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.