR. It is NOT evaluating vaccines, but only drugs to treat COVID-19. Sir Munir is not on the trial management group, and he is not directly involved in choosing the compounds for the study. Sir Munir has no involvement with any of the developers of the compounds to be studied (academic or industrial).
Sir Munir is a member of the UK COVID Therapeutics Advisory Panel (UK-CTAP), which is advising the CMO on which compounds need to be prioritised for the RECOVERY+ trial (RECOVERY is funded via NIHR/DHSC).

Professor French - Other relevant interest **-** Provides clinical care when in covering the acute medical wards where patients with COVID-19 are cared. NPNS in GSK - In September 2020 a sub-contract was signed with the Liverpool School of Tropical Medicine to undertake work evaluating the safety and effectiveness of GSK's RTS's malaria vaccine in Malawi. GSK are the primary funders to the LSTM.

Ms Hunneyball - Other relevant interest – writes articles published in the Chemist and Druggist magazine, a trade magazine for pharmacists, but receives no payment for these articles. The information referred to in the articles is in the public domain. Ms Hunneyball makes it clear that these are her personal views and reflections and references all sources of information used.

Professor Hyrich – NPNS - Professor Hyrich was co-I on an investigator-initiated research grant exploring predictors of outcome in rheumatoid arthritis. NPNS Pfizer- she is a Co-I on a grant exploring adherence to JAK inhibitors in rheumatoid arthritis. NPNS in Abbvie, Professor Hyrich gave some lectures at an education conference on effectiveness of treatment for rheumatoid arthritis.

Sir Michael Jacobs - Other relevant interest - As part of the academic role at the Liverpool School of Tropical Medicine, Sir Michael is a member of the Study Management Team and antiviral drug prioritisation group for the AGILE proof of concept (phase I/II) platform study. Sir Michael is also part of the team that submits new antiviral compounds against SARS-CoV2 for consideration by NIHR for testing on this platform. No commercial or financial interest in the trial or any of the compounds, or any pharmaceutical or biotechnology company.

Professor Lachmann – Other relevant interest as a volunteer participant in the Oxford vaccine study and no other involvement in the study.

Professor Lehner - Other relevant interest – Professor Lehner previously held a DPAC (Discovery Partnership with Academia) agreement with GSK, but this has been completed. Professor Lehner's participation in his local hospital D and T governance committee deliberations would form the normal activity and professional responsibility in his post and does not interfere with the EWG considerations (Sept 2020).

Dr Misbah - NPNS - Holds honorary Senior Lectureship with University of Oxford & Oxford University Hospitals NHS Foundation Trust.

Professor Perrie - NPNS in Pfizer & AstraZeneca arising from a contract for a grant (March 2018), which includes contributions from these companies to the University of Strathclyde, Janssen in writing a grant for a PhD (now funded), GSK – arising from an EU grant to University of Strathclyde (Jan 2019-Dec 2019).

Professor Price - NPNS in GSK and AstraZeneca – which relates to donations provided by both companies to the British Toxicology Society (BTS) to support their Annual Congress and Education and Training of which Professor Price is currently President of the Society (2020-2022).

Dr Riordan - Other relevant interests - Participant in Oxford University's ChAdOx1 nCoV-19 clinical trial –received immunisation 27/8/2020. NPNS - Postgraduate External Examiner for Oxford University (Postgraduate Diploma in Paediatric Infectious Diseases).

Professor Solomon - Other relevant interests – Professor Solomon provides clinical care for patients with Covid-19; chaired the MRC/NIHR committee which awarded funding for development of the Oxford Vaccine.

Mrs Wang – Other relevant interests arising from being highly sensitive to insect stings, and plant products such as Hyacinth bulbs, as recorded on Mrs Wang's medical records. The family of Mrs Wang lives with several rare diseases and conditions, some of which result in epileptic fits.

Professor Weir - NPNS - Imperial College and Other relevant interest arising from his department collaborates with Imperial College on a number of clinical trials.

Observers

Professor [redacted] - NPNS - University of Oxford employee (with no involvement in research or clinical trials related to Oxford AZ vaccine)
[redacted]

Dr [redacted] - Lapsed and NPNS - Regarding companies to declare interests for, prior to joining Public Health Scotland, [redacted] worked for a company that provided epidemiological services to the pharmaceutical industry. Whilst working there, [redacted] supported respiratory vaccine development activities at Janssen (Johnson & Johnson). [redacted] has now left that role.

Dr [redacted] - Other relevant interest in Pfizer & GSK- The Immunisation and Countermeasures Division has provided vaccine manufacturers (including Pfizer and GSK) with post-marketing surveillance reports on pneumococcal and meningococcal infection which the companies are required to submit to the UK Licensing authority in compliance with their Risk Management Strategy. A cost recovery charge is made for these reports.

COMMISSION ON HUMAN MEDICINES (CHM)
COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Monday 19th April 2021** at **17:15** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Mr VI G Fenton-May
Professor N French
Professor D Goldblatt
Ms S Hunneyball
Professor K Hyrich
Sir M Jacobs
Professor H J Lachmann
Professor P J Lehner
Mr R Lowe
Dr S Misbah
Professor Y Perrie
Professor S Price
Dr A Riordan
Professor T Solomon
Professor K M G Taylor
Dr R Thorpe
Professor M Turner
Dr S Walsh
Mrs M Wang

Apologies

Professor G Dougan
Professor C Robertson
Professor C Weir

Observers

[redacted]
Professor W S Lim
[redacted]

Secretariat

[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted]

Presenter supporting specific item

[redacted] - VRMM
[redacted] - VRMM
[redacted] VRMM

MHRA Observers

[redacted] - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - LD
[redacted] - Comms
Dr S Branch - VRMM
[redacted] - LD
[redacted] - MHRA-NIBSC
[redacted] - MHRA-Policy
[redacted] - VRMM
[redacted] - VRMM
[redacted] - VRMM
Dr SP Lam - LD
[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
Ms N Rose - MHRA-NIBSC
[redacted] - LD
[redacted] - LD
Dr K Wydenbach - LD
[redacted]

4th February 2022

Key
LD = Licensing Division
VRMM = Vigilance & Risk Management of Medicines
Comms = MHRA Communications
NIBSC = National Institute for Biological Standards & Control

1. Introduction and Announcement

1.1 The Chair reminded Members, invited Experts and observers that the content of papers and proceeding of the meeting are strictly confidential and should be treated as 'Official – sensitive commercial' and should not be disclosed. There is no consent for members / participants to record the meeting, take screenshots or photographs of presentations. The meeting was recorded by the MHRA Secretariat for minute taking purposes only. The Chair & Members including all participants gave full consent to the recording prior to the start of the meeting.

1.2 Conflict of Interest Policy (Annex I to the minutes)

The Chair reminded members and participants that, in accordance with the CHM Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members were also reminded to declare any other matter which could reasonably be perceived as affecting their impartiality.

1.3 Participants declared interests and other relevant interests for this meeting listed at **Annex II** to the minutes.

1.4 Apologies were received from Professors Dougan, Robertson and Weir for this meeting.

1.5 The Chair welcomed the following observers:

Mr

Dr
Public Health England

Professor

Professor Wei Shen Lim
Chair of JCVI

Dr

Dr
Public Health Scotland

Dr
Public Health Wales

Dr
National COVID-19 Vaccination Programme

2. Update on COVID-19 Vaccines and risk of thromboembolic events with concurrent thrombocytopenia

2.1 The VBR EWG was presented with the latest data on thromboembolic events with thrombocytopenia associated with the authorised COVID-19 Vaccines up to a data lock point of 14 April 2021. The data lock point for the Janssen vaccine was 12 April 2021. A summary of regulatory actions taken by the MHRA, EMA and FDA since the last EWG meeting on 12 April 2021 was also presented.

2.2 Recent published case series and a case of secondary immune thrombocytopenia following the AstraZeneca COVID-19 Vaccine were also presented.

2.3 An overview of the case reports associated with the AstraZeneca COVID-19 Vaccine was presented along with a summary table of reported second dose cases. The result of PF4 antibody testing is awaited in one probable second dose case and 4 others were considered unlikely on the basis of medical co-morbidities. The overall fatality rate has decreased to 19%.

2.4 The UK and foreign cases associated with the Pfizer, Moderna and Janssen COVID-19 vaccines were summarised using the same case definition. It was noted that PF4 antibodies were detected in a Janssen clinical trial case. The EWG recommended that all suspected cases associated with other COVID-19 vaccines should be tested for PF4 antibodies to further characterise the risk and potentially clarify any causal mechanism(s).

2.5 The estimated number of second AstraZeneca COVID-19 vaccine doses administered has significantly increased to 2.3 million whilst the number of first doses has increased slightly, in line with the current deployment programme. Age-stratified estimated case incidence rates for CVST and CVST plus non-CVST events were presented. The incidence rate following a second dose, based on a single probable case, was 0.4 (0.01, 2.4) per million compared to an overall incidence rate of 7.9 (6.8, 9.2) per million for first/unknown doses. The overall CVST incidence for first/unknown doses has increased from 2.4 to 3.6 per million doses and that for CVST and non-CVST has increased from 4.9 to 8.0 per million doses, although the overall fatal incidence rate for CVST and non-CVST cases after the first/unknown dose has increased from 1.2 to 1.7 per million. This small increase in the fatality rate is not statistically significant. The risk estimates were then compared with the expected benefits of the vaccine in age subgroups.

2.6 Proposed triggers for regulatory action were presented and the EWG considered the following 3 questions:

2.6.1 Question 1: based on the evidence presented does the EWG consider the benefit-risk balance remains favourable for all patients and for all age groups?

The EWG advised that the overall benefit-risk profile of the AstraZeneca COVID-19 Vaccine remains positive. However, the benefits of immunisation in individuals aged under 30 years is more equivocal and may begin to be outweighed by the potential risks should the incidence rate further increase, although the benefit risk was also considered dependent on the status of the COVID-19 pandemic, its severity and impact on hospitalisation. The EWG also advised that the benefit-risk ratio for those aged 30 – 39 remained positive, although this requires close attention given the apparent increased number of cases. However, the EWG considered that no further regulatory action was warranted at this stage.

2.6.2 Question 2: Does the EWG consider there might be an increased risk for the second dose of the vaccine?

The EWG advised that the estimated point estimate for the incidence of thromboembolic events with thrombocytopenia associated with the second dose is only based on a single patient. Many people receiving their second doses have not entered the known risk period or will still be in it, so an absence of cases provides little reassurance. Overall, there is insufficient information to conclude on the magnitude of any risk associated with the second dose. The MHRA should continue to monitor second dose cases closely.

2.6.3 Question 3: Does the EWG consider there is any need for action with regards to the Pfizer, Moderna or Janssen vaccines in relation to this potential risk?

Based on available data, the EWG concluded that the risk associated with the Pfizer and Moderna COVID-19 vaccines appears lower than that associated with the AstraZeneca COVID-19 Vaccine. The identification of a confirmed Janssen case raises concerns that the potential risk associated with this vaccine, also based on a viral vector, is similar, although only a small number of cases have been reported. The EWG will further consider the ongoing marketing authorisation procedure for the Janssen COVID-19 Vaccine at its next meeting on 23 April 2021.

2.7 In conclusion, the EWG did not currently identify any potential trigger for urgent regulatory action.

3. Any Other Business

None.

4. Date and time of next meeting

The next meeting is scheduled to take place on Friday 23rd April at 14:00.

The Meeting today started at 17:17 and ended at 18:32.

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Observers

Are invited to attend all meetings. Will not participate in drawing up conclusions and recommendations.

Annex II

The following participants declared interests and other relevant interests at the meeting today:

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Sir Munir is a member of the UK COVID Therapeutics Advisory Panel (UK-CTAP), which is advising the CMO on which compounds need to be prioritised for the RECOVERY+ trial (RECOVERY is funded via NIHR/DHSC).

Professor Breuer – NPNS – Professor Breuer is on the data safety monitoring committee, DSMB, a study looking at combining vaccines being run by Matthew Snape in Oxford. There does not appear to be any involvement of the vaccine manufacturers and is for already licensed vaccines. The study is funded by the NIHR (Dec 2020).

Professor French - Other relevant interest **-** Provides clinical care when in covering the acute medical wards where patients with COVID-19 are cared. NPNS in GSK - In September 2020 a sub-contract was signed with the Liverpool School of Tropical Medicine to undertake work evaluating the safety and effectiveness of GSK's RTS's malaria vaccine in Malawi. GSK are the primary funders to the LSTM.

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Professor Lachmann – Other relevant interest as a volunteer participant in the Oxford vaccine study and no other involvement in the study.

Professor Lehner - Other relevant interest – Professor Lehner previously held a DPAC (Discovery Partnership with Academia) agreement with GSK, but this has been completed. Professor Lehner's participation in his local hospital D and T governance committee deliberations would form the normal activity and professional responsibility in his post and does not interfere with the EWG considerations (Sept 2020).

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Dr Riordan - Other relevant interests - Participant in Oxford University's ChAdOx1 nCoV-19 clinical trial –received immunisation 27/8/2020. NPNS - Postgraduate External Examiner for Oxford University (Postgraduate Diploma in Paediatric Infectious Diseases).

Professor Solomon - Other relevant interests – Professor Solomon provides clinical care for patients with Covid-19; chaired the MRC/NIHR committee which awarded funding for development of the Oxford Vaccine.

Mrs Wang – Other relevant interests arising from being highly sensitive to insect stings, and plant products such as Hyacinth bulbs, as recorded on Mrs Wang's medical records. The family of Mrs Wang lives with several rare diseases and conditions, some of which result in epileptic fits.

Observers

Professor [redacted]

Professor Wei Shen Lim - NPNS arises from the institution (Nottingham University Hospitals NHS Trust) where Professor Lim works has received unrestricted investigator-initiated research funding from Pfizer for an unrelated prospective population-based cohort study of pneumococcal pneumonia in which Professor Lim is the Chief Investigator.

Dr [redacted] **-** [redacted]

COMMISSION ON HUMAN MEDICINES (CHM)
COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Friday 23rd April 2021** at **14:00** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan
Mr VI G Fenton-May
Professor N French
Professor D Goldblatt
Ms S Hunneyball
Professor K Hyrich[1]
Sir M Jacobs
Professor H J Lachmann[2]
Professor P J Lehner
Mr R Lowe
Dr S Misbah
Professor Y Perrie
Professor S Price
Professor C Robertson[3]
Professor T Solomon[4]
Professor K M G Taylor
Dr R Thorpe
Professor M Turner[3]
Dr S Walsh
Mrs M Wang
Professor C Weir

Apologies

Dr A Riordan

Invited Experts[5]

[redacted]

Observers

[redacted]
Professor W S Lim
[redacted]

Secretariat

[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted] - VRMM

Presenter supporting specific item[6]

[redacted] - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD

MHRA Observers

[redacted] - VRMM
[redacted] - LD
[redacted] - LD
Dr S Branch - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - VRMM
[redacted] - MHRA-Policy
[redacted] - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - MHRA-Comms
[redacted] - LD
[redacted] - VRMM
[redacted] - LD
Dr J Raine - MHRA CEO
Ms N Rose - MHRA-NIBSC
[redacted] - LD
[redacted] - VRMM
Mr P Tregunno - VRMM
Dr K Wydenbach - LD

1 Joined at item 5
2 Joined during item 3
3 Left during item 7
4 Joined during item 2
5 Left after item 3
6 Supported Specific items

Key
LD = Licensing Division
VRMM = Vigilance & Risk Management of Medicines
Comms = MHRA Communications
NIBSC = National Institute for Biological Standards & Control
MHRA CEO = Chief Executive

1. Introduction and Announcement

1.1 The Chair reminded Members, invited Experts and observers that the content of papers and proceeding of the meeting are strictly confidential and should be treated as 'Official – sensitive commercial' and should not be disclosed. There is no consent for members / participants to record the meeting, take screenshots or photographs of presentations. The meeting was recorded by the MHRA Secretariat for minute taking purposes only. The Chair & Members including all participants gave full consent to the recording prior to the start of the meeting.

1.2 Conflict of Interest Policy (Annex I to the minutes)

The Chair reminded members and participants that, in accordance with the CHM Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members were also reminded to declare any other matter which could reasonably be perceived as affecting their impartiality.

1.3 Participants declared interests and other relevant interests for this meeting listed at **Annex II** to the minutes.

1.4 Apologies were received from Professor Hyrich and Dr Riordan for this meeting.

1.5 The Chair welcomed the following Invited Experts, who participated for Item 3 only:

Ms [redacted]
Breastfeeding Network

Dr [redacted] Taunton and Somerset NHS Foundation Trust

Dr [redacted] BM BCh PhD
[redacted] Imperial College London
[redacted]

1.6 The Chair welcomed the following observers, who left after Item 5:

Mr [redacted]

Dr [redacted] Public Health England

Professor Wei Shen Lim
Chair of JCVI

Dr [redacted]
Public Health Scotland

Dr [redacted] Public Health Wales

Dr [redacted] National COVID-19 Vaccination Programme

2. COVID-19 Vaccines and Pregnancy/Breastfeeding

2.1 The EWG was informed of the latest Yellow Card reports received in connection with COVID-19 vaccines in pregnancy. A further 48 reports for the Pfizer-BioNTech vaccine and a further 96 reports for the Oxford-AZ vaccine have been received between 26th March and 15th April, resulting in 137 and 210 total reports respectively for these 2 vaccines. The types of exposure and suspected ADRs were similar to those reviewed previously and did not change the previous conclusions.

2.2 The EWG was informed that the advice to preferentially offer the Pfizer-BioNTech vaccine to women known to be pregnant was based on the larger amount of safety data available from use in the USA rather than any specific safety concerns with the Oxford-AZ vaccine.

2.3 The EWG noted that there are currently no restrictions on the use of COVID-19 vaccines specifically in relation to breastfeeding, since no harm is expected for breastfed infants from non-live vaccines. However sparse information is available for use of COVID-19 vaccines during breastfeeding, so the Yellow Card reports in association with breastfeeding have been monitored closely since the rollout began.

2.4 Yellow Card reports related to exposures in association with breastfeeding have been received for the Pfizer-BioNTech (n= 162), Oxford-AZ (n=778) and Moderna (n=1) vaccines from product launch up to 15/4/21. The number of women who have received the vaccine whilst breastfeeding is not currently known.

2.5 The majority of reports reported reactogenic ADRs that are seen in the general population and did not report any adverse effects either on breastfeeding or in their breastfed child (70% of Pfizer-BioNTech and 77% of Oxford-AZ vaccine).

2.6 There were a small number of reports of mastitis or mastitis-like symptoms, breast pain or breast tenderness for both Pfizer (n=6) and OxfordAZ (n=16); although some reports highlighted that these could make breastfeeding more uncomfortable, they did not appear to affect recipients' ability to breastfeed. The EWG considered these might be related to vaccine use, based on temporal association, but did not raise any particular concerns regarding breastfeeding.

2.7 There were a small number of reports of decreased lactation for both Pfizer (n=2) and OxfordAZ vaccines (n=14). The reported reductions varied from temporary complete inability to breastfeed (for 1 -2 days) to 10-20% that was sustained up to the time of report or follow up (max 5 weeks) was received.

2.8 About 20% of reports for Pfizer-BioNTech and 10% of the Oxford-AZ vaccine reported suspected ADRs in their breastfed children. The EWG considered that the reported symptoms are common conditions which occur in children of this age and may be coincidental rather than causally related to maternal vaccination.

2.9 The EWG noted that a number of factors can affect milk supply and infant behaviour, including general maternal health, amount of sleep, and anxiety. Whilst the EWG considered that some of the individual reports might be related to vaccine use, based on the information provided and temporal association, the low number of reports suggest that at most, a small number of women may experience a reduction in breast milk production.

2.10 Overall, the EWG were reassured by the reports related to breastfeeding, particularly the low number of reports and types of symptoms reported for breastfed children. The EWG recommended that no regulatory action was warranted by these data.

2.11 The EWG noted that there is a lot of uncertainty and anxiety amongst potential vaccine recipients over whether to have the vaccine or not due to lack of safety data during breastfeeding. The EWG therefore recommended communicating on the findings from these Yellow Card reports. The EWG considered that the data would not be sufficiently robust for inclusion in product information but noted that the communication via other routes, such as information on the MHRA website and/or through PHE leaflets, would be appropriate.

2.12 The breastfeeding experts highlighted that, although still limited, there is some emerging evidence on protective effects of vaccines by transfer of immunoglobulins via breastmilk, and that conveying this information from Yellow Card reports might also present an opportunity to convey this positive health benefit message.

2.13 The EWG also supported that communicating on the reports would allow messages to support contingency planning regarding having help on hand to assist with childcare if needed.

3. COVID-19 vaccine AstraZeneca post authorisation safety study protocol- C-VIPER pregnancy registry

3.1 The EWG heard an overview of the protocol for AstraZeneca's planned post authorisation safety study to look at use in pregnancy. The study is an international, prospective, observational cohort study of pregnant women which includes follow-up of liveborn infants up to one year of age.

3.2 The EWG discussed the length of follow up of babies born to mothers who received the AstraZeneca vaccine during pregnancy and whether it would be advisable to extend the follow up period beyond a year in order to detect neurodevelopmental problems. The EWG considered the difficult balance with extending follow up for gaining information on neurodevelopmental problems and reduce maintenance of participants to lengthy follow up. The EWG proposed requesting that the study organisers consider an additional questionnaire at 24 months to assess cognitive abilities. The EWG did however, comment that this could produce bias as parents of babies with a neurodevelopmental issue may be more motivated to continue to engage with the study up to 24 months.

3.3 The EWG commented that analysis on a country-by-country basis would be valuable as there may be very different prevalence rates of certain conditions in pregnancy and in babies born between countries participating in the study. The EWG acknowledged that this could raise issues with sample size, and also that some balance would be provided in the matching of cases and controls by country. The EWG also suggested that matching by region within country could also be valuable.

3.4 The EWG commented that while the study will take 5 years, major congenital malformations and other deficits will become evident early on, and so early data could provide reassurance and less significant changes can be picked up as the study continues.

3.5 Overall, the EWG was content with the proposed study.

4. Update on potential risk of GBS with COVID-19 vaccine AstraZeneca

4.1 The EWG was provided with an update on Yellow Card reports and epidemiological analyses of Guillain-Barré syndrome (GBS) up to and including 11 April 21 with the AstraZeneca vaccine. Clinical trial data and company data from the Summary Monthly Safety Review were also provided. Yellow Card reports were assessed against Brighton Collaboration Criteria for diagnosis of GBS.

4.2 The EWG commented that case numbers were increasing but there was difficulty in assessing cases using the Brighton Collaboration criteria due to a lack of information remained. Nevertheless, the EWG considered that the evidence did not require any product information updates currently and a more dedicated epidemiological study was required.

5. Updated review of COVID-19 Vaccines and the potential risk of immune thrombocytopenia

5.1 The EWG was presented with a summary of the Yellow Card reporting, company data and epidemiological evidence for Immune Thrombocytopenia (ITP) and other thrombocytopenia disorders reported following COVID-19 vaccination. This was an update to a previous assessment which had been reviewed by the EWG in February 2021.

5.2 The EWG were informed that there was very limited data on this topic for the Moderna COVID-19 vaccine due to low levels of usage in the UK. There were several UK Yellow Card reports of ITP and other thrombocytopenia events with the Pfizer COVID-19 vaccine, and it was noted that the number of fatal events was low. The company had also reported relatively low reporting of ITP events considering the global usage of the vaccine. There had been more frequent Yellow Card reporting of ITP and thrombocytopenia events with the AstraZeneca COVID-19 vaccine; however, it was noted that the data overlapped with reporting of Thrombosis with Thrombocytopenia Syndrome (TTS).

5.3 The EWG were presented with the MHRA's epidemiological analysis which did not show a signal in the observed vs expected analysis with the Pfizer COVID-19 vaccine and ITP. Similarly, in analysis by the company, the Pfizer COVID-19 vaccine did not demonstrate a signal for ITP in the global observed vs expected analysis. However, there was stronger evidence of a signal with the AstraZeneca vaccine in the MHRA's observed vs expected analysis. There was also a signal observed in the Rapid Cycle Analysis with ITP and the AstraZeneca vaccine which it was reported has been strengthening over time. A pre-print publication of an epidemiological study seen by the MHRA did not show strong evidence of an association of thrombocytopenia and bleeding events with the AstraZeneca vaccine, although some limitations to the study was noted to the EWG.

5.4 The EWG was also presented with data supporting the proposal by AstraZeneca to include thrombocytopenia as a common adverse event in the product information for the Conditional Marketing Authorisation application that is currently being reviewed by the MHRA. The limitations of the laboratory data used to support the frequency of common was described.

5.5 The EWG members highlighted the complexities of diagnosis of ITP and the range of different thrombocytopenic disorders there were with varying mechanisms. The EWG recommended that an expert haematology panel be formed to support the MHRA in reviewing reports of thrombocytopenia events following COVID-19 vaccination to underpin further review of this signal.

5.6 The EWG also noted that there appeared to be a strengthening signal of ITP with the AstraZeneca vaccine, but the experts cautioned that stimulated reporting may be impacting this signal.

5.7 The EWG supported the inclusion of thrombocytopenia in the Regulation 174 authorisation of the AstraZeneca COVID-19 vaccine with the frequency unknown and stated that the product information for the Conditional Marketing Authorisation will be discussed at the Commission on Human Medicines in due course.

6. Janssen Vaccine EU reliance Conditional Marketing Authorisation Application

6.1 The EWG noted that this is the first COVID-19 vaccine application with a single dose regimen; that this vaccine has already been approved for use by the US FDA and the EMA; and that no Regulation 174 request has been received from the DHSC.

6.2 The EWG were informed that this application was via the EU decision reliance procedure and that, in-line with the licensing division SOP, the assessment therefore focuses on 'GB specific considerations' with points raised only if considered 'decision critical'.

6.3 The EWG heard that at the time of submission, no GB specific concerns were identified that would impact the positive benefit/risk balance. However, two points were highlighted in the product information in relation to 1) inclusion of a recommendation regarding anaphylaxis for close observation for 15 minutes post vaccination and 2) that no advice is included in the product information regarding use of paracetamol for symptomatic relief of adverse events. It was noted that advice on paracetamol use is included in the PHE leaflet 'Covid-19 vaccination A guide for adults' given to all vaccine recipients.

6.4 The EWG were informed of the temporary pause in use of the Janssen vaccine in the US, EU and clinical trials whilst the FDA/CDC and EMA completed a review of US post-marketing reports of CVST with thrombocytopenia. The EWG noted the outcome of the PRAC review on 20 April 2021 that the overall benefit/risk remained positive; however, updates to the product information were required; and that these cases were considered to be very similar to those reported with COVID-19 vaccine AstraZeneca.

6.5 The EWG noted that the updates to the Janssen vaccine EU product information requested by the PRAC were very similar to those already included in the EU product information for the AstraZeneca vaccine. However, that there were some differences compared to the wording included in the UK product information for AstraZeneca. In particular, in the EU PI there is no contraindication in patients with previous HITT or HIT type 2, and no warning about administration in patients with a previous history of CVST or antiphospholipid syndrome.

6.6 The EWG agreed that the benefit risk for the Janssen vaccine was positive.

6.7 The EWG commented that if the UK are considering diverging from the EU PIL and SmPC, the 15minute observation window should be considered for removal given that a clear signal of anaphylaxis, beyond that expected for any vaccine, has not been detected. It was noted that a requirement for a 15-minute observation window might cause operational difficulties for the mass vaccination campaign.

6.8 The EWG heard that there is limited scope to change the product information in the reliance procedure, except where there are clear reasons to do so that can be justified, generally this is interpreted to be a serious issue that alters the overall benefit-risk or poses a potential risk to patient safety. With regards to removal of the 15-minute observation window it was

considered that these criteria are not met but that legal advice could be sought as to whether this could still be possible.

6.9 The EWG noted that, to lower the risk of patient harm through administration errors, the negative statement in the product information *not* to give intravascularly, intravenously, subcutaneously or intradermally should be removed. This was considered to be a clear patient safety concern.

6.10 The EWG noted that the data on the events of thrombosis with concurrent thrombocytopenia with the Janssen vaccine are based on more limited usage in the US compared with much higher usage of the AZ vaccine in the UK and EU. It was also noted that, whilst both vaccines are adenovirus vaccines, there are clear differences between the two including the type of adenovirus and DNA construct. Therefore, justifying full alignment of the product information may be difficult. It was noted that the clinical syndrome being reported for the 2 vaccines was similar and that the presence of anti-PF4 antibodies was common to cases with either vaccine. Therefore, it was considered reasonable to assume that a common form of pathophysiology is underlying the thromboembolic clinical syndromes in both the Janssen vaccine and AZ vaccine. Taking this all into consideration and that this procedure was via the EU reliance route, the EWG agreed that the updates to the proposed GB product information for Covid-19 Vaccine Janssen should be in-line with those recommended by the PRAC.

7. NVX-CoV2373 – Cycle 1 Clinical AR (immunogenicity & safety)

7.1 The EWG was presented with an assessment of the Phase I/II study of NVX-CoV2373, which enrolled about 1,500 adults up to 84 years in total. The trial evaluated adjuvanted and unadjuvanted vaccine, 2 antigen dose levels with the same dose of adjuvant, and a 1 vs 2-dose regimen.

7.2 The EWG heard the conclusions of the immunogenicity assessment, as follows. There is a need for the adjuvant and a booster dose to get a humoral response of similar magnitude to that of human convalescent sera. The adjuvant shows a significant [redacted] The antibody response in the ≥60-year olds is about half that in younger adults, but the SCR after 2 doses is >96% regardless of age. After the peak, IgG levels tend to decrease slowly up to 6 months, but more rapidly so for neutralising antibodies; nevertheless, the GMTs of neutralising antibodies at 6 months are still above 100 with SCRs around 70%. Consistent with the antibody response, adjuvant is crucial for induction of an antigen specific T cell response and a second dose of vaccine is needed to achieve a robust response. Overall, a mixed [redacted] response.

7.3 As far as reactogenicity is concerned, [redacted] especially after the second dose, when reactions increase in frequency and severity compared to the first dose. In addition, [redacted] for further development.

7.4 It is noteworthy that after a first adjuvanted dose, mild local reactions of pain and tenderness are more frequent than with placebo, but the frequencies of systemic reactions do not differ from placebo, except for myalgia. After the second dose, the most frequent reactions, which are fatigue, myalgia and headache, are each reported in about one third of the participants receiving the lower dose. These are generally short-lived (median 1 day, none after 7 days). The frequency of fever is low (4%) with only one case of Grade 3 fever (< 1%; between 39 and 40°). As expected, reactions are more frequent/severe in younger adults compared to

older subjects ≥ 60 years, but the frequency of systemic reactions after the second [redacted] dose is still lower than 50% in younger adults.

7.5 Regarding unsolicited events, their frequency appeared to be marginally increased in the adjuvanted vaccine arms compared to placebo; the difference appeared to be mostly driven by local and systemic reactions. There is no SAE of concern except for one case of acute colitis of unclear aetiology (considered as possibly vaccine related). Laboratory tests have only been provided for Part 1 of the trial and show occasional individual decreases in haemoglobin, increases in transaminases or urea across all arms without a clear pattern.

7.6 Finally, the level of vaccination discontinuation is very low, 1% overall and even lower in the vaccinated arms than in the placebo arm.

7.7 In conclusion, the [redacted] dose [redacted] selected for the Phase III trial is considered to have a very favourable reactogenicity profile, even in the younger adult population. Based on this limited safety database, unsolicited and laboratory tests do not raise any major concern. The only questions raised relate to the bioanalytical assays.

7.8 The EWG supported the findings and conclusions of the analytical procedure assessments undertaken by NIBSC assessors.

7.9 The EWG noted that the cellular response data included a prominent [redacted] which appears novel in the context of the vaccines evaluated thus far. The data broadly indicate a [redacted] profile the implications of which are not known, although hypothetically it could lead to a greater likelihood of vaccine exacerbated disease. The EWG noted the [redacted] vaccines have not been associated with a [redacted] response. Therefore, the EWG thought it to be plausible that the [redacted] response may be caused by the adjuvant included in NVX-CoV2373. The EWG noted this adjuvant is not entirely novel to vaccines, in particular recent studies of the malaria vaccine did not raise any concerns specific to this adjuvant.

7.10 The EWG was reassured by the immunogenicity data, however, should adverse events (AE) become apparent once the vaccine is marketed, the potential role of the [redacted] response in the development of AEs will need to be evaluated.

7.11 The EWG heard that the production of validation batches has been delayed. Also, the company have opted to include a different potency assay which includes [redacted] resulting in an assay that should quantify the amount of antigen. However, still outstanding is an explanation of the clinical implications of the [redacted] which will still be present in the product. The company intend to replicate the quality development of the DS process of the product used in the Phase III trial in US, in order that the quality profile at the new site is clinically qualified.

7.12 The EWG heard of inaccurate reports in the media stating that NVX-CoV2373 is expected to be authorised in the UK in the next few weeks.

8. Any Other Business

None.

9. Date and time of next meeting

The next Ad Hoc meeting on Thromboembolic events with COVID-19 Vaccines is scheduled to take place on **Monday 26th April** at **5.15pm**.

The next scheduled meeting is to take place **on Friday 30th April** at **10.00am**

The Meeting today started at 14:13 and ended at 16:50.

[redacted]

16th February 2023

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Annex I

Conflict of Interest Policy for CHM COVID-19 Vaccine Benefit Risk EWG

Chair and Members

- May not hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
- May not currently be or have previously been involved in the development of COVID-19 vaccines

Invited to all meetings, receives all papers and presentations and is permitted full participation in discussion, including drawing up conclusions and recommendations

Invited experts

- May hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
- May currently be or have previously been involved in the development of COVID-19 vaccines

May be invited to all relevant meetings, receives all papers and presentations and is permitted to participate in discussions when invited by the Chair. Does not contribute to conclusions and recommendations

Observers

Are invited to attend all meetings. Will not participate in drawing up conclusions and recommendations.

Annex II

Professor Sir Munir Pirmohamed - NPNS AstraZeneca - Research grant to UOL to support PhD in drug interactions.
Other relevant interests in Pfizer, Janssen, Sanofi – Sir Munir is part of an EU-funded IMI consortium on gene therapy, and these companies are partners in the project. The University of Liverpool will get funding from the EU (but not from the partners), this IMI project commences on 3rd November 2020.
AGILE – this is a Liverpool early phase trial platform (between University of Liverpool and Liverpool School of Tropical Medicine). It is funded by the Wellcome Trust and UKRI/DHSC/NIHR. It is NOT evaluating vaccines, but only drugs to treat COVID-19. Sir Munir is not on the trial management group, and he is not directly involved in choosing the compounds for the study. Sir Munir has no involvement with any of the developers of the compounds to be studied (academic or industrial).
Sir Munir is a member of the UK COVID Therapeutics Advisory Panel (UK-CTAP), which is advising the CMO on which compounds need to be prioritised for the RECOVERY+ trial (RECOVERY is funded via NIHR/DHSC).

Professor Breuer – NPNS – Professor Breuer is on the data safety monitoring committee, DSMB, a study looking at combining vaccines being run by Matthew Snape in Oxford. There does not appear to be any involvement of the vaccine manufacturers and is for already licensed vaccines. The study is funded by the NIHR (Dec 2020).

Professor French - Other relevant interest **-** Provides clinical care when in covering the acute medical wards where patients with COVID-19 are cared. NPNS in GSK - In September 2020 a sub-contract was signed with the Liverpool School of Tropical Medicine to undertake work evaluating the safety and effectiveness of GSK's RTS's malaria vaccine in Malawi. GSK are the primary funders to the LSTM.

Ms Hunneyball - Other relevant interest – writes articles published in the Chemist and Druggist magazine, a trade magazine for pharmacists, but receives no payment for these articles. The information referred to in the articles is in the public domain. Ms Hunneyball makes it clear that these are her personal views and reflections and references all sources of information used.

Professor Hyrich – NPNS - Professor Hyrich was co-I on an investigator-initiated research grant exploring predictors of outcome in rheumatoid arthritis. NPNS Pfizer- she is a Co-I on a grant exploring adherence to JAK inhibitors in rheumatoid arthritis. NPNS in Abbvie, Professor Hyrich gave some lectures at an education conference on effectiveness of treatment for rheumatoid arthritis.

Sir Michael Jacobs - Other relevant interest - As part of the academic role at the Liverpool School of Tropical Medicine, Sir Michael is a member of the Study Management Team and antiviral drug prioritisation group for the AGILE proof of concept (phase I/II) platform study. Sir Michael is also part of the team that submits new antiviral compounds against SARS-CoV2 for consideration by NIHR for testing on this platform. No commercial or financial interest in the trial or any of the compounds, or any pharmaceutical or biotechnology company.

Professor Lachmann – Other relevant interest as a volunteer participant in the Oxford vaccine study and no other involvement in the study.

Professor Lehner - Other relevant interest – Professor Lehner previously held a DPAC (Discovery Partnership with Academia) agreement with GSK, but this has been completed. Professor Lehner's participation in his local hospital D and T governance committee

deliberations would form the normal activity and professional responsibility in his post and does not interfere with the EWG considerations (Sept 2020).

Dr Misbah - NPNS - Holds honorary Senior Lectureship with University of Oxford & Oxford University Hospitals NHS Foundation Trust.

Professor Perrie - NPNS in Pfizer & AstraZeneca arising from a contract for a grant (March 2018), which includes contributions from these companies to the University of Strathclyde, Janssen in writing a grant for a PhD (now funded), GSK – arising from an EU grant to University of Strathclyde (Jan 2019-Dec 2019).

Professor Price - NPNS in GSK and AstraZeneca – which relates to donations provided by both companies to the British Toxicology Society (BTS) to support their Annual Congress and Education and Training of which Professor Price is currently President of the Society (2020-2022).

Professor Solomon - Other relevant interests – Professor Solomon provides clinical care for patients with Covid-19; chaired the MRC/NIHR committee which awarded funding for development of the Oxford Vaccine.

Mrs Wang – Other relevant interests arising from being highly sensitive to insect stings, and plant products such as Hyacinth bulbs, as recorded on Mrs Wang's medical records. The family of Mrs Wang lives with several rare diseases and conditions, some of which result in epileptic fits.

Professor Weir - NPNS - Imperial College and Other relevant interest arising from his department collaborates with Imperial College on a number of clinical trials.

Invited Experts & Observers

Dr [redacted]

Dr [redacted]

Professor Wei Shen Lim - NPNS arises from the institution (Nottingham University Hospitals NHS Trust) where Professor Lim works has received unrestricted investigator-initiated research funding from Pfizer for an unrelated prospective population-based cohort study of pneumococcal pneumonia in which Professor Lim is the Chief Investigator.

Dr [redacted]

COMMISSION ON HUMAN MEDICINES (CHM)
COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Monday 26th April 2021** at **17:15** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Mr VI G Fenton-May
Professor D Goldblatt
Ms S Hunneyball
Professor K Hyrich
Sir M Jacobs
Professor H J Lachmann
Professor P J Lehner
Mr R Lowe
Dr S Misbah
Professor Y Perrie
Professor S Price
Professor C Robertson
Professor T Solomon
Professor K M G Taylor
Dr R Thorpe
Professor M Turner
Dr S Walsh
Mrs M Wang
Professor C Weir

Apologies

Professor G Dougan
Professor N French
Dr A Riordan

Invited Expert

[redacted]*

Observers

[redacted]
Professor W S Lim
[redacted]
msav
[redacted]

Secretariat

[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD

Presenters supporting specific items*

[redacted] - VRMM
[redacted] - VRMM
[redacted] - VRMM

MHRA Observers

[redacted] - LD
[redacted] - VRMM
[redacted] - LD
Dr S Branch - VRMM
[redacted] - MHRA-NIBSC
[redacted] - VRMM
[redacted] - MHRA-Policy
[redacted] - VRMM
[redacted] - VRMM
[redacted] - VRMM
[redacted] - Comms
[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
Ms N Rose - MHRA-NIBSC
[redacted] - MHRA-NIBSC
[redacted] - LD
[redacted] - VRMM
Mr P Tregunno - VRMM
[redacted] - LD
[redacted]

4th February 2022

Key
LD = Licensing Division
VRMM = Vigilance & Risk Management of Medicines
Comms = MHRA Communications
NIBSC = National Institute for Biological Standards & Control

1. Introduction and Announcement

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1.2 Conflict of Interest Policy (Annex I to the minutes)

The Chair reminded members and participants that, in accordance with the CHM Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members were also reminded to declare any other matter which could reasonably be perceived as affecting their impartiality.

1.3 Participants declared interests and other relevant interests for this meeting listed at **Annex II** to the minutes.

1.4 Apologies were received from Professors Dougan, French and Dr Riordan for this meeting.

1.5 The Chair welcomed Invited Expert, Dr [redacted] from UK Health Security Agency (HAS) who presented item 2 - Update from UK HSA on Safety for AZ Vaccine.

1.6 The Chair welcomed the following observers:

Mr [redacted]

Dr [redacted] Joint Committee on Vaccination and Immunisation, UK HSA

Professor [redacted] JCVI

Dr [redacted] Public Health Agency

Professor Wei Shen Lim
Chair of JCVI

Dr [redacted]
Public Health Scotland

Dr [redacted]
UK Health Security Agency

Dr [redacted] Public Health Wales

[redacted]d
National COVID-19 Vaccination Programme

2. Update from UK HSA on Safety for AZ Vaccine

2.1 UK HSA England, AZ safety item 26/04/2021

The EWG heard a presentation from Professor [redacted] of UK Health Security Agency (UK HSA) on estimations of rates of vaccine-prevented COVID-19 cases, hospitalisations, ICU/HDU admissions and deaths. The rates of benefit were based on a wave equivalent to that of the second wave and the analysis was stratified by age and risk group status. The benefit data was based on a complete vaccination course (two doses) of the AstraZeneca Vaccine. The EWG heard that the data and calculations presented on vaccine effectiveness assumptions were largely based on data from the second wave scenario.

2.2 The EWG asked for further detail on the QCOVID score, and how this was used to benchmark rates of risk. The QCOVID data was used as one form of cross checking / data validation, and for comparison of risks between wave one and wave two. The EWG heard the QCOVID calculator computes a combination of risk of infection and the subsequent risk of acquiring a complication (if infected), in other words an absolute population risk during the 12 weeks during the first wave. The EWG also heard the rates used in the data analysis to calculate risk are available to the group for reference.

2.3 The EWG heard that projection modelling of a potential third wave is on-going. Currently, the model estimates third wave hospitalisation rates will be approximately 50% of second wave rates. The data period inputs for the model cover the first and second waves, and presently, but lack data on emerging variant strains. The current model is therefore limited in terms of its predictive accuracy in a situation where new strains may result in substantial differences in protection from the vaccine. The EWG also heard that the uncertainty level in the modelling was already very high but may improve when further data are inputted.

2.4 The Chair thanked [redacted] and the other contributors for the clear presentation on what is a complex subject.

3. Update on COVID-19 Vaccines and risk of thromboembolic events with concurrent thrombocytopenia

3.1 The VBR EWG was presented with the latest data on thromboembolic events with thrombocytopenia associated with the authorised COVID-19 Vaccines up to a data lock point of 21 April 2021. The data lock point for the Janssen vaccine was 12 April 2021. A summary of regulatory actions taken by the EMA and FDA since the last EWG meeting on 19 April 2021 was also presented.

3.2 Concerning the AstraZeneca COVID-19 vaccine, 2 recent draft publications on causal mechanisms and 4 published case reports were presented. The papers by [redacted] team on potential mechanisms suggested that the underlying causes of thromboembolic events with thrombocytopenia in Covid-19 infection were different to those following vaccination and the proposed sequence of pathophysiological events involving neutrophils was interesting and could support causality. However, some of the data on excipients was speculative and the published versions of the draft articles may contain additional information. The data presented would also require independent verification

3.3 An overview of the case reports associated with the AstraZeneca COVID-19 Vaccine was presented including a summary table of the 4 reported cases after a second dose. Four of these cases were probable or possible, two of them tested negative for PF4 antibodies and the results are awaited or unknown in the 2 other cases. Additional follow-up clarified that a case was wrongly reported as occurring during pregnancy as we have not received any thromboembolic events with thrombocytopenia in pregnancy associated with the vaccine. The overall case fatality rate for all doses is stable at 20%.

3.4 The EWG was also given an overview of available outcome data for all confirmed cases. It was noted that the majority of cases were not associated with significant comorbidities that might be expected to limit function or quality of life before vaccination. However, the data on residual disability is limited as pre- and post-vaccination status has not been assessed using validated outcome measures and neurological deficits can recover after a year or more. UK haematologists are collecting long-term outcome data alongside HaemStar and the MHRA may receive this data.

3.5 The UK and foreign cases associated with the Pfizer, Moderna and Janssen COVID-19 vaccines were summarised using the same case definition. The FDA has lifted the recommended pause on Janssen COVID-19 vaccine use after its safety review identified 15 cases of thrombosis-thrombocytopenia syndrome following the administration of more than 6.8 million doses.

3.6 The estimated number of second AstraZeneca COVID-19 vaccine doses administered has significantly increased to 4.4 million whilst the number of first doses has increased slightly, in line with the current deployment programme to 22 million. Estimated case incidence rates for CVST and CVST plus non-CVST events were presented by age-stratified 5-year intervals and by gender. The overall incidence rate is 9.3 (8.1, 10.7) per million for first/unknown doses and the overall fatal incidence rate is 1.8 (1.3, 2.5) per million doses. The risk estimates were then compared with the expected benefits of vaccine in age subgroups.

3.7 The EWG considered the following 3 questions:

3.7.1 Question 1: based on the evidence presented does the EWG consider the benefit-risk balance remains favourable for all patients and for all age groups?

The EWG advised that the overall benefit-risk profile of the AstraZeneca COVID-19 Vaccine remains positive. However, depending on the status of the COVID-19 pandemic, its severity and impact on hospitalisation, the benefits of immunisation in individuals aged under 30 years may be outweighed by the potential risks.

3.7.2 Question 2: Does the EWG consider there might be an increased risk for the second dose of the vaccine?

The EWG advised that the emerging data on the risk of thromboembolic events occurring with thrombocytopenia following second doses is reassuring but limited so the MHRA should continue to monitor second dose cases closely.

3.7.3 Question 3: Does the EWG consider there is any need for action with regards to the Pfizer, Moderna or Janssen vaccines in relation to this potential risk?

Based on available data, the risk associated with the Pfizer and Moderna COVID-19 vaccines appears lower than that associated with the AstraZeneca COVID-19 Vaccine. This risk should be monitored and there is no need for regulatory action.

3.8 In conclusion, the EWG did not identify any potential trigger for urgent regulatory action.

4. Any Other Business

None.

5. Date and time of next meeting

The next meeting is scheduled to take place on Friday 30th April at 13:00.

The Meeting today started at 17:18 and ended at 18:33.

Members are reminded that the content of papers and proceeding of the meetings are to be treated as 'Official – sensitive commercial'. Members are also reminded that, in accordance with the Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members must also declare any other matter which could reasonably be perceived as affecting their impartiality. Detailed guidance is set out in the Code of Practice

Annex I

Conflict of Interest Policy for CHM COVID-19 Vaccine Benefit Risk EWG

Chair and Members

- May not hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
- May not currently be or have previously been involved in the development of COVID-19 vaccines

Invited to all meetings, receives all papers and presentations and is permitted full participation in discussion, including drawing up conclusions and recommendations

Invited experts

- May hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
- May currently be or have previously been involved in the development of COVID-19 vaccines

May be invited to all relevant meetings, receives all papers and presentations and is permitted to participate in discussions when invited by the Chair. Does not contribute to conclusions and recommendations

Observers

Are invited to attend all meetings. Will not participate in drawing up conclusions and recommendations.

Annex II

The following participants declared interests and other relevant interests at the meeting today:

Professor Sir Munir Pirmohamed - NPNS AstraZeneca - Research grant to UOL to support PhD in drug interactions.
Other relevant interests in Pfizer, Janssen, Sanofi – Sir Munir is part of an EU-funded IMI consortium on gene therapy, and these companies are partners in the project. The University of Liverpool will get funding from the EU (but not from the partners), this IMI project commences on 3rd November 2020.
AGILE – this is a Liverpool early phase trial platform (between University of Liverpool and Liverpool School of Tropical Medicine). It is funded by the Wellcome Trust and UKRI/DHSC/NIHR. It is NOT evaluating vaccines, but only drugs to treat COVID-19. Sir Munir is not on the trial management group, and he is not directly involved in choosing the compounds for the study. Sir Munir has no involvement with any of the developers of the compounds to be studied (academic or industrial).
Sir Munir is a member of the UK COVID Therapeutics Advisory Panel (UK-CTAP), which is advising the CMO on which compounds need to be prioritised for the RECOVERY+ trial (RECOVERY is funded via NIHR/DHSC).

Professor Breuer – NPNS – Professor Breuer is on the data safety monitoring committee, DSMB, a study looking at combining vaccines being run by Matthew Snape in Oxford. There does not appear to be any involvement of the vaccine manufacturers and is for already licensed vaccines. The study is funded by the NIHR (Dec 2020).

Ms Hunneyball - Other relevant interest – writes articles published in the Chemist and Druggist magazine, a trade magazine for pharmacists, but receives no payment for these articles. The information referred to in the articles is in the public domain. Ms Hunneyball makes it clear that these are her personal views and reflections and references all sources of information used.

Professor Hyrich – NPNS - Professor Hyrich was co-I on an investigator-initiated research grant exploring predictors of outcome in rheumatoid arthritis. NPNS Pfizer- she is a Co-I on a grant exploring adherence to JAK inhibitors in rheumatoid arthritis. NPNS in Abbvie, Professor Hyrich gave some lectures at an education conference on effectiveness of treatment for rheumatoid arthritis.

Sir Michael Jacobs - Other relevant interest - As part of the academic role at the Liverpool School of Tropical Medicine, Sir Michael is a member of the Study Management Team and antiviral drug prioritisation group for the AGILE proof of concept (phase I/II) platform study. Sir Michael is also part of the team that submits new antiviral compounds against SARS-CoV2 for consideration by NIHR for testing on this platform. No commercial or financial interest in the trial or any of the compounds, or any pharmaceutical or biotechnology company.

Professor Lachmann – Other relevant interest as a volunteer participant in the Oxford vaccine study and no other involvement in the study.

Professor Lehner - Other relevant interest – Professor Lehner previously held a DPAC (Discovery Partnership with Academia) agreement with GSK, but this has been completed. Professor Lehner's participation in his local hospital D and T governance committee deliberations would form the normal activity and professional responsibility in his post and does not interfere with the EWG considerations (Sept 2020).

Dr Misbah - NPNS - Holds honorary Senior Lectureship with University of Oxford & Oxford University Hospitals NHS Foundation Trust.

Professor Perrie - NPNS in Pfizer & AstraZeneca arising from a contract for a grant (March 2018), which includes contributions from these companies to the University of Strathclyde, Janssen in writing a grant for a PhD (now funded), GSK – arising from an EU grant to University of Strathclyde (Jan 2019-Dec 2019).

Professor Price - NPNS in GSK and AstraZeneca – which relates to donations provided by both companies to the British Toxicology Society (BTS) to support their Annual Congress and Education and Training of which Professor Price is currently President of the Society (2020-2022).

Professor Solomon - Other relevant interests – Professor Solomon provides clinical care for patients with Covid-19; chaired the MRC/NIHR committee which awarded funding for development of the Oxford Vaccine.

Mrs Wang – Other relevant interests arising from being highly sensitive to insect stings, and plant products such as Hyacinth bulbs, as recorded on Mrs Wang's medical records. The family of Mrs Wang lives with several rare diseases and conditions, some of which result in epileptic fits.

Professor Weir - NPNS - Imperial College and Other relevant interest arising from his department collaborates with Imperial College on a number of clinical trials.

Observers

Professor [redacted]

Professor Wei Shen Lim - NPNS arises from the institution (Nottingham University Hospitals NHS Trust) where Professor Lim works has received unrestricted investigator-initiated research funding from Pfizer for an unrelated prospective population-based cohort study of pneumococcal pneumonia in which Professor Lim is the Chief Investigator.

Dr [redacted]

Dr [redacted]

COMMISSION ON HUMAN MEDICINES (CHM)
COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Tuesday 4th May 2021** at **14:00** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor G Dougan
Mr VI G Fenton-May
Professor N French
Professor D Goldblatt
Ms S Hunneyball
Sir M Jacobs
Professor P J Lehner
Mr R Lowe
Dr S Misbah
Professor Y Perrie
Professor S Price
Dr A Riordan
Professor C Robertson
Professor T Solomon
Professor K M G Taylor
Dr R Thorpe
Professor M Turner
Dr S Walsh
Mrs M Wang

Apologies

Professor J Breuer
Professor K Hyrich
Professor H J Lachmann
Professor C Weir

Observers

[redacted]
Professor W S Lim
[redacted]

Secretariat

[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted] - VRMM

Presenters supporting specific items

[redacted] - VRMM
[redacted] - VRMM
[redacted] - VRMM
Mr P Tregunno - VRMM

MHRA Observers

[redacted] - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - LD
Dr S Branch - VRMM
[redacted] - MHRA-NIBSC
[redacted] - MHRA-Policy
[redacted] - VRMM
[redacted] - Comms
[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - LD

[redacted]

4th February 2022

Key
LD = Licensing Division
VRMM = Vigilance & Risk Management of Medicines
Comms = MHRA Communications
NIBSC = National Institute for Biological Standards & Control

1. Introduction and Announcement

1.1 The Chair reminded Members, invited Experts and observers that the content of papers and proceeding of the meeting are strictly confidential and should be treated as 'Official – sensitive commercial' and should not be disclosed. There is no consent for members / participants to record the meeting, take screenshots or photographs of presentations. The meeting was recorded by the MHRA Secretariat for minute taking purposes only. The Chair & Members including all participants gave full consent to the recording prior to the start of the meeting.

1.2 Conflict of Interest Policy (Annex I to the minutes)

The Chair reminded members and participants that, in accordance with the CHM Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members were also reminded to declare any other matter which could reasonably be perceived as affecting their impartiality.

1.3 Participants declared interests and other relevant interests for this meeting listed at **Annex II** to the minutes.

1.4 Apologies were received from Professors Breuer, Hyrich, Lachmann and Weir for this meeting.

1.5 The Chair welcomed the following observers:

Mr [redacted]

Dr [redacted] ublic Health England

Professor [redacted] JCVI

Dr [redacted] Public Health Agency

Dr [redacted]

Professor Wei Shen Lim
Chair of JCVI

Dr [redacted]
Public Health Scotland

Dr [redacted]
Public Health England

Dr [redacted] Public Health Wales

Dr [redacted]

2. Update on COVID-19 Vaccines and risk of thromboembolic events with concurrent thrombocytopenia

2.1 The EWG was presented with the latest data on thromboembolic events with thrombocytopenia associated with the authorised COVID-19 Vaccines up to a data lock point of 28 April 2021. Summaries of the CDC/FDA and Health Canada reviews of thrombosis with thrombocytopenia syndrome associated with the Janssen COVID-19 vaccine were also presented. The data lock point for the Janssen vaccine was 12 April 2021.

2.2 A review of recent publications concerning the AstraZeneca COVID-19 vaccine identified a paper on a proposed mechanism, a study reporting the prevalence of anti-PF4 antibodies in Norwegian health care workers, 2 small case series and 3 case reports. The EWG noted that two patients in a [redacted] cases series experienced thrombotic events after receiving a 2-day course of intravenous immunoglobulin but 1 of these patients responded well to eculizumab.

2.3 The EWG was also presented with analyses of Yellow Cards reported up to the 21st April data lock point including analyses of numbers of reports by report date, by reaction date and by vaccination date. Charts were also presented showing the time between vaccination date and reporting date and days between fatal event dates and reporting dates.

2.4 An overview of the case reports associated with the AstraZeneca COVID-19 Vaccine was presented including a summary table of the 6 reported cases after a second dose. It was noted that none of the reported cases had cerebral venous sinus thromboses or platelet factor 4 antibodies.

2.5 The EWG was also given an overview of the platelet count distributions for venous and arterial thromboembolic events with thrombocytopenia. Half of those with reported platelet values and venous or arterial events had significant thrombocytopenia with platelet counts under 50 x 10^9/L, all of those with myocardial infarctions had counts under 50 whilst approximately 20% with deep vein thrombosis and/or pulmonary embolus had mild thrombocytopenia with counts of 100 or more.

2.6 The UK and foreign cases associated with the Pfizer, Moderna and Janssen COVID-19 vaccines were summarised using the same case definition.

2.7 The estimated number of second AstraZeneca COVID-19 vaccine doses administered has significantly increased to 5.9 million whilst the number of first doses has increased slightly, in line with the current deployment programme to 22.6 million. Estimated case incidence rates for CVST and CVST plus non-CVST events were presented by age-stratified 10-year intervals and by gender. The overall incidence rate is 10.5 (9.2, 11.9) per million for first/unknown doses and the overall fatal incidence rate is 2.1 (1.6, 1.8) per million doses. The estimated case incidence rate following a second dose is 1 per million doses. The risk estimates were then compared with the expected benefits of vaccine in age subgroups. The reported incidence rates are now plateauing, consistent with complete reporting of retrospective cases, so the estimated case incidence rates can be considered reliable.

2.8 The EWG considered the following 3 questions:

2.8.1 Question 1: based on the evidence presented does the EWG consider the benefit-risk balance remains favourable for all patients and for all age groups?

The EWG advised that the overall benefit-risk profile of the AstraZeneca COVID-19 Vaccine remains positive. However, the benefits of immunisation in individuals aged under 30 years may be outweighed by the potential risks, depending on the status of the COVID-19 pandemic, its severity and impact on hospitalisation.

2.8.2 Question 2: Does the EWG consider there might be an increased risk for the second dose of the vaccine?

The EWG advised that the emerging data on the risk of thromboembolic events occurring with thrombocytopenia following second doses is reassuring but limited, and so the MHRA should continue to monitor second dose cases closely.

2.8.3 Question 3: Does the EWG consider there is any need for action with regards to the Pfizer, Moderna or Janssen vaccines in relation to this potential risk?

Based on available data, the risk associated with the Pfizer and Moderna COVID-19 vaccines appears lower than that associated with the AstraZeneca COVID-19 Vaccine. This risk should be continuously monitored and there is currently no need for further regulatory action.

2.9 In conclusion, the EWG did not identify any potential trigger for regulatory action.

3. Any Other Business

None.

4. Date and time of next meeting

The next meeting is scheduled to take place on Friday 7h May. Time to be confirmed.

The Meeting today started at 14:02 and ended at 15:01.

Members are reminded that the content of papers and proceeding of the meetings are to be treated as 'Official – sensitive commercial'. Members are also reminded that, in accordance with the Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members must also declare any other matter which could reasonably be perceived as affecting their impartiality. Detailed guidance is set out in the Code of Practice

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Observers

Are invited to attend all meetings. Will not participate in drawing up conclusions and recommendations.

Annex II

The following participants declared interests and other relevant interests at the meeting today:

Professor Sir Munir Pirmohamed - NPNS AstraZeneca - Research grant to UOL to support PhD in drug interactions.
Other relevant interests in Pfizer, Janssen, Sanofi – Sir Munir is part of an EU-funded IMI consortium on gene therapy, and these companies are partners in the project. The University of Liverpool will get funding from the EU (but not from the partners), this IMI project commences on 3rd November 2020.
AGILE – this is a Liverpool early phase trial platform (between University of Liverpool and Liverpool School of Tropical Medicine). It is funded by the Wellcome Trust and UKRI/DHSC/NIHR. It is NOT evaluating vaccines, but only drugs to treat COVID-19. Sir Munir is not on the trial management group, and he is not directly involved in choosing the compounds for the study. Sir Munir has no involvement with any of the developers of the compounds to be studied (academic or industrial).
Sir Munir is a member of the UK COVID Therapeutics Advisory Panel (UK-CTAP), which is advising the CMO on which compounds need to be prioritised for the RECOVERY+ trial (RECOVERY is funded via NIHR/DHSC).

Professor French - Other relevant interest - Provides clinical care when in covering the acute medical wards where patients with COVID-19 are cared. NPNS in GSK - In September 2020 a sub-contract was signed with the Liverpool School of Tropical Medicine to undertake work evaluating the safety and effectiveness of GSK's RTS's malaria vaccine in Malawi. GSK are the primary funders to the LSTM.

Ms Hunneyball - Other relevant interest – writes articles published in the Chemist and Druggist magazine, a trade magazine for pharmacists, but receives no payment for these articles. The information referred to in the articles is in the public domain. Ms Hunneyball makes it clear that these are her personal views and reflections and references all sources of information used.

Sir Michael Jacobs - Other relevant interest - As part of the academic role at the Liverpool School of Tropical Medicine, Sir Michael is a member of the Study Management Team and antiviral drug prioritisation group for the AGILE proof of concept (phase I/II) platform study. Sir Michael is also part of the team that submits new antiviral compounds against SARS-CoV2 for consideration by NIHR for testing on this platform. No commercial or financial interest in the trial or any of the compounds, or any pharmaceutical or biotechnology company.

Professor Lehner - Other relevant interest – Professor Lehner previously held a DPAC (Discovery Partnership with Academia) agreement with GSK, but this has been completed. Professor Lehner's participation in his local hospital D and T governance committee deliberations would form the normal activity and professional responsibility in his post and does not interfere with the EWG considerations (Sept 2020).

Dr Misbah - NPNS - Holds honorary Senior Lectureship with University of Oxford & Oxford University Hospitals NHS Foundation Trust.

Professor Perrie - NPNS in Pfizer & AstraZeneca arising from a contract for a grant (March 2018), which includes contributions from these companies to the University of Strathclyde, Janssen in writing a grant for a PhD (now funded), GSK – arising from an EU grant to University of Strathclyde (Jan 2019-Dec 2019).

Professor Price - NPNS in GSK and AstraZeneca – which relates to donations provided by both companies to the British Toxicology Society (BTS) to support their Annual Congress and Education and Training of which Professor Price is currently President of the Society (2020-2022).

Dr Riordan - Other relevant interests - Participant in Oxford University's ChAdOx1 nCoV-19 clinical trial –received immunisation 27/8/2020. NPNS - Postgraduate External Examiner for Oxford University (Postgraduate Diploma in Paediatric Infectious Diseases).

Professor Solomon - Other relevant interests – Professor Solomon provides clinical care for patients with Covid-19; chaired the MRC/NIHR committee which awarded funding for development of the Oxford Vaccine.

Mrs Wang – Other relevant interests arising from being highly sensitive to insect stings, and plant products such as Hyacinth bulbs, as recorded on Mrs Wang's medical records. The family of Mrs Wang lives with several rare diseases and conditions, some of which result in epileptic fits.

Observers

Professor [redacted]

Professor Wei Shen Lim - NPNS arises from the institution (Nottingham University Hospitals NHS Trust) where Professor Lim works has received unrestricted investigator-initiated research funding from Pfizer for an unrelated prospective population-based cohort study of pneumococcal pneumonia in which Professor Lim is the Chief Investigator.

Dr [redacted]

Dr [redacted]

COMMISSION ON HUMAN MEDICINES (CHM)
COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the Ad Hoc meeting held on **Monday 10th May 2021** at **17:15** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan
Mr VI G Fenton-May
Professor N French
Professor D Goldblatt
Ms S Hunneyball
Professor K Hyrich
Sir M Jacobs
Professor H J Lachmann
Professor P J Lehner
Mr R Lowe
Dr S Misbah
Professor Y Perrie
Professor S Price
Dr A Riordan
Professor C Robertson
Professor T Solomon
Professor K M G Taylor
Dr R Thorpe
Professor M Turner
Dr S Walsh
Mrs M Wang
Professor C Weir

Observers

[redacted]

Secretariat

[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted] - VRMM

Presenters supporting specific items

[redacted] - VRMM
[redacted] - VRMM
[redacted] VRMM

MHRA Observers

[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
Dr S Branch - VRMM
[redacted] - MHRA-NIBSC
[redacted] - MHRA-Policy
[redacted] - VRMM
[redacted] - VRMM
[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
[redacted] - Comms
[redacted] - VRMM
Mr P Tregunno - VRMM
[redacted] - LD
[redacted] - VRMM
Dr K Wydenbach - LD

[redacted]

4th February 2022

Key
LD = Licensing Division
VRMM = Vigilance & Risk Management of Medicines
Comms = MHRA Communications
NIBSC = National Institute for Biological Standards & Control

1. Introduction and Announcement

1.1 The Chair reminded Members, invited Experts and observers that the content of papers and proceeding of the meeting are strictly confidential and should be treated as 'Official – sensitive commercial' and should not be disclosed. There is no consent for members / participants to record the meeting, take screenshots or photographs of presentations. The meeting was recorded by the MHRA Secretariat for minute taking purposes only. The Chair & Members including all participants gave full consent to the recording prior to the start of the meeting.

1.2 Conflict of Interest Policy (Annex I to the minutes)

The Chair reminded members and participants that, in accordance with the CHM Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members were also reminded to declare any other matter which could reasonably be perceived as affecting their impartiality.

1.3 Participants declared interests and other relevant interests for this meeting listed at **Annex II** to the minutes.

1.5 The Chair welcomed the following observers:

Dr [redacted]
[redacted] Public Health England

Professor [redacted]
[redacted] JCVI

Dr [redacted]
[redacted] Public Health Agency

Dr [redacted]
[redacted]

Professor [redacted]
[redacted] JCVI

Dr [redacted]
[redacted] Public Health Wales

2. Update on COVID-19 Vaccines and risk of thromboembolic events with concurrent thrombocytopenia

2.1 The EWG was presented with the latest data on thromboembolic events with thrombocytopenia associated with the authorised COVID-19 Vaccines up to a data lock point of 5 May 2021. The data lock point for the Janssen vaccine was 28 April 2021.

2.2 The EWG was informed of the updated statement on the AstraZeneca COVID-19 vaccine published by the Joint Committee on Vaccination and Immunisation (JCVI) on 7 May 2021. It was also made aware of new guidance aligned with this statement issued by Public Health England on 9 May 2021.

2.3 The EWG was then presented with a review of recent publications concerning the COVID-19 vaccines including: recommendations on clinical and laboratory diagnosis of vaccine-induced immune thrombotic thrombocytopenia (VITT) made by the Platelet Immunology Subcommittee of the International Society on Thrombosis and Haemostasis (ISTH); an expert opinion article intended to provide practical guidance to healthcare professionals; and a description of a flow cytometric assay to detect platelet activating antibodies in VITT that could be adopted by more laboratories as it does not require washed platelets. The EWG noted that the ISTH recommendations included primary and secondary immune thrombocytopenia and considered isolated thrombocytopenia with abnormal coagulation parameters as a possible early sign of VITT. The MHRA has also identified possible cases of thrombosis with thrombocytopenia and isolated thrombocytopenia associated with PF4 antibodies so the current case definition should be reconsidered. The EWG was also aware of the proposed Brighton Collaboration criteria for thrombosis-thrombocytopenia syndrome although these criteria do not necessitate prior COVID-19 vaccine exposure and are intended for epidemiological studies rather than regulatory or clinical use.

2.4 An overview of the case reports associated with the AstraZeneca COVID-19 Vaccine was presented including a summary table of the 8 reported cases after a second dose. It was noted that none of the reported second dose cases were associated with cerebral venous sinus thromboses or had platelet factor 4 antibodies. The EWG was reassured by the emerging data but advised that second dose cases should remain under close monitoring as the vaccine programme moves into younger patients. An extra case was identified after the presentation was circulated and although there were not significant overall changes to the assessment, a revised version of the slides will be circulated for audit purposes.

2.5 The UK and foreign cases associated with the Pfizer, Moderna and Janssen COVID-19 vaccines were summarised using the same case definition. The EWG was also informed of the regulatory actions taken by the EMA following a signal assessment of thromboembolic events with thrombocytopenia conducted by the PRAC for the Janssen COVID-19 vaccine.

2.6 The estimated number of second AstraZeneca COVID-19 vaccine doses administered has increased to 7.5 million whilst the number of first doses has increased slightly, in line with the current deployment programme to 23.3 million. Estimated case incidence rates for CVST and CVST plus non-CVST events were presented by age-stratified 10-year intervals and by gender. The overall incidence rate is stable at 10.9 (9.6, 12.3) per million for first/unknown doses and the overall fatal incidence rate is 2.1 (1.6, 2.8) per million doses. The risk estimates were then compared with the expected benefits of the vaccine in age subgroups. The reported incidence rates are now plateauing, consistent with complete reporting of retrospective cases, so the estimated case incidence rates can be considered reliable.

2.7 The EWG then considered the following 3 questions:

2.7.1 Question 1: based on the evidence presented does the EWG consider the benefit-risk balance remains favourable for all patients and for all age groups?

The EWG advised that the overall benefit-risk profile of the AstraZeneca COVID-19 Vaccine remains positive although the benefits of immunisation in individuals aged under 40 years are probably outweighed by the potential risks, depending on the status of the COVID-19 pandemic, its severity and impact on hospitalisation. The benefit-risk assessment has not changed since it was reviewed on 4 May 2021.

2.7.2 Question 2: Does the EWG consider there might be an increased risk for the second dose of the vaccine?

The EWG advised that the emerging data on the risk of thromboembolic events occurring with thrombocytopenia following second doses is reassuring but limited so the MHRA should continue to monitor second dose cases closely, particularly as younger patients will now be receiving their booster immunisations.

2.7.3 Question 3: Does the EWG consider there is any need for action with regards to the Pfizer, Moderna or Janssen vaccines in relation to this potential risk?

Based on available data, the risk associated with the Pfizer and Moderna COVID-19 vaccines appears lower than that associated with the AstraZeneca COVID-19 Vaccine. This risk should be monitored and there is no need for regulatory action.

2.8 In conclusion, the EWG did not identify any potential trigger for regulatory action.

3. Any Other Business

None.

4. Date and time of next meeting

The next scheduled meeting is to take place **on Friday 14th May** at **10.30am**.

The Meeting today started at 17:15 and ended at 17:52.

Members are reminded that the content of papers and proceeding of the meetings are to be treated as 'Official – sensitive commercial'. Members are also reminded that, in accordance with the Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members must also declare any other matter which could reasonably be perceived as affecting their impartiality. Detailed guidance is set out in the Code of Practice

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Observers

Are invited to attend all meetings. Will not participate in drawing up conclusions and recommendations.

Annex II

The following participants declared interests and other relevant interests at the meeting today:

Professor Sir Munir Pirmohamed - NPNS AstraZeneca - Research grant to UOL to support PhD in drug interactions.
Other relevant interests in Pfizer, Janssen, Sanofi – Sir Munir is part of an EU-funded IMI consortium on gene therapy, and these companies are partners in the project. The University of Liverpool will get funding from the EU (but not from the partners), this IMI project commences on 3rd November 2020.
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Sir Munir is a member of the UK COVID Therapeutics Advisory Panel (UK-CTAP), which is advising the CMO on which compounds need to be prioritised for the RECOVERY+ trial (RECOVERY is funded via NIHR/DHSC).

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Ms Hunneyball - Other relevant interest - writes articles published in the Chemist and Druggist magazine, a trade magazine for pharmacists, but receives no payment for these articles. The information referred to in the articles is in the public domain. Ms Hunneyball makes it clear that these are her personal views and reflections and references all sources of information used.

Professor Hyrich – NPNS - Professor Hyrich was co-I on an investigator-initiated research grant exploring predictors of outcome in rheumatoid arthritis. NPNS Pfizer- she is a Co-I on a grant exploring adherence to JAK inhibitors in rheumatoid arthritis. NPNS in Abbvie, Professor Hyrich gave some lectures at an education conference on effectiveness of treatment for rheumatoid arthritis.

Sir Michael Jacobs - Other relevant interest - As part of the academic role at the Liverpool School of Tropical Medicine, Sir Michael is a member of the Study Management Team and antiviral drug prioritisation group for the AGILE proof of concept (phase I/II) platform study. Sir Michael is also part of the team that submits new antiviral compounds against SARS-CoV2 for consideration by NIHR for testing on this platform. No commercial or financial interest in the trial or any of the compounds, or any pharmaceutical or biotechnology company.

Professor Lachmann – Other relevant interest as a volunteer participant in the Oxford vaccine study and no other involvement in the study.

Professor Lehner - Other relevant interest - Professor Lehner previously held a DPAC (Discovery Partnership with Academia) agreement with GSK, but this has been completed. Professor Lehner's participation in his local hospital D and T governance committee deliberations would form the normal activity and professional responsibility in his post and does not interfere with the EWG considerations (Sept 2020).

Dr Misbah - NPNS - Holds honorary Senior Lectureship with University of Oxford & Oxford University Hospitals NHS Foundation Trust.

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Professor Price - NPNS in GSK and AstraZeneca – which relates to donations provided by both companies to the British Toxicology Society (BTS) to support their Annual Congress and Education and Training of which Professor Price is currently President of the Society (2020-2022).

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Professor Solomon - Other relevant interests - Professor Solomon provides clinical care for patients with Covid-19; chaired the MRC/NIHR committee which awarded funding for development of the Oxford Vaccine.

Mrs Wang – Other relevant interests arising from being highly sensitive to insect stings, and plant products such as Hyacinth bulbs, as recorded on Mrs Wang's medical records. The family of Mrs Wang lives with several rare diseases and conditions, some of which result in epileptic fits.

Professor Weir - NPNS - Imperial College and Other relevant interest arising from his department collaborates with Imperial College on a number of clinical trials.

Observers

Professor [redacted] - NPNS - University of Oxford employee (with no involvement in research or clinical trials related to Oxford AZ vaccine)
[redacted] JCVI

Professor [redacted] **-** NPNS arises from the institution ([redacted] University Hospitals NHS Trust) where Professor [redacted] works has received unrestricted investigator-initiated research funding from Pfizer for an unrelated prospective population-based cohort study of pneumococcal pneumonia in which Professor [redacted] s the Chief Investigator.

COMMISSION ON HUMAN MEDICINES (CHM)
COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Friday 14th May 2021** at **14:00** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan
Mr VI G Fenton-May
Professor N French
Professor D Goldblatt
Ms S Hunneyball
Professor K Hyrich
Sir M Jacobs
Professor P J Lehner
Mr R Lowe
Dr S Misbah
Professor Y Perrie
Professor S Price[1]
Dr A Riordan[2]
Professor T Solomon
Professor K M G Taylor
Dr R Thorpe
Professor M Turner[3]
Dr S Walsh
Mrs M Wang

Apologies

Professor H J Lachmann
Professor C Robertson
Professor C Weir

Secretariat

[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea – LD
[redacted]

Presenters supporting specific items

[redacted] – VRMM
[redacted] – LD
[redacted] – VRMM
[redacted] – LD

MHRA Observers

[redacted] – LD
Dr S Branch – VRMM
[redacted] – VRMM
[redacted] – Comms
[redacted] – LD
[redacted] – LD
[redacted] – VRMM
[redacted] – VRMM
Dr K Wydenbach – LD

[redacted]

16th February 2023

[1] joined during item 2
[2] joined during item 4
[3] left during item 5

Key
LD = Licensing Division
VRMM = Vigilance & Risk Management of Medicines
Comms = MHRA Communications

1. Introduction and Announcements

1.1 The Chair reminded Members, invited Experts and observers that the content of papers and proceeding of the meeting are strictly confidential and should be treated as 'Official – sensitive commercial' and should not be disclosed. There is no consent for members / participants to record the meeting, take screenshots or photographs of presentations. The meeting was recorded by the MHRA Secretariat for minute taking purposes only. The Chair & Members including all participants gave full consent to the recording prior to the start of the meeting.

1.2 Conflict of Interest Policy (Annex I to the minutes)

The Chair reminded members and participants that, in accordance with the CHM Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members were also reminded to declare any other matter which could reasonably be perceived as affecting their impartiality.

1.3 Participants declared interests and other relevant interests for this meeting listed at **Annex II** to the minutes.

1.4 Apologies were received from Professors Lachmann, Robertson and Weir for this meeting.

2. Review of the possible risk of neurological autoimmune conditions with COVID-19 vaccines

2.1 The EWG was presented with an assessment of data for the adverse events of multiple sclerosis, optic neuritis, transverse myelitis and Neuromyelitis Optica Spectrum Disorder (NMOSD) reported following vaccination with the AstraZeneca, Pfizer-BioNTech and Moderna COVID-19 Vaccines. The assessment included a review of the UK Yellow Card data, data from the most recent safety summary surveillance report for each of the vaccines, and epidemiological analyses (observed vs expected analyses of Yellow Card reports and rapid cycle analyses using the CPRD).

2.2 For the AstraZeneca vaccine, the EWG were informed that the number of reports of neurological autoimmune conditions was low in the context of the usage of the AstraZeneca vaccine. For transverse myelitis, the majority of reports met the case definition, but had very rapid onset times not associated with transverse myelitis. For multiple sclerosis and optic neuritis, the majority of reports were consistent with reactogenicity reactions and were transient, short-duration reactions. Company observed vs expected analysis did not identify an increase in these events.

2.3 For the Pfizer/BioNTech vaccine, the EWG were informed that there had been limited reports of multiple sclerosis, optic neuritis or transverse myelitis and no reports of NMOSD. The EWG noted that there was no clear patterns of onset times or occurrence after a specific dose, and company data did not show an increased risk of these events. For all events the number of reports was small in the context of the use of the vaccine.

2.4 For the Moderna vaccine, the EWG noted there had been no Yellow Card reports of multiple sclerosis, optic neuritis, transverse myelitis or NMOSD and that there were very few reports from international data.

2.5 The EWG were presented the MHRA epidemiological data, with observed vs expected analysis identifying a signal of transverse myelitis for the AstraZeneca vaccine assuming 100% reporting for all age groups, and for the Pfizer/BioNTech vaccine assuming 50% reporting in the under 50 years age group, and 25% reporting in the 50-64 years age group. Rapid cycle analysis did not identify any signals for any of the neurological autoimmune conditions or vaccines.

2.6 The EWG considered that the majority of reports of multiple sclerosis, optic neuritis and NMOSD were not related to new onset of these events, with the reports describing either flare-up of these events or reactogenicity events. For transverse myelitis, the EWG considered that for the AstraZeneca vaccine, while reports did meet the case definition, the reports did not relate to new-onset of transverse myelitis. The EWG considered that transverse myelitis should continue to be closely monitored and was aware of potential epidemiological studies that would be investigating this. The EWG concluded that the available evidence did not support any updates to the product information for any of the COVID-19 vaccines.

3. Risk of Capillary Leak Syndrome with COVID-19 Vaccine AstraZeneca

3.1 The VBR EWG was reminded that it had previously considered an assessment of UK cases of capillary leak syndrome (CLS) reported following vaccination with COVID-19 Vaccine AstraZeneca at its meeting on 12 April 2021. At that time the EWG advised that a causal association could not be determined based on the data available, and that the signal should be closely monitored.

3.2 The EWG was presented with an updated review of this signal which included an assessment of UK cases of CLS reported for COVID-19 Vaccine AstraZeneca via the Yellow Card Scheme, together with an assessment of a cumulative review of worldwide clinical study and post-authorisation cases and a literature review submitted by the company.

3.3 The EWG agreed that the currently available data did not suggest an association between COVID-19 Vaccine AstraZeneca and CLS. Causality assessment was difficult in some cases because the patients had a prior history of CLS or other significant illness. Causality was also considered unlikely in some cases due to the time to onset being inconsistent with a vaccine-related effect. The EWG also noted that most cases did not have the IgG paraprotein typical of classical CLS.

3.4 The EWG agreed that no updates to the SmPC or Risk Management Plan for COVID-19 Vaccine AstraZeneca were warranted based on the data presented and supported the proposal to keep the issue under review.

4. COVID-19 Vaccine AstraZeneca: Assessment of the draft protocol for a Post Authorisation Safety Study (PASS) to ascertain the incidence rate of adverse events of special interest

4.1 The VBR EWG was presented with an assessment of the draft protocol for a secondary database study in the VAC4EU (Vaccine Monitoring Collaboration for Europe) research environment to ascertain the incidence rates of adverse events of special interest in individuals vaccinated with COVID-19 Vaccine AstraZeneca.

4.2 The EWG agreed with the assessment of the study protocol and with the comments and lists of questions for the company proposed by the MHRA and the European Medicines Agency (EMA).

4.3 In particular, the EWG agreed with concerns raised about the proposed timelines for the study given the pace of roll out of the vaccine in the UK, and fully supported the proposal to ask the company to submit the first interim report and the statistical analysis plan (SAP) much sooner than had been proposed in the protocol. The EWG also recommended that the company should be asked to provide further information about when the study will start; information that had not been included in the draft protocol.

4.4 The EWG discussed the limitations of the cohort study design which the company proposed to use as the primary study approach. The EWG supported the concerns raised regarding the likely issues with finding concurrent controls for the cohort study as more unvaccinated individuals become vaccinated with time. The EWG discussed the company's rationale for proposing the cohort design as the primary approach (that the self-controlled risk interval (SCRI) design is less able to study outcomes with a gradual onset, such as multiple sclerosis and peripheral neuropathies) but agreed with the assessment that these difficulties could be overcome by using the date of onset of first symptoms as the index date rather than date of diagnosis, and by studying a range of different risk intervals. The EWG supported proposals to make the SCRI design rather than the cohort design as the primary study approach.

The EWG further suggested that the company be asked to consider a more sophisticated statistical approach to the SCRI design, for example by modelling exponential decline in risk rather than specifying 'at risk' and 'not at risk' periods.

4.5 In addition, the EWG expressed concerns as to whether data on individuals taking immunosuppressants and individuals living with HIV would be adequately collected in the study. The EWG questioned whether this information was captured in the two non-UK databases proposed by the company to be used in the study, noting that information about use of immunomodulators other than methotrexate would not be captured in CPRD (the 3rd database to be proposed for the study) and was not readily available from other sources in the UK. Similarly, information about individuals living with HIV would not be adequately captured in CPRD. The EWG suggested that these data may be more readily available in other European countries. The EWG recommended that the company further explore the availability of data on immunosuppressed individuals and those living with HIV in the databases currently proposed for the study and if necessary, to include additional European databases in the study to ensure that the safety of the vaccine in this important group of individuals can be evaluated in the study. If adequate data are not available, this should be included as an important limitation of the study in the protocol.

4.6 The EWG noted that only 3 databases had been selected by the company for the study. To increase the power of the study and yield more meaningful data, the EWG suggested that the company be requested to select a number of additional European databases for the study.

5. Brief Update on COVID-19 Vaccines

5.1 The VBR EWG was updated on the progress status of each of the vaccines under review or to be evaluated in the future. Regarding the SPC for the Janssen vaccine, the EWG agreed with the company proposal to include 'Patients with a history of heparin-induced thrombocytopenia and thrombosis (HITT or HIT type 2)' as a warning in section 4.4 rather than a contraindication in section 4.3.'

6. <u>Any Other Business</u>

6.1 None.

7. Date and time of next meeting

The next Ad Hoc meeting on Thromboembolic events with COVID-19 Vaccines is scheduled to take place on **Monday 17th May** at **5.15pm**.

The next scheduled meeting is to take place **on Friday 21st May** at **2.30pm**.

The Meeting today started at 10:34 and ended at 12:32.

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Annex I

Conflict of Interest Policy for CHM COVID-19 Vaccine Benefit Risk EWG

Chair and Members

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Invited experts

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COMMISSION ON HUMAN MEDICINES (CHM)
COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the Ad Hoc meeting held on **Monday 17th May 2021** at **17:15** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan
Mr VI G Fenton-May
Professor N French
Professor D Goldblatt
Ms S Hunneyball
Professor K Hyrich
Sir M Jacobs
Professor H J Lachmann
Professor P J Lehner
Mr R Lowe
Dr S Misbah
Professor Y Perrie
Professor S Price
Dr A Riordan
Professor C Robertson
Professor K M G Taylor
Dr R Thorpe
Professor M Turner
Dr S Walsh
Mrs M Wang
Professor C Weir

Apologies

Professor T Solomon

Observers

[redacted]
Professor W S Lim
[redacted]

Secretariat

[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted] - VRMM

Presenters supporting specific items

[redacted] - VRMM
[redacted] - VRMM
[redacted] - VRMM

MHRA Observers

[redacted] - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - LD
Dr S Branch - VRMM
[redacted] - MHRA-NIBSC
[redacted] - MHRA-Policy
[redacted] - VRMM
[redacted] - VRMM
[redacted] - VRMM
[redacted] - Comm
[redacted] - VRMM
[redacted] - VRMM
Mr P Tregunno - VRMM
[redacted] - LD
[redacted] - VRMM

[redacted]

4th February 2022

Key
LD = Licensing Division
VRMM = Vigilance & Risk Management of Medicines
Comms = MHRA Communications
NIBSC = National Institute for Biological Standards & Control

1. Introduction and Announcement

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1.3 Participants declared interests and other relevant interests for this meeting listed at **Annex II** to the minutes.

1.4 Apologies were received from Professor Tom Solomon for this meeting.

1.5 The Chair welcomed the following observers:

Dr [redacted]
[redacted], Public Health England

Professor [redacted]
[redacted] JCVI

Dr [redacted]
Locum Consultant in Health Protection, Public Health Agency

Dr [redacted]

Professor [redacted]
[redacted] JCVI

Dr [redacted]
Public Health Scotland

2. Update on the review for major thrombotic events associated with thrombocytopenia

2.1 The EWG was presented with the latest data on thromboembolic events with thrombocytopenia associated with the authorised COVID-19 Vaccines up to a data lock point of 12 May 2021.

2.2 The EWG was informed of the updated recommendations issued by the [redacted] on 3rd May 2021.

2.3 The EWG was then presented with a summary of recent publications concerning the AstraZeneca COVID-19 vaccine including: interim reactogenicity and safety data results from the COM-CoV study of heterologous prime-boost COVID-19 vaccines; a review of 20 published cases of vaccine-associated immune thrombosis and thrombocytopenia; a review of COVID-19 vaccine platforms that included a proposed causal mechanism to explain observed events of thrombosis with thrombocytopenia; and a small study reporting the frequency and platelet-activation properties of PF4 antibodies detected in healthy volunteers after immunisation with the AstraZeneca and Pfizer COVID-19 vaccines.

2.4 An overview of the case reports associated with the AstraZeneca COVID-19 Vaccine was presented including summary tables of the 15 reported cases occurring after a second dose.

2.4.1 It was noted that a female of unknown age had experienced cerebral venous sinus thrombosis and deep vein thrombosis with severe thrombocytopenia at 8 days after her second dose although her PF4 antibody status was not known.

2.4.2 Another case was reviewed in detail: an elderly female with localised lymphoma in remission developed an incidental hepatic vein thrombosis with mild thrombocytopenia about 28 days after her first dose of the vaccine. She experienced an acute occipital arterial infarct associated with moderate thrombocytopenia and PF4 antibodies (optical density 2.46). The events following the second dose were confounded by recent COVID-19 infection. The EWG advised that this was probably a positive rechallenge case confounded by COVID-19 infection. It also noted that second doses are contraindicated in patients who have experienced major venous and/or arterial thrombosis occurring with thrombocytopenia following vaccination with any COVID-19 vaccine which seems to be supported by this particular case.

2.4.3 The EWG advised that the emerging data on second dose cases might have identified a different clinical phenotype to early first dose cases but is based on an older group. More data on the risks associated with second doses in younger people is required and so this issue should remain under close monitoring as the vaccine programme moves into younger patients. It also requested that age-stratified second dose incidence rate data should be presented at future weekly meetings.

2.5 The UK and foreign cases associated with the Pfizer, Moderna and Janssen COVID-19 vaccines were summarised using the same case definition. The EWG noted that the case incidence rates for the Janssen COVID-19 vaccine reported by the [redacted] are gradually increasing and are now comparable to those for the AstraZeneca COVID-19 vaccine.

2.6 The estimated number of second AstraZeneca COVID-19 vaccine doses administered has increased to 9.0 million whilst the number of first doses has increased slightly, in line with the current deployment programme to 23.9 million. Estimated case incidence rates for CVST and CVST plus non-CVST events were presented by age-stratified 10-year intervals and by gender. The overall incidence rate is stable at 12.3 (10.9, 13.7) per million for first/unknown doses and the overall fatal incidence rate is also stable at 2.3 (1.7, 3.0) per million first/unknown doses. The incidence rate associated with second doses has increased slightly from 1.1 to 1.7 (0.9, 2.7) per million doses but the 95% confidence intervals are overlapping. The risk estimates were then compared with the expected benefits of vaccine in age subgroups. The EWG noted that all new fatal cases have cerebral venous sinus thromboses. The reported incidence rates showed a small increase since last data lock point, while risk-benefit ratio remained relatively unchanged.

2.7 The EWG then considered the following 3 questions:

2.7.1 Question 1: based on the evidence presented does the EWG consider the benefit-risk balance remains favourable for all patients and for all age groups?

The EWG advised that the overall benefit-risk profile of the AstraZeneca COVID-19 Vaccine remains positive although the benefits of immunisation in individuals aged under 40 years are probably outweighed by the potential risks, depending on the status of the COVID-19 pandemic, its severity and impact on hospitalisation. The benefit-risk assessment has not changed since it was reviewed on 10 May 2021.

2.7.2 Question 2: Does the EWG consider there might be an increased risk for the second dose of the vaccine?

The EWG advised that the emerging data on the risk of thromboembolic events occurring with thrombocytopenia following second doses is reasonably reassuring but limited, and so the MHRA should continue to monitor second dose cases closely, particularly as younger patients will now be receiving their second doses. The case of positive rechallenge reported after the second dose of the AstraZeneca COVID-19 vaccine, although confounded, validates the contraindication in those with thrombotic events associated with thrombocytopenia after a first dose of any COVID-19 vaccine.

2.7.3 Question 3: Does the EWG consider there is any need for action with regards to the Pfizer, Moderna or Janssen vaccines in relation to this potential risk?

Based on available data, the risk associated with the Pfizer and Moderna COVID-19 vaccines appears lower than that associated with the AstraZeneca COVID-19 Vaccine. This risk should be monitored and there is no need for regulatory action.

2.8 In conclusion, the EWG did not identify any potential trigger for regulatory action.

3. <u>Any Other Business</u>

None.

4. <u>Date and time of next meeting</u>

The next scheduled meeting is to take place on **Friday 21st May 2021** at **2.30pm**.

The Meeting today started at 17:17 and ended at 18:03.

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Sir Munir is a member of the UK COVID Therapeutics Advisory Panel (UK-CTAP), which is advising the CMO on which compounds need to be prioritised for the RECOVERY+ trial (RECOVERY is funded via NIHR/DHSC).

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Professor French - Other relevant interest - Provides clinical care when in covering the acute medical wards where patients with COVID-19 are cared. NPNS in GSK - In September 2020 a sub-contract was signed with the Liverpool School of Tropical Medicine to undertake work evaluating the safety and effectiveness of GSK's RTS's malaria vaccine in Malawi. GSK are the primary funders to the LSTM.

Ms Hunneyball - Other relevant interest - writes articles published in the Chemist and Druggist magazine, a trade magazine for pharmacists, but receives no payment for these articles. The information referred to in the articles is in the public domain. Ms Hunneyball makes it clear that these are her personal views and reflections and references all sources of information used.

Professor Hyrich – NPNS - Professor Hyrich was co-I on an investigator-initiated research grant exploring predictors of outcome in rheumatoid arthritis. NPNS Pfizer- she is a Co-I on a grant exploring adherence to JAK inhibitors in rheumatoid arthritis. NPNS in Abbvie, Professor Hyrich gave some lectures at an education conference on effectiveness of treatment for rheumatoid arthritis.

Sir Michael Jacobs - Other relevant interest - As part of the academic role at the Liverpool School of Tropical Medicine, Sir Michael is a member of the Study Management Team and antiviral drug prioritisation group for the AGILE proof of concept (phase I/II) platform study. Sir Michael is also part of the team that submits new antiviral compounds against SARS-CoV2 for consideration by NIHR for testing on this platform. No commercial or financial interest in the trial or any of the compounds, or any pharmaceutical or biotechnology company.

Professor Lachmann – Other relevant interest as a volunteer participant in the Oxford vaccine study and no other involvement in the study.

Professor Lehner - Other relevant interest - Professor Lehner previously held a DPAC (Discovery Partnership with Academia) agreement with GSK, but this has been completed. Professor Lehner's participation in his local hospital D and T governance committee deliberations would form the normal activity and professional responsibility in his post and does not interfere with the EWG considerations (Sept 2020).

Dr Misbah - NPNS - Holds honorary Senior Lectureship with University of Oxford & Oxford University Hospitals NHS Foundation Trust.

Professor Perrie - NPNS in Pfizer & AstraZeneca arising from a contract for a grant (March 2018), which includes contributions from these companies to the University of Strathclyde, Janssen in writing a grant for a PhD (now funded), GSK – arising from an EU grant to University of Strathclyde (Jan 2019-Dec 2019).

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Professor Weir - NPNS - Imperial College and Other relevant interest arising from his department collaborates with Imperial College on a number of clinical trials.

Observers

Professor [redacted] - NPNS - University of Oxford employee (with no involvement in research or clinical trials related to Oxford AZ vaccine)
[redacted] JCVI

Professor [redacted] **-** NPNS arises from the institution ([redacted] University Hospitals NHS Trust) where Professor [redacted] works has received unrestricted investigator-initiated research funding from Pfizer for an unrelated prospective population-based cohort study of pneumococcal pneumonia in which Professor [redacted] is the Chief Investigator.

Dr [redacted] – Lapsed and NPNS - Regarding companies to declare interests for, prior to joining Public Health Scotland, Dr [redacted] worked for a company that provided epidemiological services to the pharmaceutical industry. Whilst working there, she supported respiratory vaccine development activities at Janssen (Johnson & Johnson). Dr [redacted] has now left that role.

COMMISSION ON HUMAN MEDICINES (CHM)
COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Friday 21st May 2021** at **14:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan[1]
Mr VI G Fenton-May
Professor N French
Professor D Goldblatt
Ms S Hunneyball
Professor K Hyrich[1]
Sir M Jacobs[2]
Professor H J Lachmann
Mr R Lowe
Dr S Misbah
Professor Y Perrie
Professor S Price
Dr A Riordan
Professor K M G Taylor
Dr R Thorpe
Professor M Turner
Dr S Walsh
Professor C Weir

Apologies

Professor P J Lehner
Professor C Robertson
Professor T Solomon
Mrs M Wang

Observers (left after item 3)

[redacted]

Secretariat

[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted] - VRMM

Presenters supporting specific items

[redacted] - LD
[redacted] - VRMM
[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD

MHRA Observers

[redacted] - VRMM
[redacted] - LD
[redacted] - LD
Dr S Branch - VRMM
[redacted] - LD
[redacted] - NIBSC
[redacted] - MHRA-Policy
[redacted] - VRMM
[redacted] - Comms
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
Mr P Tregunno - VRMM
[redacted] - VRMM

[redacted]

3rd August 2021

[1] Left during item 5
[2] Joined during item 3

Key
LD = Licensing Division
VRMM = Vigilance & Risk Management of Medicines
NIBSC = National Institute for Biological Standards & Control
Comms = MHRA Communications

1. Introduction and Announcement

1.1 The Chair reminded Members and observers that the content of papers and proceeding of the meeting are strictly confidential and should be treated as 'Official – sensitive commercial' and should not be disclosed. There is no consent for members / participants to record the meeting, take screenshots or photographs of presentations. The meeting was recorded by the MHRA Secretariat for minute taking purposes only. The Chair & Members including all participants gave full consent to the recording prior to the start of the meeting.

1.2 Conflict of Interest Policy (Annex I to the minutes)

The Chair reminded members and participants that, in accordance with the CHM Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members were also reminded to declare any other matter which could reasonably be perceived as affecting their impartiality.

1.3 Participants declared interests and other relevant interests for this meeting listed at **Annex II** to the minutes.

1.4 Apologies were received from Professors Lehner, Robertson, Solomon and Mrs Wang for this meeting.

1.5 The Chair welcomed the following observers:

Professor [redacted]
[redacted] JCVI

Dr [redacted]
Public Health Scotland

2. Communications on COVID-19 vaccine safety

2.1 The EWG discussed a paper which presented options for analyses of safety data related to the occurrence of thrombotic events with concurrent thrombocytopenia that could be considered for routine publication within the `Coronavirus vaccine – weekly summary of Yellow Card reporting'.

2.2 The EWG supported transparency with regards to the publication of data on this risk but advised that the data needs to be carefully presented to ensure its limitations are clear and that estimates based on small numbers which may be unstable and/or inadvertently disclose confidential patient information should be avoided.

2.3 The EWG supported the publication of age-stratified incidence reporting rates for thrombosis with concurrent thrombocytopenia following both doses of the COVID-19 AstraZeneca vaccine alongside an accessible and clear description of the benefits and risks of vaccination.

3. Update on the Safety Data for the Moderna COVID-19 vaccine

3.1 The EWG was presented with the first safety update for the Moderna COVID-19 vaccine, which covered the first month following deployment in the UK, with a data lock point of 12th

May 2021. The EWG was informed that the ADRs reported were broadly in line with the known safety profile for the vaccine and that had been seen in clinical trials. The EWG heard a signal of dizziness has been identified for the Moderna COVID-19 vaccine, which included reports of dizziness alongside psychogenic, reactogenic and vestibular events. The EWG were informed that the Marketing Authorisation Holder (MAH) had been requested to review the signal of dizziness with a particular interest in cases reporting vestibular events such as tinnitus. The meeting supported the continuous review of dizziness reports. An update to the EWG will be provided following the MAH review.

3.2 The EWG were informed that a large proportion of the Yellow Cards reported for the Moderna vaccine were related to delayed injection site reactions. These reactions include a large, raised, itchy red rash around the injection site around 7 to 8 days after vaccination. The meeting was informed that the MAH had updated their Company Core Data Sheet (CCDS) to include these delayed injection site reactions and were planning to update the product information in due course. The meeting supported the proposed update to the product information to highlight these delayed reactions to patients.

3.3 The EWG concluded that based on the data presented, the safety profile for COVID-19 vaccine Moderna was broadly in line with the expected safety profile from clinical trials. The EWG supported the proposed actions on the delayed injection site reactions and dizziness signals.

4. Covid-19 mRNA vaccine BNT162b2

4.1 The EWG heard that immunobridging of neutralising antibody levels between adolescents aged 12-15 years and young adults aged 16-25 years has been established and that the neutralising antibody levels seen in adolescents actually exceeded those in young adults.

4.2 The EWG noted that these immunobridging results are supported by a very high level of short-term efficacy data in adolescents against symptomatic disease after 2 doses of the vaccine.

4.3 The EWG heard that the safety data in adolescents was generally comparable with that seen in young adults, with the majority of adverse events being mild to moderate and relating to reactogenicity. Additionally, no new adverse events are identified in the trial. The EWG noted that 3 serious adverse events of depression were reported in the adolescent group compared with 2 non-serious reports in the placebo group. All 3 subjects had a significant past medical history that included depression, but none were considered related to the vaccine and 2 of the 3 cases resolved after 5 days. The EWG agreed that currently there was no basis to list depression as a safety concern in the RMP. However, this will be kept under review in the post authorisation period, through the monthly summary safety reports submitted by the company.

4.4 The EWG noted that overall, when compared to adults 16-55 years of age, there is an increase in reactogenicity seen in adolescents. However, it was agreed that this is not unexpected as the same trend was seen previously in subjects 16-55 years compared with those aged > 55 years of age. This trend is already reflected in the GB SmPC for the conditional marketing authorisation and this wording will be aligned in the Regulation 174 product information.

4.5 The EWG were made aware of an open letter that has been received by the MHRA, signed by over 40 UK doctors, raising their concerns about covid-19 vaccination in children. Other media coverage was highlighted on the ethics of vaccinating children and adolescents that have a low risk of severe COVID-19 whilst the majority of the adult population worldwide is

not yet vaccinated. The EWG concluded that while the latter is an important moral and ethical question it is not one for the EWG to address as the licensing remit of the MHRA focuses on the assessment of the quality, safety, and efficacy of medicinal products.

4.6 The EWG discussed the adequacy of the efficacy and safety follow-up duration available in subjects aged 12-15 years (median > 2months). It was noted that this duration is the same as what was previously agreed for subjects aged 16 years and over. The EWG agreed with the Paediatric Medicines EAG that it seems reasonable to be on the same line for adolescents, particularly given the significant post-marketing safety data now available for this vaccine. The EWG noted that it is anticipated for younger children under 12 years of age, longer term safety data would be requested before any approval.

4.7 The EWG were made aware that no notable changes were proposed by the company to the risk management plan in terms of the safety concerns, pharmacovigilance plan or risk minimisation measures. The EWG agreed that based on the available safety data, no additional safety concerns specific to the adolescents aged 12-15 years are required at this time.

4.8 The EWG noted that the list of adverse events of special interest (AESIs) for COVID-19 vaccine BNT162b2 already includes events of relevance to the adolescent age group, including narcolepsy, chronic/post viral fatigue syndrome, myalgic encephalomyelitis, post orthostatic tachycardia syndrome and paediatric inflammatory multisystem syndrome. The EWG noted that these events will be subject to observed-expected analyses and that age-appropriate background rates should be considered by the company. The EWG agreed with the proposed questions to the company, including requesting a discussion on how safety data in the adolescent population could be collected in existing PASS studies, and the inclusion of a separate analysis of safety data in the adolescent population in the monthly summary safety reports.

4.9 The EWG noted the clinical trial data continues to be blinded to participants and clinical trial investigators except if participants are offered vaccination under emergency use authorisation, but the data have been unblinded to the independent scientists that undertook the statistical analysis.

4.10 The EWG noted immunogenicity and safety data in the 12-15 year olds provides a good level of reassurance. The efficacy data is also supportive of a positive recommendation albeit that the data is limited in this age group.

4.11 The EWG noted vaccination of 12-15-year olds could be an important means by which to limit the evolution of SARS-CoV-2 through controlling circulation of the virus.

4.12 The EWG noted that careful consideration may need to be paid to the natural background mental and behavioural health of 12-15-year-olds when assessing vaccine surveillance safety data, as this age group are likely to have been particularly affected by the pandemic.

4.13 The EWG agreed that six months follow-up data in 12-15 years should be added as a condition.

4.14 The EWG agreed with the conclusions of the Paediatric Medicines EAG. The EWG endorsed the clinical assessor's recommendation, that the Regulation 174 approval can be amended to lower the indication age to 12 years and above.

5. A single-blind, randomised, phase II study to determine safety and immunogenicity of the Coronavirus Disease (COVID-19) vaccine ChAdOx1 in UK healthy children and adolescents (aged 6-17) COV006

5.1 The EWG heard the proposal to continue dosing in the Oxford paediatric trial and to administer booster/second doses is supported by the CTU. Use of the AstraZeneca COVID-19 (AZD1222) vaccine in UK national deployment has been restricted by the Joint Committee on Vaccination and Immunisation (JCVI) following reports of extremely rare adverse events of concurrent thrombosis and thrombocytopenia following vaccination with the first dose of AZD1222. However, such a risk has not yet been convincingly demonstrated for second doses.

5.2 The risk of thrombosis with concurrent thrombocytopaenia has not been demonstrated for any doses in children and is therefore not known. A total of 261 children aged 6-17 years have received the prime dose with no complications and 74 children aged 12-17 years have been given their booster doses on Day (D) 28 also with no complications. The EWG heard, the MHRA-CTU has reviewed the safety profile of the 74 children in the older age group (12-17 years), where the prime and booster doses were administered on D28 with no safety concerns identified; and together with consideration of the updated benefit risk assessment provided by the Sponsor, the proposal to administer a booster dose to the remaining 76 older children and the remaining 111 younger children (aged 6-11years) in this trial is supported.

5.3 The EWG also heard that appropriate additional safety blood tests have been introduced, at D2 and D7 for a subset of 6-11 year olds (20 participants at each timepoint post boost). These include full blood count (FBC), urea and electrolytes (U&E), liver function tests (LFT) and C-Reactive protein (CRP), with clotting studies. Trial participants will also be fully informed of the potential risks (with the ability to withdraw should they choose). Administering booster doses to the children in this trial will provide data to demonstrate efficacy which could be crucial for having a COVID-19 vaccine for specific groups within the paediatric population in the future and for any future variant vaccine. Immunogenicity data from prime (single-dose) dosing in the COV006 cohort is pending. However adult studies show that a single dose provides 76% protection against symptomatic infection, which persists over at least a 12-week period rising to >82% after a second and providing prolonged protection. If similar results can be extrapolated to the paediatric population, a second dose is required for prolonged efficacy and if the booster doses are not given trial participants will complete the trial having not been fully vaccinated, i.e. not fully covered against COVID-19, which has ethical considerations.

5.4 The EWG heard on 19th May the Paediatric Medicines EAG broadly agreed that the trial could proceed with administering booster doses. And, that overall, the risk mitigation in place was considered appropriate. However, there was discussion around the updated patient information and the advice that those with headaches persisting more than 4 days after vaccination should seek medical assessment. Experts noted that 4 day headaches are rarer in children compared to adults and felt this should be reconsidered and trial participants asked to seek advice earlier.

5.5 The EWG was asked to provide advice to the Clinical Trails Unit (CTU) regarding dosing of second doses to paediatric subjects within an ongoing clinical trial using the AZD1222, and to discuss the 4 day duration of headache in the patient advice.

5.6 The EWG noted the additional safety blood tests, and proposed D-Dimer to also be included. A member noted that the trial should be allowed to proceed on the basis of a) the

additional blood tests to be included b) that no convincing cases of thrombosis with concurrent thrombocytopenia have occurred at second dose, and c) that participants and parents / guardians of participants will be reapproached for consent with much clearer information. The member also noted that it is also important to complete the study in order to gain as much data / information as possible.

5.7 The EWG noted an argument in favour of providing a booster dose, and the possibility of enhanced protection which could be afforded to the participants. This argument was noted to carry two substantial caveats: the majority of the paediatric population has not been vaccinated because the risk of moderate / severe disease is extremely low in these young age groups, and secondly the purpose of a clinical trial is not to provide clinical care to the participants. In an interconnected point the EWG also referred to good clinical practice (GCP) and the stipulation to protect trial participants from risk supersedes the need for science to understand the article being tested. In this trial there is a very small but potentially very serious risk of thrombosis with concurrent thrombocytopenia associated with the vaccine at first dose, which could theoretically occur with the second dose in children.

5.8 The EWG noted if the trial was to proceed, the interval between doses will be approximately 3.5 months for those children awaiting their second dose and this would make data comparison e.g. immune bridging of data difficult to interpret because the data collected from adults is of a shorter interval.

5.9 The EWG noted that recent surveillance data in adults has identified cases of thrombosis with concurrent thrombocytopenia after the second dose. However, the rate is far less than that reported following first dose and it is not clear whether the rate is any higher than the expected background rate.

5.10 Thrombotic events in adults appear to be immune mediated, as such, it is plausible that the incidence could also be similar in children, who are capable of powerful immune responses. However, the data to help understand the aetiology or mechanism of this SAE is limited in adults and non-existent in children. Therefore, predictions of incidence of the risk of thrombosis with concurrent thrombocytopenia upon vaccination in children will be unreliable at this stage. The member disclosed a conflict of interest, i.e. being the father of two children in the age ranges that are subject of the trial.

5.11 The EWG noted that second doses of AZD1222 are being given to people in the general UK population (including those under 40 years) who have had their first dose of the same vaccine.

5.12 The EWG noted that should the trial continue, the data gathered could be relevant / valuable to future vaccine campaigns in other nations. Notable limitations were also discussed: children in developing countries often respond differently to vaccination, surveillance systems to identify rare adverse events are often not available in many developing countries, and campaigns in these countries in many cases are only just beginning to vaccinate older at-risk populations.

5.13 The EWG further discussed the pros and cons of continuing the trial through to completion. The group arrived at the below list of questions to be sent to the trial Sponsor in expectation that the answers may help to better inform the Commission on Human Medicines (CHM).

1. The original purpose of the trial has been questioned. The original study was presumably set up to study immunogenicity of ChadOx1 in younger age groups to aid the extension of any approval to younger age groups. How will D112 booster data be used to aid in the evaluation of ChadOx1 in young children in

the UK, for example to support national rollout or to support vaccination of specific vulnerable groups?

2. If not relevant to UK children (given the fact it is unlikely the AZ vaccine will be rolled out to children in the UK) how could data from the trial be used to support / inform dosing in children in other countries e.g. under developed countries.

3. How will the fact that the data generated from continuation of the trial which may be of little value to children in the UK be shared with trial participants / parents in patient facing documents?

4. D-dimers should be added to the safety bloods.

5. Blood testing measures are possibly falsely reassuring given that once abnormalities are detected there is often no successful intervention (seen in the VITT first dose patients). Would this be explained to families?

6. The direct benefit of the trial to the individual or generally is quite remote. Individual benefit of vaccination with this vaccine for younger individuals when balanced against risk is low and it is unlikely to be used in the UK in this population. If used in the rest of the world, the patient population will be different from the population in this trial.

7. Does the immunogenicity data suggest that a second dose is actually needed for children?

8. How will the data generated by boosting the remaining children be of use (since the AZ vaccine is unlikely to be given to children in resource rich settings and not a priority in resource poor settings)?

5.14 In post meeting email correspondence, a small number of additional questions were also suggested by members of the EWG, these are listed below for ease of reference:

1. Will parents be asked to re-consent for the booster dose as the balance of risk/ benefit has changed since their original consent was taken?

2. Even if the issues can be addressed by a very detailed consent process, should this population be asked to give consent? It is already a difficult population for consent purposes, i.e. parents of nearly Gillick competent children and/or immature but Gillick competent children. They will be subject to the pressure of being asked to continue in a trial for a life-saving vaccination by a world leading institution in face of a global pandemic. Trial participants will be under pressure to consent and such pressure is increased given that if they say no, other subjects cannot be obtained, and the trial cannot proceed. Individual choice is usually favoured however in such circumstances it is questionable whether consent can be ethically attempted.

3. The paper states that there “There have been no clearly identified safety concerns identified for thrombosis/thrombocytopenia associated with the second dose of the AstraZeneca (AZD1222) vaccine.” This statement does not refer to the very rapid increase in understanding, and possible future position; in that information is building slowly but as it is a rare disease and more first doses given than second the picture may not be complete. The risk, albeit slight, is confirmed by introduction

of blood testing measures in the study itself. Would this slight risk be communicated to participants?

4. 'Thrombosis' should be added as a stopping criterion.

6. Any Other Business

None.

7. Date and time of next meeting

The next Ad Hoc meeting on Thromboembolic events with COVID-19 Vaccines is scheduled to take place on **Monday 24th May** at **5.15pm**.

The next scheduled meeting is to take place **on Tuesday 25th May** at **12.00pm**.

The Meeting today started at 14:31 and ended at 16:05.

Annex I

Conflict of Interest Policy for CHM COVID-19 Vaccine Benefit Risk EWG

Chair and Members

- May not hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
- May not currently be or have previously been involved in the development of COVID-19 vaccines

Invited to all meetings, receives all papers and presentations and is permitted full participation in discussion, including drawing up conclusions and recommendations

Invited experts

- May hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
- May currently be or have previously been involved in the development of COVID-19 vaccines

May be invited to all relevant meetings, receives all papers and presentations and is permitted to participate in discussions when invited by the Chair. Does not contribute to conclusions and recommendations

Observers

Are invited to attend all meetings. Will not participate in drawing up conclusions and recommendations.

Annex II

The following participants declared interests and other relevant interests at the meeting today:

Professor Sir Munir Pirmohamed - NPNS AstraZeneca - Research grant to UOL to support PhD in drug interactions.
Other relevant interests in Pfizer, Janssen, Sanofi – Sir Munir is part of an EU-funded IMI consortium on gene therapy, and these companies are partners in the project. The University of Liverpool will get funding from the EU (but not from the partners), this IMI project commences on 3rd November 2020.
AGILE – this is a Liverpool early phase trial platform (between University of Liverpool and Liverpool School of Tropical Medicine). It is funded by the Wellcome Trust and UKRI/DHSC/NIHR. It is NOT evaluating vaccines, but only drugs to treat COVID-19. Sir Munir is not on the trial management group, and he is not directly involved in choosing the compounds for the study. Sir Munir has no involvement with any of the developers of the compounds to be studied (academic or industrial).
Sir Munir is a member of the UK COVID Therapeutics Advisory Panel (UK-CTAP), which is advising the CMO on which compounds need to be prioritised for the RECOVERY+ trial (RECOVERY is funded via NIHR/DHSC).

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Ms Hunneyball - Other relevant interest – writes articles published in the Chemist and Druggist magazine, a trade magazine for pharmacists, but receives no payment for these articles. The information referred to in the articles is in the public domain. Ms Hunneyball makes it clear that these are her personal views and reflections and references all sources of information used.

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Sir Michael Jacobs - Other relevant interest - As part of the academic role at the Liverpool School of Tropical Medicine, Sir Michael is a member of the Study Management Team and antiviral drug prioritisation group for the AGILE proof of concept (phase I/II) platform study. Sir Michael is also part of the team that submits new antiviral compounds against SARS-CoV2 for consideration by NIHR for testing on this platform. No commercial or financial interest in the trial or any of the compounds, or any pharmaceutical or biotechnology company.

Professor Lachmann – Other relevant interest as a volunteer participant in the Oxford vaccine study and no other involvement in the study.

Dr Misbah - NPNS - Holds honorary Senior Lectureship with University of Oxford & Oxford University Hospitals NHS Foundation Trust.

Professor Perrie - NPNS in Pfizer & AstraZeneca arising from a contract for a grant (March 2018), which includes contributions from these companies to the University of Strathclyde, Janssen in writing a grant for a PhD (now funded), GSK – arising from an EU grant to University of Strathclyde (Jan 2019-Dec 2019).

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Mrs Wang – Other relevant interests arising from being highly sensitive to insect stings, and plant products such as Hyacinth bulbs, as recorded on Mrs Wang's medical records. The family of Mrs Wang lives with several rare diseases and conditions, some of which result in epileptic fits.

Professor Weir - NPNS - Imperial College and Other relevant interest arising from his department collaborates with Imperial College on a number of clinical trials.

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Professor [redacted] - NPNS - University of Oxford employee (with no involvement in research or clinical trials related to Oxford AZ vaccine)
[redacted] JCVI

Dr [redacted] - Lapsed and NPNS - Regarding companies to declare interests for, prior to joining Public Health Scotland, Dr [redacted] worked for a company that provided epidemiological services to the pharmaceutical industry. Whilst working there, she supported respiratory vaccine development activities at Janssen (Johnson & Johnson). Dr [redacted] has now left that role.

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COMMISSION ON HUMAN MEDICINES (CHM)
COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the Ad Hoc meeting held on **Monday 24th May 2021** at **17:15** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan
Mr VI G Fenton-May
Professor D Goldblatt
Ms S Hunneyball
Professor K Hyrich
Sir M Jacobs
Professor H J Lachmann
Professor P J Lehner
Mr R Lowe
Dr S Misbah
Professor Y Perrie
Professor S Price
Dr A Riordan
Professor C Robertson
Professor T Solomon
Professor K M G Taylor
Dr R Thorpe
Dr S Walsh
Mrs M Wang
Professor C Weir

Apologies

Professor N French
Professor M Turner

Observers

[redacted]

Secretariat

[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted] - VRMM

Presenters supporting specific items

[redacted] - VRMM
[redacted] - VRMM
[redacted] - VRMM

MHRA Observers

[redacted] - VRMM
[redacted] - LD
[redacted] VRMM
[redacted] - LD
Dr S Branch - VRMM
[redacted] - MHRA-NIBSC
[redacted] – VRMM
[redacted] – MHRA Policy
[redacted] - Comms
[redacted] - VRMM
[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
Mr P Tregunno - VRMM
[redacted] - LD
[redacted] - VRMM

[redacted]

4th February 2022

Key
LD = Licensing Division
VRMM = Vigilance & Risk Management of Medicines
Comms = MHRA Communications
NIBSC = National Institute for Biological Standards & Control

1. Introduction and Announcement

1.1 The Chair reminded Members, invited Experts and observers that the content of papers and proceeding of the meeting are strictly confidential and should be treated as 'Official – sensitive commercial' and should not be disclosed. There is no consent for members / participants to record the meeting, take screenshots or photographs of presentations. The meeting was recorded by the MHRA Secretariat for minute taking purposes only. The Chair & Members including all participants gave full consent to the recording prior to the start of the meeting.

1.2 Conflict of Interest Policy (Annex I to the minutes)

The Chair reminded members and participants that, in accordance with the CHM Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members were also reminded to declare any other matter which could reasonably be perceived as affecting their impartiality.

1.3 Participants declared interests and other relevant interests for this meeting listed at **Annex II** to the minutes.

1.5 The Chair welcomed the following observers:

Dr [redacted], Public Health Agency

Dr [redacted]

Professor [redacted] JCVI

Dr [redacted] Public Health Scotland

Dr [redacted]

2. Update on COVID-19 Vaccines and risk of thromboembolic events with concurrent thrombocytopenia

2.1 The EWG was presented with the latest data on thromboembolic events with thrombocytopenia associated with the authorised COVID-19 Vaccines up to a data lock point of 19 May 2021.

2.2 The EWG heard that the MHRA met with representatives of the Expert Haematology Panel (EHP) to discuss case definition for events associated with the AstraZeneca COVID-19 vaccine on 21 May 2021. The EHP are revising their case definitions for vaccine-induced thrombocytopenia (VIT) and vaccine-induced thrombosis and thrombocytopenia (VITT) and

are considering introducing threshold values for optical densities for PF4 antibodies in confirmed cases and are also reconsidering D-dimer threshold values. Platelet activation tests may be required in all cases or in those with negative PF4 antibodies if the clinical suspicion of VITT is high. The EHP also mentioned that some patients are experiencing recurrent thrombocytopenia on follow-up and thromboembolic events have occurred despite anticoagulation. Some patients are requiring rituximab treatment and PF4 antibodies have persisted in all cases on follow-up of up to 8 weeks. Additionally, the EHP commented that some confirmed cases associated with the Pfizer COVID-19 vaccine have also been reported with a longer time-to-onset than those following immunisation with the AstraZeneca (AZ) COVID-19 vaccine. The EWG agreed to keep the topic of case definition open for consideration as new evidence emerges.

2.3 The EWG was informed of the updated product information recommendations issued by the Committee for Medicinal Products for Human Use on 21 May 2021. The new contraindication and advice for expert haematology input are similar to UK guidance provided in the Reg 174 information for Healthcare Professionals.

2.4 The EWG was then presented with a summary of a recent publication describing a French case series of 9 patients with suspected VITT and the results of different tests for PF4 antibodies. A PF4-enhanced serotonin release assay was positive in 7 patients, but all of these patients tested negative in rapid immunoassays and the sensitivity of different ELISA tests varied with only the Lifecodes PF4 IgG Immunocor ELISA test identifying all patients with platelet activation. The EWG noted the therapeutic potential of imlifidase in patients with refractory VITT that has not responded to intravenous immunoglobulin therapy.

2.5 An overview of the case reports associated with the AstraZeneca COVID-19 Vaccine was presented including summary tables of the 17 reported probable and possible UK cases occurring after a second dose and a fatal cerebral venous sinus thrombosis case associated with thrombocytopenia in pregnancy from Brazil. The EWG was reassured by the clinical phenotypes of the second dose cases but advised that AstraZeneca should be requested to provide data on all foreign cases.

2.6 The UK and foreign cases associated with the Pfizer, Moderna and Janssen COVID-19 vaccines were summarised using the same case definition. The clinical details of 2 confirmed Pfizer cases reported from the UK were reviewed. The EWG commented that similar cases have not been reported from countries with much greater Pfizer vaccine usage but this could reflect differences in the effectiveness of post-marketing monitoring, adherence to national expert guidance on investigating VITT cases, different case definitions or different background event rates. The EWG advised that the MHRA should continue to closely monitor Pfizer cases.

2.7 The estimated number of second AstraZeneca COVID-19 vaccine doses administered has increased to 10.7 million whilst the number of first doses has increased slightly, in line with the current deployment programme to 24.2 million. Estimated case incidence rates for CVST and CVST plus non-CVST events were presented by age-stratified 10-year intervals and by gender. The overall incidence rate is stable at 13.0 (11.6, 14.5) per million for first/unknown doses and the overall fatal incidence rate is also stable at 2.4 (1.8, 3.0) per million first/unknown doses. The age-stratified incidence rates associated with second doses were presented and the overall rate was stable at 1.6 (0.9, 2.6) per million doses. The risk estimates were then compared with the expected benefits of vaccine in age subgroups. The reported incidence rates showed a small increase since the last data lock point, while the risk-benefit balance remained relatively unchanged.

2.8 The EWG was updated on ongoing work to ascertain background incidence rates of thrombosis with thrombocytopenia. It was noted that two presentations from different

research groups looking at the rate of thrombosis with thrombocytopenia with and without vaccination will be given at the next EWG meeting on 25 May.

2.9 The EWG then considered the following 3 questions:

2.9.1 Question 1: based on the evidence presented does the EWG consider the benefit-risk balance remains favourable for all patients and for all age groups?

The EWG advised that the overall benefit-risk profile of the AstraZeneca COVID-19 Vaccine remains positive although the benefits of immunisation in individuals aged under 40 years are probably outweighed by the potential risks. The benefit-risk assessment has not changed since it was reviewed on 17 May 2021.

2.9.2 Question 2: Does the EWG consider there might be an increased risk for the second dose of the vaccine?

The EWG advised that the emerging data on the risk of thromboembolic events occurring with thrombocytopenia following second doses is reasonably reassuring but limited, and so the MHRA should continue to monitor second dose cases closely, particularly as younger patients will now be receiving their second doses.

2.9.3 Question 3: Does the EWG consider there is any need for action with regards to the Pfizer, Moderna or Janssen vaccines in relation to this potential risk?

Based on available data, the risk associated with the Pfizer and Moderna COVID-19 vaccines appears lower than that associated with the AstraZeneca COVID-19 Vaccine. This risk should be monitored and there is no need for regulatory action. Events associated with the Pfizer COVID-19 vaccine should continue to be closely monitored.

2.10 In conclusion, the EWG did not identify any potential trigger for regulatory action.

3. <u>Future Steps / Any Other Business</u>

None.

4. <u>Date and time of next meeting</u>

The next scheduled meeting is to take place on **Tuesday 25th May 2021** at **12.00pm**.

The Meeting today started at 17:18 and ended at 17:57.

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Annex I

Conflict of Interest Policy for CHM COVID-19 Vaccine Benefit Risk EWG

Chair and Members

- May not hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
- May not currently be or have previously been involved in the development of COVID-19 vaccines

Invited to all meetings, receives all papers and presentations and is permitted full participation in discussion, including drawing up conclusions and recommendations

Invited experts

- May hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
- May currently be or have previously been involved in the development of COVID-19 vaccines

May be invited to all relevant meetings, receives all papers and presentations and is permitted to participate in discussions when invited by the Chair. Does not contribute to conclusions and recommendations

Observers

Are invited to attend all meetings. Will not participate in drawing up conclusions and recommendations.

Annex II

The following participants declared interests and other relevant interests at the meeting today.

Professor Sir Munir Pirmohamed - NPNS AstraZeneca - Research grant to UOL to support PhD in drug interactions.
Other relevant interests in Pfizer, Janssen, Sanofi – Sir Munir is part of an EU-funded IMI consortium on gene therapy, and these companies are partners in the project. The University of Liverpool will get funding from the EU (but not from the partners), this IMI project commences on 3rd November 2020.
AGILE – this is a Liverpool early phase trial platform (between University of Liverpool and Liverpool School of Tropical Medicine). It is funded by the Wellcome Trust and UKRI/DHSC/NIHR. It is NOT evaluating vaccines, but only drugs to treat COVID-19. Sir Munir is not on the trial management group, and he is not directly involved in choosing the compounds for the study. Sir Munir has no involvement with any of the developers of the compounds to be studied (academic or industrial).
Sir Munir is a member of the UK COVID Therapeutics Advisory Panel (UK-CTAP), which is advising the CMO on which compounds need to be prioritised for the RECOVERY+ trial (RECOVERY is funded via NIHR/DHSC).

Professor Breuer - NPNS - Professor Breuer is on the data safety monitoring committee, DSMB, a study looking at combining vaccines being run by Matthew Snape in Oxford. There does not appear to be any involvement of the vaccine manufacturers and is for already licensed vaccines. The study is funded by the NIHR (Dec 2020).

Ms Hunneyball - Other relevant interest - writes articles published in the Chemist and Druggist magazine, a trade magazine for pharmacists, but receives no payment for these articles. The information referred to in the articles is in the public domain. Ms Hunneyball makes it clear that these are her personal views and reflections and references all sources of information used.

Professor Hyrich – NPNS - Professor Hyrich was co-I on an investigator-initiated research grant exploring predictors of outcome in rheumatoid arthritis. NPNS Pfizer- she is a Co-I on a grant exploring adherence to JAK inhibitors in rheumatoid arthritis. NPNS in Abbvie, Professor Hyrich gave some lectures at an education conference on effectiveness of treatment for rheumatoid arthritis.

Sir Michael Jacobs - Other relevant interest - As part of the academic role at the Liverpool School of Tropical Medicine, Sir Michael is a member of the Study Management Team and antiviral drug prioritisation group for the AGILE proof of concept (phase I/II) platform study. Sir Michael is also part of the team that submits new antiviral compounds against SARS-CoV2 for consideration by NIHR for testing on this platform. No commercial or financial interest in the trial or any of the compounds, or any pharmaceutical or biotechnology company.

Professor Lachmann – Other relevant interest as a volunteer participant in the Oxford vaccine study and no other involvement in the study.

Professor Lehner - Other relevant interest - Professor Lehner previously held a DPAC (Discovery Partnership with Academia) agreement with GSK, but this has been completed. Professor Lehner's participation in his local hospital D and T governance committee deliberations would form the normal activity and professional responsibility in his post and does not interfere with the EWG considerations (Sept 2020).

Dr Misbah - NPNS - Holds honorary Senior Lectureship with University of Oxford & Oxford University Hospitals NHS Foundation Trust.

Professor Perrie - NPNS in Pfizer & AstraZeneca arising from a contract for a grant (March 2018), which includes contributions from these companies to the University of Strathclyde, Janssen in writing a grant for a PhD (now funded), GSK – arising from an EU grant to University of Strathclyde (Jan 2019-Dec 2019).

Professor Price - NPNS in GSK and AstraZeneca – which relates to donations provided by both companies to the British Toxicology Society (BTS) to support their Annual Congress and Education and Training of which Professor Price is currently President of the Society (2020-2022).

Dr Riordan - Other relevant interests - Participant in Oxford University's ChAdOx1 nCoV-19 clinical trial –received immunisation 27/8/2020. NPNS - Postgraduate External Examiner for Oxford University (Postgraduate Diploma in Paediatric Infectious Diseases).

Professor Solomon - Other relevant interests - Professor Solomon provides clinical care for patients with Covid-19; chaired the MRC/NIHR committee which awarded funding for development of the Oxford Vaccine.

Mrs Wang – Other relevant interests arising from being highly sensitive to insect stings, and plant products such as Hyacinth bulbs, as recorded on Mrs Wang's medical records. The family of Mrs Wang lives with several rare diseases and conditions, some of which result in epileptic fits.

Professor Weir - NPNS - Imperial College and Other relevant interest arising from his department collaborates with Imperial College on a number of clinical trials.

Observers

Professor [redacted] - NPNS arises from the institution [redacted] University Hospitals NHS Trust) where Professor [redacted] works has received unrestricted investigator-initiated research funding from Pfizer for an unrelated prospective population-based cohort study of pneumococcal pneumonia in which Professor [redacted] is the Chief Investigator.

Dr [redacted] – Lapsed and NPNS - Regarding companies to declare interests for, prior to joining Public Health Scotland, Dr [redacted] worked for a company that provided epidemiological services to the pharmaceutical industry. Whilst working there, she supported respiratory vaccine development activities at Janssen (Johnson & Johnson). Dr [redacted] has now left that role.

COMMISSION ON HUMAN MEDICINES (CHM)
COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Tuesday 25th May 2021** at **12:00** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Mr VI G Fenton-May
Professor D Goldblatt
Ms S Hunneyball
Professor K Hyrich
Professor H J Lachmann
Professor P J Lehner
Mr R Lowe
Dr S Misbah
Professor Y Perrie
Professor S Price
Dr A Riordan
Professor C Robertson[1]
Professor T Solomon
Professor K M G Taylor
Dr R Thorpe
Dr S Walsh
Mrs M Wang
Professor C Weir

Apologies

Professor G Dougan
Professor N French
Sir M Jacobs
Professor M Turner

Visiting Experts

[redacted]

Observers (left after item 4)

[redacted]

Secretariat

[redacted]

[1] Left during item 5

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted] - VRMM

Presenters supporting specific items

[redacted] - LD

MHRA Observers

[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
Dr S Branch - VRMM
[redacted] - VRMM
[redacted] - VRMM
[redacted] - Comms
[redacted] - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
Dr J Raine - MHRA CEO
[redacted] - VRMM
Mr P Tregunno - VRMM
[redacted] - LD
Dr K Wydenbach - LD

[redacted]

4th February 2022

Key
LD = Licensing Division
VRMM = Vigilance & Risk Management of Medicines
MHRA CEO = Chief Executive
Comms = MHRA Communications

1. Introduction and Announcement

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1.3 Participants declared interests and other relevant interests for this meeting listed at **Annex II** to the minutes.

1.4 Apologies were received from Professors Dougan, French, Turner and Sir Michael Jacobs for this meeting.

1.5 The Chair welcomed the following Visiting Experts:

Dr [redacted]
[redacted] Public Health England

Professor [redacted]
[redacted] University of Oxford

Professor [redacted] MA MPH BMBCh PhD FRCP FRCPath FMedSci
Professor of Clinical Microbiology, Wellcome Senior Fellow in Clinical Science
[redacted]

Professor [redacted] ChB MD FRCP DRCOG FRCGP
Professor of Clinical Epidemiology and General Practice
Professorial Fellow, [redacted]

1.6 The Chair welcomed the following observers:

Dr [redacted]
[redacted], Public Health Agency

Dr [redacted]
[redacted]

2. Update from COG-UK on Spread of the Variant first identified in India

2.1 The EWG was presented with information on the emergence and biological properties of SARS-CoV-2 B.1.617. The EWG heard that lineage B.1.617 is now of global significance. There are two main lineages of B.1.617 (B.1.617.1 and B.1.617.2). A furin cleavage mutation (P681R) that increases host cell-cell fusion is common to both. The B.1.617.1 lineage has two mutations (L452R and E484Q) in the receptor binding domain (RBD) that partially evade mRNA elicited neutralising antibody. Evidence of additive / synergistic effects of the two mutations in the RBP has not been found.

2.2 The EWG heard Cambridge Institute for Therapeutic Immunology and Infectious Disease are investigating the effect of patient age on T-cell immunity but only with Wild Type (WT) virus. Other groups are exploring T-cell immunity and vaccine escape, where the data show that the variant B.1.351 includes escape mutations in T-cell epitopes, but the relevance of this finding is less clear. The findings in the literature indicate that to prevent infection with SARS-CoV-2, antibodies are required because the virus is highly infectious. The role of T-cells in COVID-19 most likely occupies the later phases of infection and may contribute to hindering the progression of disease and severity of disease.

2.3 The EWG heard the samples were taken from healthcare professionals (HCPs) who were recently vaccinated (earliest January 2021) and the vaccine interval was understood to be 4 weeks, but the specific interval data is due. The Chair noted the interval used in the UK is 12 weeks for ChadOx1. The invited expert was uncertain if the higher peak antibody levels observed with an interval of 12 weeks would be sustained.

2.4 The EWG commented that serum samples of breakthrough cases have shown very high antibody levels (Hacisuleyman et al, 2021; NJEM 2021). The invited expert segued into a question, do the variant studies provide greater understanding of vaccine breakthrough considering that there are a number of other factors aside from phenotypic changes involved in the process of breakthrough (such as viral load). The EWG heard that by way of example the mutation at the furin cleavage site mutation (P681) potentially promotes the ability of the virus to tolerate neutralising antibodies through modulation of S1/S2 cleavage. The EWG heard there also appears to be good consistency between in vitro data and trial data, whilst the invited expert acknowledged multiple mechanisms would be involved in vaccine breakthrough. Reassuringly the fold changes in a reduction of neutralisation seen with the B.1.617 lineages do not yet confer a loss of vaccine efficacy in terms of severe disease.

2.5 The EWG noted interpretation of the molecular epidemiology data from India requires careful consideration of the limitations, since approximations of transmissibility are known to be affected by the number of samples versus the extent and evenness of geographical coverage. In India, sequencing is currently very concentrated in a few areas. The data from India may indicate that B.1.617.2 is outcompeting B.1.617.1, but it is not known if it is also outcompeting B.1.1.7. The most robust data on transmission is UK based, covering almost all positives to a high level of viral genome coverage and the data show a fairly steady rise of B.1.617.2 that has spread outside areas of travel, and is therefore, less likely to be an artefact of people movement and more likely due to increased transmissibility as a trait of B.1.617.2.

2.6 The EWG noted that vaccine breakthrough data are not reliable due to the absence of unvaccinated sera controls. Without this, the level of breakthrough cannot be assessed compared to the other variants or WT virus, but hitherto can only show that the variant circulating in and around the period of sample collection is able to breakthrough. The EWG also noted that B1.617.2 is representative of a selective sweep and thus would not reveal adequate information about transmissibility. The EWG noted that interpretations from the

data should be conservative, with careful consideration of denominator data. The UK HAS England data do not appear to show that B.1.617 lineages are producing more events of vaccine breakthrough. However, if this understanding changes, it also needs to be understood if lineages of B.1.617 are associated with more severe cases of COVID, i.e. result in more hospitalisations and deaths.

2.7 The EWG noted that mutations altering the phenotype are common in respiratory viruses and tend to become part of the background variation not often associated with more severe disease. Norovirus maybe one of a number of exceptions where disease can become more severe seasonally as the viral genome acquires mutations.

2.8 The Invited expert agreed that due to sweep of B1.617.2, from these data it is not possible to determine if B1.617.2 is more able than other variants or WT to breakthrough. The expert however, maintained that the consistency of findings in the in vitro and in vivo data supports a hypothesis that phenotypic variation enables a biological mechanism for B1.617 to breakthrough, but caveated this by noting that further data would be required to substantiate this claim.

2.9 The EWG heard that B1.617.2 is concentrated in discrete locations in the UK, and therefore, until there is a more generalised B1.617.2 epidemic, analysis of UK epidemiological data will carry limitations. As the time expires awaiting this scenario, as well as that required to confirm that the infectivity and virulence of B1.617.2 is greater—the human cost will likely have already been accrued. The EWG noted that an exception may be if there is a clear signal.

2.10 The EWG heard, in terms in importations from other locations in the subcontinent, that in a current outbreak in Nepal, 33 out of 35 randomly sampled sequences were B1.617.2, but data from other countries was not readily available.

2.11 The EWG heard that bamlanivimab loses binding affinity for B1.617.2 completely, but, the other Regeneron antibody cocktail (dual therapy) still has neutralising activity. In terms of the real world situation, this is currently not a pressing issue as access to monoclonals is very limited.

3. Presentation form Prof [redacted] on thrombocytopenia/thrombosis

3.1 The EWG was presented with data on the short-term risks of thrombocytopenia and thromboembolism associated with vaccination or natural infection during the vaccine roll out in the 2nd and 3rd pandemic waves in England. The study was in a population that was the largest, most representative, and diverse to date. The main limitations of the study included the short exposure window (28 days), a reliance on clinical coding and therefore, an absence of formal adjudication of outcomes, study of 1st vaccine dose only, and those still in hospital not included with the potential for misclassification or under-ascertainment of outcomes—likely to be non-differential with regard to each vaccine.

3.2 The key findings consisted of:

- increased risk of thrombocytopenia, venous thromboembolism VTE, and other rare arterial thrombotic events following first dose of the AstraZeneca vaccine
- increased risk of arterial thromboembolism (ATE) and ischemic stroke following a first dose of Pfizer/BioNTech. Increased risk of cerebral venous sinus thrombosis (CVST) was found following a first dose of both AstraZeneca vaccine or Pfizer/BioNTech in the 8-14 day and 15-21 risk windows respectively.

- importantly the risk of these outcomes following vaccination were much lower than those associated with SARS-CoV-2 infection in the same population.

3.3 To contextualise their findings the group estimated the number of exposures needed for one excess event and the excess number of events per 10 million exposed for each outcome.

3.4 For the AstraZeneca vaccine the excess events were 107 for thrombocytopenia, 66 for VTE and 7 for CVST. For the Pfizer/BioNTech vaccine there were 143 extra cases of ischemic stroke and 5 of CVST. For SARS-CoV-2 infection, there were an estimated 934 additional cases of thrombocytopenia, 12,614 of VTE, 1,699 of ischemic stroke and 20 of CVST.

3.5 The EWG was presented with a draft visualisation of a lay summary of findings from the study.

3.6 Question and Answer

3.6.1 The EWG heard that the analysis of thrombocytopenia was conducted separately to that of thrombosis. The diagnosis of thrombocytopenia but without platelet counts work is being undertaken to obtain this information from hospital systems for future analysis in real-time. The study data on thrombocytopenia with thrombosis can be analysed together but will not be linked to platelet counts.

3.6.2 The EWG heard a sub-group analysis grouped by age (below 50 year and 50 and over) produced results that were fairly consistent but with wide confidence intervals.

3.6.3 The EWG noted the association of Pfizer with ischemic stroke appears to be a novel finding and highlighted a distinction in the US where despite wider use of this vaccine in the US, a signal of stroke has not been identified by the FDA. The EWG heard there was a possibility that the finding of stroke could possibly be due to chance, another possibility is that CVST was mis-coded as ischemic stroke. The Chair noted this may apply particularly to the elderly where a CT venogram may not have been completed. The EWG heard the group did not identify any particular bias that applied to stroke but not the other outcomes. The EWG heard there were some cases of stroke in younger people <50 years, but to give a specific number the data would be required to be checked.

3.6.4 The EWG heard in the self-controlled case series the 28 days before vaccination was removed from the baseline comparator risk period to limit risk of bias due to prior VTE. When studying the 28-day period data, there was a reduced risk of VTE, indicating that the patients were postponing vaccination until recovery or discharge from hospital following a VTE event. The expert noted that the same period in the Scottish study was 14 days, in the age stratified analysis an association with VTE was not identified for either of the two vaccines.

3.6.5 The EWG heard a call is planned with haematologists with an aim of improving validation of clinical outcomes against hospital coded data, which if successful will help to substantiate the study outcomes.

3.6.6 The EWG noted with a self-controlled case series one limitation is the end of follow-up in conjunction with the person time beyond 28 days. If there is lack of completion in the cases, cases may be missed from the analysis that otherwise would have been included in the study period - if it were not for the delay to obtain the information. This could result in a case deficit / underreporting of adverse outcomes. Similarly, for the pre-period if there was a permanent deferral or contraindication, the pre-data is prone to a lower incidence in that period. The invited expert acknowledged when compared to other options there are strengths and weaknesses of using a self-controlled case series and mentioned that the

scope for biases needs to be controlled as well as possible. In terms of the beyond 28 days, the vaccination outcomes drop to ~1 (22-28 days post-vaccination) but there could still be some increased risk, more particularly with SARS-CoV-2 infection the increased risk had not reduced by 28 days.

3.6.7 The EWG heard the study included individuals with SARS-CoV-2 infection pre-vaccination and after vaccination numbers were considered insufficient to explore the interactions between the two. The EWG noted that the invited experts may revisit this and remarked that this would be of benefit because the effect of infection lasts for longer in terms of the risk of thrombosis.

3.6.8 The invited experts confirmed they have not yet evaluated the potential causes or mechanisms that may account for the differing dates of onset of CVST in the period following vaccination, for each of the two vaccines.

3.6.9 The invited experts confirmed that an analysis of thrombocytopenia with thrombosis as combined outcome could be undertaken, and these results could be included in the same publication. The invited experts also confirmed that once completed the analysis and results would be made available to the EWG.

3.6.10 The EWG noted that the term 'slight risk' in the lay messaging may exaggerate the risk given the rate is per 10 million exposed, for example for CVST with is 5 additional cases for Pfizer. The EWG suggested terminology that maintains a context of an exceedingly rare event. The invited experts volunteered to refer the comments / subject to the patient group.

4. Update on PHE analysis of thrombosis with thrombocytopenia

4.1 The EWG was presented with upon on cohort analysis of Secondary Uses Service SUS data after COVID-19 vaccines from PHE.

4.2 The EWG heard the PHE data shows that following vaccination with the AZ vaccine, there is an increased risk of: dose specific thrombotic events, thrombocytopenia, and concurrent thrombocytopenia with thrombotic events. The EWG heard that the longer follow-up time increases the confidence in these associations. However, coding changes could occur due to prior awareness of these potential associations amongst medical professionals. This denotes a caveat to the results, though it is likely to be minor.

4.3 The EWG heard it was not possible to adjust for known SARS-CoV-2 infection when using the cohort analysis approach, and therefore, changing infection risk can only be evaluated in relation to the time period by number of weeks in the study.

4.4 The EWG heard from the MHRA, that there has been indication of signal of myocarditis in the Israeli data particularly after the second dose and in males (age ~30 and below).

4.5 In the US, the CDC have not detected an imbalance in their observed-expected figures of myocarditis, but they have identified a clustering of reports post second dose in a very similar demographic to that of Israel for both mRNA vaccines (Moderna and Pfizer). The CDC do not stratify their observed expected by age. The MHRA observed expected data have also not shown any imbalance with respect to myocarditis age-related or generally.

4.6 The invited expert mentioned acute myocarditis was included in the PHE analysis in direct response to the indication of a signal from Israel. The EWG heard events of arterial thromboembolism were also included in the UK PHE analysis.

5. COVID-19 Vaccine AstraZeneca (ChAdOx1-S [recombinant]), 1 x 1011vp-mL, solution for injection

5.1 The EWG heard a presentation on the submission of a conditional marketing authorisation (CMA) for Covid-19 vaccine AstraZeneca (AZD1222) in Great Britain (GB). Covid-19 Vaccine AstraZeneca has been granted a temporary authorisation under Regulation 174 of the Human Medicines Regulations 2012 (Regulation 174 authorisation) on 29 December 2020.

5.2 Similarly, to the Regulation 174 authorisation, no quality major objections have been raised with this conditional marketing authorisation (CMA) application as all other concerns have been appropriately addressed. The EWG heard, that initially there will be concurrent supply of the regulation 174 authorisation packs alongside the CMA packs in order to ensure uninterrupted supply to Northern Ireland.

5.3 The EWG heard there were no new clinical trial data received since the last update of the Reg. 174 public assessment report. The United Stated (US) trial data, very recently submitted by the Company, will be assessed in the near future. Of interest are two pre-prints provided by the Company, which describe similar immune response in people living with human immunodeficiency virus (HIV) (under treatment and immunocompetent) compared to healthy subjects.

5.4 The EWG heard about the non-clinical assessment of the product. An updated biodistribution study showed no unexpected results, i.e. the replication incompetent virus does not travel far from the injection site. Separately, the report from GLP inspection for the reproductive toxicity study was satisfactory.

5.5 The EWG heard the content of the product information and conditions require consideration. The assessment team have aimed to abide by two principles: to align as far as possible with the EU/NI product information, and where the UK has additional data /experience in the Regulation 174 authorisation to carry this over to the CMA as 'additional text'.

5.6 The EWG agreed that the SmPC sections 1 & 2 should updated to be brought closer in line with the EU/NI SmPC. It was also agreed to remove the negative statement regarding routes of administration present in section 4.2 of the EU/NI SmPC

5.7 Of note, the EWG heard that, in-line with the R174 product information, it is not proposed to include a recommendation for a15-minute observation period post vaccination in Section 4.4 of the GB SmPC. The EU/NI SmPC includes this recommendation, in keeping with all Covid-19 vaccines approved in the EU to date. The EWG noted that, in view of the significant clinical experience accrued in the UK with over 30 million COVID-19 Vaccine AstraZeneca ChAdOx1 (AZD1222) vaccinees, in terms of a broad recommendation for protocols in mass vaccination centres it was considered appropriate not to include this recommendation.

5.8 The EWG noted that, in-line with the R174 product information, a cautionary statement about use in individuals with a history of heparin-induced thrombocytopenia and thrombosis (HITT or HIT type 2) was to be retained in the GB SmPC due to the possibility of an interconnected pathophysiology with Thrombosis with Thrombocytopenia Syndrome (TTS). However, the EWG heard this information is now to be located under section 4.4, special warnings and precautions, rather than in section 4.3, contraindications.

5.9 Given the quantity of accruing data that does not show any evidence for an association between APS and TTS, it was considered to be an overly cautious approach to include APS in section 4.4, noting it places an unnecessary burden on haematologists, i.e. a resource

cost to other patients. Therefore, the EWG agreed that the cautionary statement about use in individuals with anti-phospholipid syndrome (APS) that was previously included in the R174 PI, can be removed from section 4.4. because there are no confirmed cases of patients with a history of anti-phospholipid syndrome developing TTS following vaccination.

5.10 The EWG noted cerebral venous sinus thrombosis (CVST) is a far rarer condition and it would be practical to recommend a patient with a history of CVST seeks an alternative vaccine. The EWG noted that they would welcome confirmation from neurology experts on the CHM as to whether they agree with the EWG view that, on a precautionary basis, the text on administration of the vaccine in individuals with a past history of CVST included in the R174 PI, should be retained in section 4.4 of the GB SmPC.

5.11 The EWG agreed with the Agency's proposals to largely harmonise text in section 4.4.with the EU/NI SPC, but with a slight divergences in some areas: a) to include angioedema under the umbrella of hypersensitivity reactions, b) to reflect clinical parameters from cases of TTS rather than the average age at onset of TTS which was not reflective of UK experience of b) to give national advice on the healthcare pathway for patients with TTS and c) to include a statement about real-world efficacy data in elderly subjects.

5.12 The EWG heard that fertility and pregnancy information in the EU/NI SmPC is not yet furnished with information on animal studies; the proposal for the UK SPC is to include the outcomes of relevant animal studies in the fertility, pregnancy, and lactation (section 4.6).

5.13 The EWG heard all figures in the tabulated summary of ADRs in section 4.8 have been updated in accordance with the December safety analysis—EU/NI text has not yet been updated.

5.14 The EWG supported the proposal to include the recommendation on use of analgesic and/or anti-pyretic medicinal products if required to manage symptomatic relief from post vaccination ADRs that is already in the R174 product information, in the GB SmPC.

5.15 On rare and very rare ADRs, the EWG heard that defined frequency designations must be followed, which can lead to difficulties when trying to contextualise the likelihood of a particular ADR/s and to avoid what could be interpreted as contradictions between the ADR frequency range and the paragraphs of text in the SmPC and PIL. The EWG noted the need to reassure patients that these events are extremely rare by adding context to the frequency of events of thrombosis with thrombocytopenia syndrome in the PIL. The EWG acknowledged the potential limitations but asked the agency to aim to minimise any disconnect between the ADR table designated frequency and the contextualised information / retain as much clarity as possible.

5.16 The EWG heard the approximate frequency in figures of TTS proposed by the company has not been included in the EU/NI SmPC. The EWG noted it would be favourable to adopt the same position because the frequency is evolving, and the distribution of cases by age is also uneven.

5.17 The EWG noted there was a risk that 'influenza like illness' could be misconstrued by readers to be related to an active infection acquired through vaccination, which is obviously not the case. However, EWG concluded that the text should remain because this terminology has been present in the regulation 174 authorisation for many months without causing any notable issue. The EWG also considered there to be some added descriptive value in using the term to healthcare professionals.

5.18 The EWG noted text in section 4.8 on neuroinflammatory disorders should be retained because there is data emerging on GBS.

5.19 The EWG agreed that section 5.3 of the SmPC contained an appropriate level of detail was commensurate with the scope of studies submitted.

5.20 The EWG heard that both the former and proposed versions of the GB SmPC still refer to advice on 6 hour in use times (section 6.6), text in the proposed SmPC also includes a statement to align with the EU/NI SmPC that the product may be kept in-use at temperatures up to 30°C for a single period of up to 6 hours, but due to the inclusion of the word may, this does not contradict the UK recommendation for use up to 25°C.

5.21 The EWG supported the specific obligations for the CMA and the obligations to conduct post-authorisation measures.

6. Any Other Business

None.

7. Date and time of next meeting

The next Ad Hoc meeting on Thromboembolic events with COVID-19 Vaccines is scheduled to take place on **Tuesday 1st June at 3.15pm**.

The next scheduled meeting is to take place **on Friday 4th June** at **10.30am**.

The Meeting today started at 12:01 and ended at 14:14.

Members are reminded that the content of papers and proceeding of the meetings are to be treated as 'Official – sensitive commercial'. Members are also reminded that, in accordance with the Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members must also declare any other matter which could reasonably be perceived as affecting their impartiality. Detailed guidance is set out in the Code of Practice

Annex I

Conflict of Interest Policy for CHM COVID-19 Vaccine Benefit Risk EWG

Chair and Members

- May not hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
- May not currently be or have previously been involved in the development of COVID-19 vaccines

Invited to all meetings, receives all papers and presentations and is permitted full participation in discussion, including drawing up conclusions and recommendations

Invited experts

- May hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
- May currently be or have previously been involved in the development of COVID-19 vaccines

May be invited to all relevant meetings, receives all papers and presentations and is permitted to participate in discussions when invited by the Chair. Does not contribute to conclusions and recommendations

Observers

Are invited to attend all meetings. Will not participate in drawing up conclusions and recommendations.

Annex II

The following participants declared interests and other relevant interests at the meeting today:

Professor Sir Munir Pirmohamed - NPNS AstraZeneca - Research grant to UOL to support PhD in drug interactions.
Other relevant interests in Pfizer, Janssen, Sanofi – Sir Munir is part of an EU-funded IMI consortium on gene therapy, and these companies are partners in the project. The University of Liverpool will get funding from the EU (but not from the partners), this IMI project commences on 3rd November 2020.
AGILE – this is a Liverpool early phase trial platform (between University of Liverpool and Liverpool School of Tropical Medicine). It is funded by the Wellcome Trust and UKRI/DHSC/NIHR. It is NOT evaluating vaccines, but only drugs to treat COVID-19. Sir Munir is not on the trial management group, and he is not directly involved in choosing the compounds for the study. Sir Munir has no involvement with any of the developers of the compounds to be studied (academic or industrial).
Sir Munir is a member of the UK COVID Therapeutics Advisory Panel (UK-CTAP), which is advising the CMO on which compounds need to be prioritised for the RECOVERY+ trial (RECOVERY is funded via NIHR/DHSC).

Professor Breuer - NPNS – Professor Breuer is on the data safety monitoring committee, DSMB, a study looking at combining vaccines being run by Matthew Snape in Oxford. There does not appear to be any involvement of the vaccine manufacturers and is for already licensed vaccines. The study is funded by the NIHR (Dec 2020).

Ms Hunneyball - Other relevant interest – writes articles published in the Chemist and Druggist magazine, a trade magazine for pharmacists, but receives no payment for these articles. The information referred to in the articles is in the public domain. Ms Hunneyball makes it clear that these are her personal views and reflections and references all sources of information used.

Professor Hyrich – NPNS - Professor Hyrich was co-I on an investigator-initiated research grant exploring predictors of outcome in rheumatoid arthritis. NPNS Pfizer- she is a Co-I on a grant exploring adherence to JAK inhibitors in rheumatoid arthritis. NPNS in Abbvie, Professor Hyrich gave some lectures at an education conference on effectiveness of treatment for rheumatoid arthritis.

Professor Lachmann – Other relevant interest as a volunteer participant in the Oxford vaccine study and no other involvement in the study.

Professor Lehner - Other relevant interest – Professor Lehner previously held a DPAC (Discovery Partnership with Academia) agreement with GSK, but this has been completed. Professor Lehner's participation in his local hospital D and T governance committee deliberations would form the normal activity and professional responsibility in his post and does not interfere with the EWG considerations (Sept 2020).

Dr Misbah - NPNS - Holds honorary Senior Lectureship with University of Oxford & Oxford University Hospitals NHS Foundation Trust.

Professor Perrie - NPNS in Pfizer & AstraZeneca arising from a contract for a grant (March 2018), which includes contributions from these companies to the University of Strathclyde, Janssen in writing a grant for a PhD (now funded), GSK – arising from an EU grant to University of Strathclyde (Jan 2019-Dec 2019).

Professor Price - NPNS in GSK and AstraZeneca – which relates to donations provided by both companies to the British Toxicology Society (BTS) to support their Annual Congress and Education and Training of which Professor Price is currently President of the Society (2020-2022).

Dr Riordan - Other relevant interests - Participant in Oxford University's ChAdOx1 nCoV-19 clinical trial –received immunisation 27/8/2020. NPNS - Postgraduate External Examiner for Oxford University (Postgraduate Diploma in Paediatric Infectious Diseases).

Professor Solomon - Other relevant interests – Professor Solomon provides clinical care for patients with Covid-19; chaired the MRC/NIHR committee which awarded funding for development of the Oxford Vaccine.

Mrs Wang – Other relevant interests arising from being highly sensitive to insect stings, and plant products such as Hyacinth bulbs, as recorded on Mrs Wang's medical records. The family of Mrs Wang lives with several rare diseases and conditions, some of which result in epileptic fits.

Professor Weir - NPNS - Imperial College and Other relevant interest arising from his department collaborates with Imperial College on a number of clinical trials