COMMISSION ON HUMAN MEDICINES (CHM)

COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Sunday 3rd January 2021** at **15:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor H J Lachmann
Professor P J Lehner
Dr S Misbah

Members of the CTBV Expert Advisory Group

Professor M Turner

Professional Staff of MHRA Present

Principal Assessor

Dr J Bonnerjea - LD

Presenters supporting specific items[1]

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

Secretariat

[redacted]

[1] supporting specific items

MHRA Observers

Dr S Atkinson - Directorate
Dr S Branch - VRMM
[redacted] – LD
Dr SP Lam - LD
[redacted] – Government Legal Team
[redacted] - MHRA-NIBSC
[redacted] - LD
Dr J Raine – MHRA CEO
[redacted] - LD
[redacted] - LD

[redacted]

19th July 2021

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

1. Introduction and Announcement

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

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

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

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

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

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

CTBV

Professor Turner – NPNS interest. Professor Turner is a Non Executive Director (non-remunerated) on the Board of the Cell and Gene Therapy Catapult (CGT).

CGT have been tasked by UK Government with re-purposing a factory in [redacted] to manufacture either a vaccine or a therapeutic mAb. No decision has been made as to whether or what product CGT [redacted] may be asked to manufacture and that decision will be made by UK Government. Professor Turner does not believe that CGT Board will have any material input into the decision as to what product may be manufactured.

2. HLA Sensitisation Issue – MHRA and AZ Risk Assessments

2.1 The EWG was presented with a risk assessment of the potential signal of HLA sensitisation for recipients of the Covid-19 vaccine AstraZeneca which had been raised following cases of HLA sensitisation in subjects in a clinical trial of CMV vaccine.

2.2 The EWG noted the following points:

2.2.1 Covid19 vaccine AstraZeneca uses an adenovirus vector, which is non-enveloped. This is in contrast with the CMV virus vaccine which raised the signal (which uses a Lymphocytic Choriomeningitis Virus vector which is enveloped) and the other vaccine for which sensitisation has been reported which is HIV, also an enveloped virus. Therefore, host cell HLA is unlikely to be incorporated into Covid19 vaccine AstraZeneca virion particles as it would during the formation of an envelope during the budding off of an enveloped virion.

2.2.2 Details of the [redacted] performed by AstraZeneca to test a Covid19 vaccine AstraZeneca product batch for Host Cell Proteins and HLA did not find any HLA protein/peptides and the detection levels achieved were sufficiently sensitive.

2.2.3 Analysis of samples from 595 male subjects from Covid-19 vaccine AstraZeneca trials did not identify any sensitisation of vaccine recipients. All potentially HEK293 HLA-reactive antibodies detected in post vaccination samples were present in baseline samples taken prior to vaccination.

2.3 The EWG endorsed the findings of the risk assessment and considered that the available data does not present evidence of a risk and therefore should not be a barrier to transplant candidates and recipients receiving Covid-19 vaccine AstraZeneca.

2.4 The EWG made the following recommendations:

2.4.1 The EWG supported the proposal that AstraZeneca, as an additional pharmacovigilance measure, should conduct analysis of further samples from a larger proportion of trial participants, with comparison to samples from participants who received active control, on the basis of a valid statistical plan.

2.4.2 The EWG also supported the proposal that AstraZeneca, as additional pharmacovigilance, should perform LC-MS analysis of a small additional number of Covid19 vaccine AstraZeneca product batches. Further details should also be provided of the methods used for LC-MS including the relative sensitivities to detect membrane-bound and soluble proteins.

2.4.3 These additional pharmacovigilance measures should be performed as soon as possible and completed within a timescale to be determined by MHRA.

2.4.4 The EWG recommended that no update to the Covid19 vaccine AstraZeneca product information was required and that no proactive communications were required to patients and healthcare professionals.

2.5 The EWG reflected on the risks that Covid-19 infection poses to transplant candidates and recipients and the importance of their access to Covid-19 vaccination.

3. Future Steps / Any Other Business

None.

4. Date and time of next meeting

TBC

The Meeting started at 15:35 and ended at 16:22

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COMMISSION ON HUMAN MEDICINES (CHM)
COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Wednesday 13th January 2021** at **15:30** via videoconference

Participants Present

Members

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

Apologies

Professor S Price
Professor T Solomon

Members of the CTBV Expert Advisory Group

Professor B K Park
Professor M Turner

Members of the CPS Expert Advisory Group

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

Secretariat

[redacted]

Minute Taker

[redacted] - LD - Medical Writer

[1] Joined at item 2
[2] supporting specific items

Professional Staff of MHRA Present

Principal Assessors[2]

Dr J Bonnerjea - LD
Dr P Bryan - VRMM

Presenters supporting specific items[2]

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

MHRA Observers

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

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

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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.

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

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

Mrs Wang – Other relevant interest arising from being highly sensitive to insect stings, and plant products such as Hyacinth bulbs, which are recorded on Mrs Wang's medical records. This declared interest is only specific for this meeting.

Professor Weir - NPNS - Imperial College and Other relevant interest arising from his department collaborates with Imperial College on a number of clinical trials.

CTBV

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

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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

1.4 Apologies have been received from Professor Price and Professor Solomon for this meeting.

2. mRNA COVID-19 vaccines – Safety data in those with prior COVID-19 infection

2.1 The EWG heard a paper on safety in those with prior COVID-19 infection.

The EWG discussed the potential for increased reactogenicity, particularly with the Pfizer vaccine, in those who have previously had COVID-19 infection. The EWG agreed that although there may be a theoretical reason to anticipate a lower magnitude of antibody response in the AZ vaccine compared with the Pfizer vaccine, at present both vaccines can be considered similar in this respect. The EWG noted the lack of standardised assays and head to head studies to evaluate whether the vaccines induce a different magnitude of antibody response. The EWG also noted that a small percentage of individuals in clinical trials were seropositive at baseline and data from clinical trials did not indicate an increased risk of reactogenic events in these individuals.

2.2 The EWG noted that immune-complex type reactions, including serum sickness and vasculitides, were also theoretical and no risk was observed in the clinical trials. The EWG noted that the risk of immune-complex deposition was unlikely and would be more likely to occur in the event of prolonged antigen production, for example with a live vaccine.

2.3 The EWG discussed possible approaches for continued monitoring and noted that patients with previous COVID-19 infections may have a higher immune response with symptomatic disease than with asymptomatic disease.

2.4 The EWG agreed that given the evolving landscape with COVID-19 to enhance current monitoring, the MHRA should include immune-complex events as Adverse Events of Special Interests (AESIs). These would include events such as glomerulonephritis and vasculitis.

2.5 The EWG considered that the correlates or the true biological markers of protection are still unknown. The EWG noted the need for ongoing studies in order to understand if the immune response to each individual batch is the same and a baseline blood sample would be useful to carry this out and to link the subsequent reactions in those with pre-existing antibodies. The EWG considered that such a study might be coordinated by PHE and would likely have a number of individuals with pre-existing antibodies.

2.6 The EWG briefly discussed long COVID-19 and noted it would be useful to know if individuals are collecting data on this.

2.7 The EWG noted the issue of antibody enhancement of disease. There EWG heard there is potential concern that poor levels of neutralising antibodies may lead to enhancement of

disease when individuals encounter COVID-19 if they are naïve at the time of vaccination. In cases where the second dose is delayed in mRNA vaccines, high levels of IgG are observed post dose 1; however, the levels of neutralising antibodies stay low which theoretically is a situation that could lead to enhancement.

2.8 The EWG heard that approximately 300000 individuals have had the second dose and noted a proportion of them would have had a prior infection. The EWG discussed whether the second dose could induce the same kind of immune complex disease in those individuals that have not previously had COVID-19. The EWG also considered that a greater antibody response might be expected after two doses. The EWG noted that there is some evidence, i.e. from the Moderna study, that the second dose induces more of a response.

2.9 The EWG were relatively reassured for the present time by the results of the clinical trial data in terms of both reactogenicity and immune-complex events in individuals who were seropositive at baseline who have received the vaccine but noted the need for continued vigilance.

3. Risk of anaphylaxis with Pfizer/BioNTech and Moderna COVID-19 vaccines

3.1 The EWG heard a paper of the risk of anaphylaxis with Pfizer/BioNTech and Moderna COVID-19 vaccines. The EWG were reassured that the rate of anaphylaxis remained similar to that previously reported. The EWG agreed the 15-minute observation period should be maintained.

3.2 The EWG noted that the patient group directions (PGDs) for Oxford/AstraZeneca and Pfizer vaccines should be the same with respect to contraindications due to pre-existing allergies and that some patients have been incorrectly refused vaccination due to, for example, penicillin allergy. MHRA agreed to raise this with PHE.

4. Update on the Safety Data for the Pfizer/BioNTech COVID-19 vaccine
Example Publication to get view on structure

4.1 The EWG heard a paper on an update on the safety data for the Pfizer/BioNTech COVID-19 vaccine. The EWG agreed that the data were broadly reassuring.

4.2 The EWG were assured that low levels of lymphadenopathy were observed, and this event is listed in Section 4.8 of the SmPC.

4.3 The EWG heard there were no cases of appendicitis.

4.4 The EWG heard there are risk windows for each of the adverse events of special interest. For Bell's Palsy the window is between 7- and 42-days post dose 1 vaccination. These windows are then compared to the rates of Bell's Palsy in unexposed populations.

4.5 The EWG discussed the risk of lack of care in individuals following their first dose of vaccine has led to a number of cases of COVID-19 disease. The EWG also noted that some cases of COVID-19 could be contracted in the vaccine centre.

The EWG discussed individuals who contract a fever post vaccination. The EWG heard that most were healthcare professionals, and some did report symptoms of fever and joints aches/pains. A proportion of these did report positive COVID-19 tests.

4.6 MHRA informed 500 yellow cards have been received concerning the AZ vaccine which do not indicate any signals.

The EWG reviewed an example COVID-19 vaccine adverse reaction summary publication.

The EWG gave advice to MHRA on the language, content and structure of the example publication. Some members of the EWG offered their time to input further on the publication, including lay members, to ensure the publication is understood in the context of the number of doses of vaccine administered.

5. Future Steps / Any Other Business

5.1 Update on Independent Batch Release

5.1.1 The EWG heard an update on Independent Batch Release from NIBSC on Pfizer (12 batches) and AZ vaccines (5 batches) of which 10 Pfizer batches and 3 AZ batches have been certificated.

5.1.2 The EWG heard that approximately 7 million doses of COVID-19 vaccines have now been certificated. The number of doses that have been batch tested and are awaiting manufacturers testing data to allow certification is approximately another 6 million.

5.1.3 The EWG heard that by the end of January 2021 batches representing approximately 5.5 million doses are expected to have been submitted to NIBSC for testing.

5.1.4 Overall, the number of batches tested and released by the end of January by NIBSC will represent between 15 and 20 million doses in total, depending on the manufacturers' data (Lot Release Protocol) submission dates.

5.1.5 The EWG heard that the duration of the longest test is 4 days for the AZ vaccine, and 5-6 days for the Pfizer vaccine.

5.2 Members were reminded that:

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

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

6. Date and time of next meeting

The next meeting is scheduled to take place on Monday 18th January 2021 at 10:30

The Meeting today started at 15:34 and ended at 16:58

[redacted]

24th March 2021

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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 H J Lachmann
Dr S Misbah
Professor S Price
Dr A Riordan
Professor C Robertson
Professor P Shah
Professor T Solomon
Dr R Thorpe
Mrs M Wang
Professor C Weir

Apologies

Professor P J Lehner

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Professor B K Park
Professor M Turner

Members of the CPS Expert Advisory Group

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

PHE Representatives

[redacted]

COG-UK Representatives

[redacted]

Professional Staff of MHRA Present

Principal Assessors

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

MHRA Presenters supporting specific items[2]

[redacted] - LD

MHRA Observers

[redacted] - LD
Dr M Bailey - MHRA-NIBSC
[redacted] - VRMM
[redacted] - VRMM
[redacted] - MHRA-NIBSC
[redacted] - LD
Dr S Branch - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD - Medical Writer
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - MHRA-NIBSC
Ms N Rose - MHRA-NIBSC
[redacted] - LD
[redacted] - IE&S
[redacted] - MHRA-NIBSC
[redacted] - LD
[redacted] - LD

[redacted]

24th March 2021

Secretariat

[redacted]

[1] Left after item 2
[2] Left after item 4
[3] supporting specific items

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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.

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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.

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CGT have been tasked by UK Government with re-purposing a factory in Braintree to manufacture either a vaccine or a therapeutic mAb. No decision has been made as to whether or what product CGT Braintree may be asked to manufacture and that decision will be made by UK Government. Professor Turner does not believe that CGT Board will have any material input into the decision as to what product may be manufactured.

CPS

Mr V'lain Fenton-May – None

Mr Robert Lowe – None

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

Professor Kevin Taylor – None

Dr Susannah Walsh – None

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

1.5 The Chair welcomed [redacted] (Consultant epidemiologist) & [redacted] (Scientific Lead) from PHE. The Chair also welcomed [redacted] and [redacted] from COG-UK.

2. Presentation by PHE

2.1 Early assessment of COVID-19 vaccine effects using Pillar1 and 2 data

2.1.1 The EWG viewed slides and heard a presentation from PHE on the early assessment of COVID-19 vaccine effects using Pillar1 and Pillar 2 data.

2.1.2 The EWG questioned the possibility that individuals are becoming infected in vaccination centres themselves. PHE confirmed that in their enhanced surveillance they are adding questions around the vaccination visit in order to understand more.

2.1.3 The EWG noted it is concerning that the dynamics in first week post-vaccination follow what is known about infections with COVID-19.

2.1.4 PHE informed there are a group of people being tested as they developed symptoms post vaccination.

2.1.5 The EWG heard that in terms of comparison with data from other countries who also rolled vaccine out quickly such as Israel or the US, UK data may be consistent with Israel but more data is needed to make a comparison.

2.1.6 The EWG noted that in cases where those that have been vaccinated and show symptoms, there is a need to check carefully for virus escape. People who are asymptomatic can become carriers of the disease. It is particularly important to keep the asymptomatic under review in the elderly population. PHE informed that this may form part of what ONS are doing.

2.1.7 The EWG discussed the possibility that the apparent increase in risk of disease in the short time period immediately after vaccination could theoretically be due to an antibody sump which then dissipates when the vaccine takes effect.

2.1.8 The EWG heard that overall, these results are similar to those seen in Scotland, with the exception of the increase 2–3 days post vaccination.

2.1.9 The EWG noted concern about deaths observed in the few days after vaccination in care home residents and heard there are specific studies set up to look at these. The VIVALDI study will be used to look at this, but all care homes will be incorporated into an analysis.

2.1.10 The EWG heard that the initial group of data from PHE includes a significant number of people who have received their second dose at 21 days.

2.1.11 The EWG questioned whether there is increased testing in people who have had the vaccine by virtue of being symptomatic to the vaccine itself? PHE stated there is no dramatic rise but overall, the numbers tested do go up a little in the period 3-13 days post vaccination.

2.1.12 The EWG noted that some of these vaccines are quite novel and questioned whether after vaccination each individual might be expressing the antigen in body fluids and that vaccination could be giving false positives. The EWG noted that PCR tests involve multiple sites on virus but could theoretically capture vaccine mRNA depending on protocol used; however, it is unlikely the vaccine could be responsible for false positives.

2.1.13 The EWG heard that PHE does also hold information on lateral flow test results but these are not presented here.

2.1.14 The EWG found the data presented of great interest and looked forward to hearing more from future analyses.

2.2 Analysis of reinfections from the SIREN cohort

2.2.1 The EWG viewed slides and heard a presentation on interim analysis of the SIREN study.

2.2.2 The EWG heard that those who had symptoms had less severe symptoms from the initial review but PHE informed that this will be looked at in more detail going forward.

2.2.3 The EWG queried whether an inverse analysis had been performed on reinfections to evaluate whether the first infection was symptomatic or asymptomatic and see if it was linked to the second infection. PHE informed that they know all cases that were symptomatic in first infection; however, work still needs to be done with regard to asymptomatic infections.

2.2.4 The EWG noted that it is important to link with COG-UK and follow asymptomatic and symptomatic infections and questioned whether these cases are reinfections or re-emergence of original infection. PHE informed that this work is on-going and some may be reclassified at a later stage to ‘persistent’.

2.2.5 Results from interim analysis has all been done at hospital sites and is qualitative. PHE will carry out a quantitative analysis. PHE collect medical histories at enrolment.

3. Presentation by COG-UK

3.1 The EWG viewed slides and heard a presentation by COG-UK.

3.2 The EWG noted it is important to look at the genotype of the virus as demonstrated by COG-UK.

3.3 The EWG noted it is important to do forecasting and evaluate how to do it and how accurately it can be done. The significance of mutations is not known and the role of combinations or consolation of mutations as well as single mutations was discussed.

3.4 The EWG heard that COG-UK are ahead in terms of collating mutations but that there was a long way to go to translate that into what it really means for the future. Excellent surveillance methods are required to keep track of the incidence of severe disease and death and mechanisms to pick up people who are re-infected after vaccination or natural infections and mechanism to see if there is a surge in cases. The transmissibility with impairment to immunity will be most concerning.

3.5 The EWG discussed how vaccine companies get access to data and how to feedback from COG-UK and PHENO to discuss with the companies what they need if they should need to redesign their vaccines. The EWG heard much information is freely available on COG-UK website and COG-UK are happy to engage with companies but in an organised structured way. The EWG heard access to data in real time is important. MHRA will talk to vaccine companies this week and plan to discuss the regulatory approach to tweaking the vaccines. MHRA informed that a paper will come to EWG in the near future.

3.6 The EWG discussed the potential adaptation of coronavirus vaccines to mutations. We do not have an example of another virus where there is escape from the vaccine apart from flu which changes rapidly. The EWG heard that coronavirus mutates much more slowly than the flu virus. The number of transmissions drives the infection rate and what happens in people who are chronically infected. If transmission is stopped then that would reduce the likelihood of escape mutants.

4. Presentation on Agility Project

4.1 The EWG viewed slides and heard a presentation on the CEPI funded Agility Project.

4.2 The EWG heard that the Syrian hamster model was originally developed for SARS-2CoV as being an effective model for this virus and it is an appropriate model to look at vaccines.

4.3 The EWG that heard PHE have sufficient capacity to look at different antivirals and vaccines.

4.4 The EWG discussed the sources of convalescent plasma used. The EWG heard that PHE have eight sera supplied in large volumes from NIBSC sourced from blood transfusion service in the early part of outbreak (no later than summer). The EWG heard the sera used in this study is from healthy volunteers from blood transfusion service.

4.5 The EWG noted it would be interesting to look at virus as it moves back into animal system to see if counter-evolution occurs.

4.6 The EWG heard PHE are doing a [redacted] assay which is not technically intracellular but would be keen to talk about this off-line.

5. EWG discussion on *in vivo* adventitious agent testing for Covid-19 vaccine AZD1222

5.1 The EWG viewed slides and heard a presentation on *in vivo* adventitious agent testing for COVID-19 vaccine AZD1222.

5.2 The EWG had no particular concerns with removing *in vivo* adventitious agent testing for COVID-19 vaccine AZD1222. The EWG noted a test by test analysis may be required at some point.

5.3 The EWG discussed the use of intermittent metagenomics and agreed to ask the company if they are considering this approach for the future.

6. Review of Minutes

6.1 Wednesday 18th November 2020
Saturday 21st November 2020
Tuesday 24th November 2020
Friday 27th November 2020
Saturday 28th November 2020
Monday 7th December 2020
Thursday 10th December 2020
Thursday 17th December 2020
Tuesday 22nd December 2020
Thursday 24th December 2020
Tuesday 29th December 2020

6.1.1 The minutes listed above were approved as a true and accurate record of the proceedings, subject to some amendments to the relevant minutes.

7. Future Steps / Any Other Business

7.1 Members were reminded that:

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

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

8. Date and time of next meeting

The next meeting is scheduled to take place on Friday 22nd January 2021 at 15:30

The Meeting today started at 10:31 and ended at 12:56

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

COMMISSION ON HUMAN MEDICINES (CHM)
COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Friday 22nd January 2021** at **15:30** via videoconference

Participants Present

Members

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

Members of the CTBV Expert Advisory Group

Professor B K Park[1]
Professor M Turner

Members of the CPS Expert Advisory Group

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

Observer

Professor S Ralston (Chair of CHM)

Secretariat

[redacted]

Professional Staff of MHRA Present

Principal Assessors[2]

Dr J Bonnerjea - LD
Dr P Bryan - VRMM

MHRA Presenters supporting specific items[2]

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

MHRA Observers

[redacted]
Dr S Branch - VRMM
[redacted]
Mr K McDonald - LD
[redacted]
Dr J Raine - MHRA CEO
Ms N Rose - MHRA-NIBSC
[redacted] LD
Mr P Tregunno - VRMM
[redacted]

[1] Joined during item 3
[2] supporting specific items

[redacted]

[redacted]

19th July 2021

Key

LD = Licensing Division
NIBSC = National Institute for Biological Standards & Control
VRMM = Vigilance & Risk Management of Medicines
CTBV = Clinical Trials, Biologicals & Vaccines EAG
CPS = Chemistry, Pharmacy & Standards EAG
CHM = Commission on Human Medicines
MHRA CEO = Chief Executive
IE&S = Inspection, Enforcement & Standards
NIBSC = National Institute for Biological Standards & Control
COMMS = Deputy Director of News, Digital & Content

1. Introduction and Announcement

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

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

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

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

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

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

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

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

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

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

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

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

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

Professor Weir - NPNS - Imperial College and Other relevant interest arising from his department collaborates with Imperial College on a number of clinical trials.

CTBV

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

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either a vaccine or a therapeutic mAb. No decision has been made as to whether or what product CGT Braintree may be asked to manufacture and that decision will be made by UK Government. Professor Turner does not believe that CGT Board will have any material input into the decision as to what product may be manufactured.

CPS

Mr V'lain Fenton-May – None

Mr Robert Lowe – None

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Professor Kevin Taylor – None

Dr Susannah Walsh – None

CHM

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

1.4 MHRA Press Interaction

1.4.1 The EWG heard advice from the MHRA Communications Division regarding MHRA Press Interaction. MHRA advice remains that EWG members should not speak on behalf of or as a representative of the EWG/CHM or discuss EWG/CHM business. In these cases, EWG members are advised to pass these queries to the MHRA news centre. MHRA to circulate the contact details to EWG members post meeting.

1.4.2 The EWG were reminded of the code of practice for scientific advisory committees (communication with media is covered in paragraphs 139-142). MHRA to provide link to this document following the meeting.

1.4.3 The EWG heard that where information is already in public domain and decision or advice already been made or given when that advice is in the public domain then members can repeat the outcome to the press.

1.4.4 The EWG were informed that EWG members are not to interact with the press about any live issues that are under consideration or any other issues that could potentially come up in the future.

1.4.5 MHRA advised EWG members to avoid putting themselves in positions where they might get asked questions around COVID-19 vaccines and their role as an EWG member wherever possible. MHRA informed EWG members that the MHRA news centre staff are always available to discuss any press queries members receive with them and to provide support and advice and to agree what can and can't be said.

2. Minutes of the COVID-19 VBR EWG meeting held on Thursday 24th December 2020

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

3. Regulatory strategy for authorised Covid-19 vaccines in case of strain changes

3.1 The EWG heard a draft paper about the regulatory strategy for authorised COVID-19 vaccines in case of strain changes.

3.2 The EWG heard the difference between antigen drift and antigen shift, where antigen shift would mean a new gene assortment, and the regulatory concepts associated with both. The EWG heard that at present the coronavirus is mutating in line with what would be considered antigen drift.

3.3 The EWG heard how this antigen drift could be managed along the same lines as the annual flu vaccine updates. The EWG heard the quality requirements MHRA would expect to see in order to update the COVID-19 vaccines in this way.

3.4 The EWG heard that is not yet known if antibody response is a good indicator of a response, and that a challenge study with SAR-Cov2 would be required which would be time consuming. A hamster study would also be required in the post-marketing phase. Cross protection should also be evaluated to ensure any new vaccine would protect against previous versions of the virus as well as recent versions.

3.5 The EWG heard that immunogenicity data would be required as outlined in the draft paper.

3.6 The EWG discussed the human challenge model and whether it has a role to play in the path to rapid approval for new vaccine strains. The EWG heard there are some ethical concerns that may relate to how dangerous any new strain of the virus would be but could be looked at on a case by case basis. The EWG heard that challenge studies may not be necessary if it is possible to bridge via immunogenicity data and an occurrence of disease would not be required. The EWG agreed it would be useful to have a session on human challenge trials at a future meeting.

3.7 The EWG heard that the human challenge studies are a fairly quick process and could provide a route to understand correlates of protection and to measure escape processes of the virus. The EWG heard that already there are different variants in 3 different continents, and it is not known which strain should be targeted by an updated vaccine. Human challenge model may be the only way to find out. The EWG heard any strategy needs to be internationally regulated. The EWG heard there may be similarities between coronavirus and norovirus and how it changes in different continents.

3.8 The EWG discussed whether we have reached the trigger point for manufacturers to start thinking about creating new vaccines to combat the new variants.

3.9 The EWG heard that the live virus will show the full complement of the mutations occurring whereas a pseudovirus will only give some of the mutations but not necessarily any occurring outside the RBD domain.

3.10 The EWG heard that recipients of Pfizer vaccine are able to produce neutralizing antibodies against variant 501; however, the trigger point for production for new vaccine may almost be reached. The EWG also noted the level of IgG produced after vaccination with the Pfizer vaccine. The EWG noted that the role of cellular immunity is not yet fully understood.

The EWG discussed the use of the human challenge studies and their use to determine natural immunity to the virus as well as immunity to the virus following vaccination with a new vaccine.

3.11 The EWG discussed how a new vaccine to be used in challenge studies would be approved. The EWG heard it could be used at Phase II level and would not have to be a licensed vaccine.

3.12 The EWG heard discussion around a sample size of 300 participants being exposed to an updated vaccine and agreed it seemed reasonable that this number might meet adequate levels of precision and practicality.
The EWG discussed the use of multiple virus sequences in the same vaccine to combat variants.

3.13 The EWG discussed whether non-clinical or quality data could be used alone and did not agree that this could be the case.
The EWG discussed the minimum level of evidence required to develop an updated vaccine.
The EWG heard that the paper will be updated and that the next logical step would be to have discussions with WHO being mindful of the impact that any delay might have and any potential changes of the pandemic.

4. Update on fatal ADRs

4.1 The EWG heard an update on the safety data from fatal ADRs. The EWG heard a summary of the fatal cases in Norway following administration of the Pfizer/BioNTech COVID-19 vaccination in frail and elderly patients, and that no connection with the vaccine had been established.

4.2 The EWG heard that the majority of the fatal cases in the UK following vaccination with the Pfizer vaccine are in the 80+ age group. The ADR cases were also summarized and were largely in line with events expected considering the ages and comorbidities in the patients. There were also some cases reporting diarrhoea and vomiting.

4.3 The EWG heard a summary of fatal cases in the UK following vaccination with the AstraZeneca vaccine in those aged 65 – 96 years of age. The events reported in fatal cases for AstraZeneca COVID-19 vaccine were also considered expected due to the age and comorbidities in the patients.

4.4 The EWG heard that currently there is no evidence of an increased risk of fatal events in frail patients and the benefit/risk profile remains the same in these patients.

4.5 The EWG requested more information on the cases of toxic epidermal necrolysis and the fatal cases where the onset of symptoms occurred within 25 minutes of vaccination. The EWG heard that generally speaking the fatalities occurred within a week of vaccination.

4.6 The EWG agreed that there does not seem to be a signal for an increased risk of fatalities in the elderly and frail patients with either the Pfizer COVID-19 vaccine or the AstraZeneca COVID-19 vaccine. The EWG agreed that the regulatory procedures put in place by the MHRA currently seem adequate.

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

None.

6. Date and time of next meeting

The next meeting scheduled to take place on Monday 25th January has been cancelled.

The next meeting is scheduled to take place on **Friday 29th January 2021** at **13:30**

The Meeting today started at 15:31 and ended at 17:37

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COMMISSION ON HUMAN MEDICINES (CHM)
COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Friday 29th January 2021** at **13:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer[1]
Professor G Dougan
Professor N French
Professor D Goldblatt
Ms S Hunneyball
Professor K Hyrich
Sir M Jacobs
Professor H J Lachmann[2]
Professor P J Lehner
Dr S Misbah[3]
Professor S Price
Dr A Riordan
Professor C Robertson
Professor T Solomon
Dr R Thorpe
Mrs M Wang
Professor C Weir

Apologies

Professor P Shah

Members of the CTBV Expert Advisory Group

Professor B K Park
Professor M Turner

Members of the CPS Expert Advisory Group

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

Observers

[redacted] (Imperial)
Professor S Ralston (Chair of CHM)

Invited Experts

[redacted]

Professional Staff of MHRA Present

Principal Assessors[4]

Dr J Bonnerjea - LD
Dr P Bryan - VRMM

MHRA Presenters supporting specific items[4]

[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - VRMM
[redacted] - LD
[redacted] - Government Legal Team
[redacted] - VRMM

MHRA Observers

[redacted] - LD - Medical Writer
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
Dr S Branch - VRMM
[redacted] - MHRA-NIBSC
[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - LD - Medical Writer
[redacted] - VRMM
Dr SP Lam - LD
Mr K McDonald - LD
[redacted] – VRMM
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - MHRA-NIBSC
Ms N Rose - MHRA-NIBSC
[redacted] - MHRA-NIBSC
[redacted] - LD
[redacted] - LD
[redacted] - VRMM
Mr P Tregunno - VRMM
[redacted] - Government Legal Team
[redacted] - MHRA-NIBSC
[redacted] - LD
[redacted] - LD

[redacted] - VRMM
Dr K Wydenbach - LD

Secretariat

[redacted]

[redacted]

19th July 2021

[1] Joined during item 3
[2] left during item 9
[3] left during item 6
[4] supporting specific items

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

Professor Dougan – Personal interest specific to this meeting **–** Works with and is partially paid by the Wellcome Trust. Professor Dougan arranges the invite. At the chair's discretion, Professor Dougan was permitted to participate by answering specific questions from the chair, but not raise spontaneous comments or questions.

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

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

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

Sir Michael Jacobs - Other relevant interest - As part of the academic role at the Liverpool School of Tropical Medicine, Sir Michael is a member of the Study Management Team and antiviral drug prioritisation group for the AGILE proof of concept (phase I/II) platform study. Sir Michael is also part of the team that submits new antiviral compounds against SARS-CoV2 for consideration by NIHR for testing on this platform. No commercial or financial interest in the trial or any of the compounds, or any pharmaceutical or biotechnology company. Personal interest specific to this meeting – Sir Michael is a member of the Human Challenge Steering Committee. At the chair's discretion, Sir Michael was permitted to participate by answering specific questions from the chair, but not raise spontaneous comments or questions.

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

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

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

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

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

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

Professor Weir - NPNS - Imperial College and Other relevant interest arising from his department collaborates with Imperial College on a number of clinical trials.

CTBV

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

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

CPS

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

CHM

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

1.4 The Chair welcomed the following invited experts for item 3:

[redacted] Human Challenge, Vaccines Taskforce
[redacted] Human Challenge, Vaccines Taskforce
[redacted] University of Southampton & Human Challenge Board Member
Read R.C.
[redacted] Imperial College (Study PI)

The Chair welcomed the following invited experts for item 4:

[redacted]

The Chair also welcomed [redacted] from Imperial who attended as an Observer.

2. Update on off-label prescribing of vaccines (for information)

2.1 The EWG was given an update regarding the previously raised questions about how the Regulation 174 approvals legally interact with the Specials Regime.

2.2 The EWG heard that a clause has now been introduced to the wording of conditions of all Regulation 174 vaccine approvals that covers off-label prescribing. This clause clarifies that an authorisation under Regulation 174 does not displace or preclude the reliance on the specials route of administration in the appropriate situations.

2.3 The EWG heard that the off-label use of vaccines cannot be further recommended or specified by MHRA and that the added clause merely states that the Regulation 174 approval does not displace or preclude the use of specials route of administration where these may appropriate in the judgement of individual prescribers or subject to the recommendations and priorities specified by the JCVI or other similar bodies.

2.4 The EWG were reminded that the added clause does not affect the liabilities of the prescriber as explained under Regulations 345 of the Human Medicines Regulations 2012. The added clause does not amount to a recommendation of use under Regulation 174. A healthcare professional prescribing this product off-label would not be considered to be doing it pursuant to the recommendation made under Regulation 174.

3. Presentation from Imperial/VTF – Human Challenge Study

3.1 The EWG viewed slides and heard a presentation from the Imperial/VTF on the general principles of human challenge studies, their strengths and requirements and how they are expected to accelerate the development of new vaccines. This type of study aims to answer questions such as the effect of vaccines and other treatments on viral shedding, and the effect of previous infections and any protection generated from this on viral shedding.

3.2 The EWG heard that these studies can look at critical challenges that may present themselves such as decisions regarding dosing or interval schedules, reduction of transmission and when to re-vaccinate.

3.3 The EWG heard that this type of study can also include non-vaccine therapies, such as therapeutics used for prophylaxis, antivirals and monoclonal antibodies as the study uses a disease model rather than an infection model.

3.4 The EWG discussed the benefits and limitations of these studies following the presentation from Wellcome on the Human Challenge Study.

4. Presentation from Wellcome – Human Challenge Study

4.1 The EWG viewed slides and heard a presentation from the Wellcome Trust. The EWG heard about the Wellcome programme of human challenge studies, with a goal to establish these studies in a low resource endemic setting so that vaccines can be tailored towards a target population.

4.2 The EWG heard about the programme of human challenge studies for SARS-CoV-2, which include characterisation studies and how they can be conducted ethically and safely. Current risk mitigation strategies in terms of treatment include pre-emptive remdesevir, monoclonal antibody cocktails, and dexamethasone.

4.3 The EWG discussed that there is a need to bridge clinical challenge data from young healthy adult individuals to target populations such as the elderly.

4.4 The EWG noted that the study will need to ensure a duty of care towards the volunteers especially in regard to persistent infections. The EWG noted that the presence of counselling young adult volunteers was reassuring and was the step in the right direction to ensure viral shedding was not taking place in the community.

4.5 The EWG heard that the study will carefully clinically screen individuals to ensure no prior history of recurrent infectious disease was present to exclude subjects with immune defects. The EWG raised concerns about the long-term effects of COVID infection in some individuals (long-COVID).

4.6 The EWG questioned the trigger points for the interventions and rescue therapies for the characterisation study, when a young adult patient is presenting symptoms of severe disease. The EWG heard that the trigger points were based around the physiological responses in those volunteers, such as gas exchange in the individual and untoward pro-inflammatory responses, with the potential use of remdesivir, monoclonal antibodies and dexamethasone in severe manifestations of the disease. Such subjects would be treated in a NHS unit independent from the study.

4.7 The EWG were reassured to hear the steps taken by the team to ensure the involvement of public in terms of public engagement studies which showed immense public support for the human challenge studies. The task force clarified that the work around spreading a clear message to the public is ongoing and continually monitored.

4.8 The EWG discussed the limitations to the challenge study such as the use of viral shedding rather than a disease model, as this does not allow for a clinical readout. The EWG questioned how efficacy will be inferred from viral replication in the upper respiratory tracts and whether this was sufficient for correlation with the efficacy of the vaccines. It was noted that this was the preferred model of choice in order to ensure the safety of the volunteers. To overcome the limitations of the disease model, the invited experts suggested alternative surrogate measures of efficacy, such as pathology seen on radiological imaging to serve as a form of a clinical readout.

4.9 The EWG agreed that challenge models will be critical going forward in understanding the different variants of SARS-CoV-2. The models will also provide an opportunity to determine whether the virus being detected is infectious.

4.10 The EWG noted the need for future discussions regarding the benefits if any of improvements to the approval pathway in terms of the nature and speed of the data these studies can produce for the current pandemic and future diseases.

4.11 The EWG expressed concern that preventing viral replication/load in the model would be a very high bar to set for any vaccine. It was raised that a model based on preventing symptoms of viral infection, especially for the accelerated vaccine development and testing, would be better.

4.12 The EWG felt that we are now moving from a previous situation of a fairly homogenous virus in a naïve population to a population who have had either had virus exposure or vaccination, and a virus that has variants. The human challenge models won't replace current research work but will add value in the nature of the data that it can produce.

5. Janssen non-clinical review

5.1 The EWG viewed slides and heard a presentation on the non-clinical aspects and the rolling review of the Janssen COVID-19 vaccine. The vaccine is an adenovirus type 26 vector.

5.2 The EWG were informed that the European Medicines Agency are reviewing the same dataset and it has been agreed that MHRA will consider what questions MHRA needs to put to the company after reviewing interactions between the European Medicines Agency and the company.

5.3 The EWG heard that the data presented on pharmacodynamics in terms of immunogenicity was reassuring. However, some discordance was noted with regards to the intracellular cytokine studies in mice and Rhesus monkeys. In mice, the intracellular cytokine response is predominantly confined to CD8 rather than CD4 cells. In Rhesus monkeys, the cytokine response is concordant between CD4 and CD8 cells. This may need to be explained by the company, as it is an unexpected finding, although it does not seem to affect the level of protection.

5.4 The EWG noted that the MHRA is awaiting toxicology data to be submitted. The EWG is keen to understand the reproductive toxicity, and whether the difference in lung pathology induced by SARS CoV-2 virus in the challenge study in rhesus monkeys between males and females could be due to lack of age matching between males and females).

5.5 The EWG discussed the possible requirements for future 1-dose and 2-dose studies (e.g. persistence of infection and persistence of antibodies in 1-dose studies). The EWG enquired as to what animal studies could be done to investigate this. The EWG considered whether 1-dose human studies would require longer-term follow-up on immunogenicity.

5.6 The MHRA confirmed that based on the rolling review data submitted in this sequence, there is no indication of whether the company will come to MHRA with a proposal for a 1-dose or 2-dose vaccine.

5.7 The EWG heard that data regarding the effects of SARS CoV2 challenge in vaccinated hamsters will be provided in sequence 2, due by the end of January. The EWG agreed that this data would provide a better understanding of immunogenicity.

The EWG concluded that the non-clinical package submitted so far was promising, but more data would be required, as outlined above.

6. Clinical AR – Update on AZD1222 efficacy and immunogenicity

6.1 The EWG viewed slides and heard a presentation on updated AZD1222 efficacy and additional immunogenicity data.

6.2 The EWG noted that efficacy was approximately 78% at dosing interval of 12 weeks or more and approximately 55% at dosing intervals of 4 to 8 weeks. However, not enough data is available to amend the dosing intervals at this stage. The EWG was concerned that early homologous boosting was confusing the data that were being presented.

6.3 The EWG discussed the available information on the clinical trial participants from South Africa and Brazil with regards to reinfection following vaccination, especially in terms of the new variants in those countries. The EWG noted that current data which depicts this sort of information is not available, however, will be requested from the company.

6.4 The EWG requested long-term data to be made available on the time of events in terms of infection to the time of vaccination in order to analyse the trends in infection rates. The EWG asked if more data would be made available on asymptomatic carriers.

6.5 The EWG noted that PHE are performing weekly analysis and will provide Pillar testing data versus vaccine records by mid-February.

6.6 The EWG concluded that the efficacy results were reassuring. The EWG advised that the product information (Information for Healthcare Professionals, Information for Recipients of the Vaccine and UK Public Assessment Report) should be amended to include updates on the age and dosage interval efficacy data based on the study data submitted; however, it was advised to wait for further data from the US (due in March) before considering a change in the dose interval recommendation in section 4.2 of the HCP information.

7. Verbal update on trends in reactogenic adverse reactions with the Pfizer and AZ vaccines

7.1 The EWG heard an update on the reactogenic adverse reactions in participants who received the Pfizer/BioNTech and the AZ COVID-19 vaccines. The EWG heard that a higher proportion of reactogenicity events had been reported in younger recipients of the vaccine.

7.2 The EWG heard that a comparison of the data collected from the Yellow Cards for the flu vaccine from 2011 up to the present day was compared against the data collected and reported for the Pfizer/BioNTech and the AZ COVID-19 vaccines. Analysis of the data was made using reports which were flagged as serious. Serious events were defined as causing disability and incapacitation, being life-threatening, causing hospitalisation, death or other (which includes definitions such as the inability to carry out daily activities).

7.3 The EWG heard that from the data collected, the cases flagged as serious (serious as defined within the categories mentioned above) were 42% for AZ vaccine and 34% from the Pfizer/BioNTech data and 48% for the flu vaccine. Within those figures, the proportion of each type of event was similar between the AZ and Pfizer/BioNTech, and slightly higher for the flu vaccines. For example, disability and incapacitation was observed in 6.5%, 6% and 9% of AZ, Pfizer and flu vaccine recipients, respectively.

7.4 The EWG heard that the frequency of serious reports flagged for the AZ vaccine was slightly higher than that for the Pfizer/BioNTech vaccine; however this figure was similar to the figure reported for the flu vaccine. The types of serious events observed with the vaccine were also comparable with those observed with the flu vaccine, typically reactogenicity (e.g. headache, myalgia, pyrexia).

7.5 It was also noted that the proportion reporting serious events was much higher amongst the under 65 age group versus over 65 age group. Similarly, for the type of serious event, the frequency of reporting was higher in the under 65 age group than the over 65 age group. For example, of the disability/incapacitation occurring in recipients of the Pfizer vaccine, 82% were under 65, and 84% for recipients of the AZ vaccine, and 55% for the flu vaccine. The potential for higher reporting was assumed to be in part due to more awareness in the younger age group regarding the yellow card scheme (particularly as a lot of these will be healthcare workers) and access to technology. However, further stratification of these events by age group is needed.

7.6 During the clinical trials, reactogenicity events were more frequently reported in the under 65 age group, although serious events in general were reported in the over 65 age group.

7.7 Preliminary information from the Zoe app shows a higher proportion of reactogenicity in those recipients of the Pfizer/BioNTech vaccine that have had previous COVID-19 infection (which was not reflected in the clinical trial data) and also in recipients after the second dose of vaccine. This data is also corroborated by the Yellow Card data. PHE does have a cohort of patients with prior COVID-19 infection confirmed by antibody testing, who could be useful in comparing with these data.

7.8 The increased reactogenicity observed in the under 65 age group is thought to correspond with a stronger immune response in this age group.

7.9 The EWG was informed that so far there has been no indication of a decrease of recipients under 65 refusing any of the vaccines because of the increased occurrence of reactogenicity events. However, it is something that will need careful monitoring and communication to ensure that it does not affect uptake of the vaccines in this age group.

7.10 The EWG noted that further data is being collected in terms of Yellow Card vaccine monitoring, and ongoing collaborations are present with PHE, and data from surveillance applications such as monitoring of the ZOE app. The EWG also noted the potential bias of reporting using Yellow Card towards more severe/serious events.

7.11 The EWG enquired about the current stage of the Yellow Card vaccine monitor, which recruits individuals who have been invited for vaccination. Invitations have been sent out to recipients and it is being considered whether to add questions concerning prior COVID-19 infection, but there is a concern as to how reliable that data will be. Apps have been launched in the US and Germany, which will also provide useful data.

7.12 The EWG raised concerns that there could be an under-reporting of events, especially from healthcare professionals, who may be more reluctant to report on themselves, even with increased familiarity of Yellow Card.

7.13 The EWG concluded that the data was on interest, as part of an ongoing monitoring of events experienced by recipients of the vaccines.

8. Verbal overview of safety data with AZ

8.1 The EWG heard that the AZ vaccine was authorised on 4 January 2021. To date, up to 1.6 million vaccines have been administered. It was noted that up to 25 January 2021, the MHRA has received 68069 ADR reports (~4 Yellow Card reports per 1000 doses). Reactogenicity reports were as expected, including ADRs such as headaches, chills, nausea, and injection site reactions. As had been mentioned previously, these were more prevalent in younger vaccine recipients, who were also predominantly healthcare professionals. A reduction in reactogenicity with the second dose has been observed with the AZ vaccine in clinical trials, but it is not possible to analyse this effect properly at this time. A small overall population of vaccinated recipients have reported reactogenicity symptoms (less than 0.5% of the population reporting as serious events).

8.2 The EWG heard that 36 fatal cases had been reported, most of which affected frail elderly care home residents with end stage diseases. As a result, it was noted that a number of reports were being submitted where an association with vaccination was not necessarily suspected but the reporter considered it good practice to report given the temporality of the fatality with vaccination.

8.3 The EWG heard events of special interest were also being reported; 10 cases reported facial paralysis but not all cases of facial paralysis were consistent with Bell's palsy with some describing facial numbness.

8.4 The EWG heard that one case of transverse myelitis had also been reported. This event was also reported in the clinical trials and is an adverse event of special interest.

8.5 The EWG confirmed further monitoring is taking place for all neurological adverse drug reactions via detailed follow up forms to help understand the exact nature of these adverse drug reactions.

8.6 The EWG noted that at the request of the FDA, AstraZeneca was requested to set up an independent panel to monitor the neurological adverse drug reactions of this vaccine. The panel considered that MHRA and the EWG should also be kept informed of its findings.

8.7 MHRA confirmed that a paper would be submitted to the EWG for next week's meeting.

9. Anaphylaxis data for AstraZeneca

9.1 The EWG heard a brief update on the anaphylaxis data for the AZ vaccine. They heard that although this vaccine does not contain the polyethylene glycol (PEG) component of the mRNA vaccines which can cause severe anaphylaxis, it does however contain a component known as polysorbate which is cross reactive with PEG.

9.2 The EWG heard that unlike PEG, polysorbate has been used as an excipient in other biological medicines as well vaccines used in the routine immunisation schedule (e.g. Fluad), Fluad has been part of the UK's annual influenza vaccination campaign for the past three years and millions of doses have been administered and no signal of anaphylaxis has been detected to date.

9.3 The EWG also heard that no signal for anaphylaxis was seen in clinical trials.

9.4 The EWG heard that a total of 14 cases reporting anaphylactic or anaphylactoid reactions were reported to the MHRA. Only a small proportion of cases reported immediate onset following vaccination (i.e. within 30 minutes of vaccination). Most cases did not appear to have the same level of severity as cases seen with the Pfizer vaccine and a specific waiting time after vaccination, as is in place for the Pfizer vaccine, was not deemed necessary at this point. In addition to this, current evidence on polysorbate as a vaccine excipient does not suggest that we would expect the rate of anaphylaxis to be increased with the AZ vaccine and clinical trial data did not identify any cases of anaphylaxis which were likely related to the vaccine.

9.5 The EWG heard that a number of hypersensitivity reactions were being reported post authorisation. It was noted that this reaction was also seen in the clinical trials.

9.6 The EWG noted that the frequency of anaphylaxis is more frequent in the Pfizer/BioNTech vaccine. The EWG considered that there was no strong basis for the inclusion of anaphylaxis in the product information and the 15 minute onset time noted with the Pfizer vaccine; however, it was agreed that the inclusion of any wording in the product information should be discussed with company. With regards to the inclusion of information for quantifying anaphylaxis in the Information for Healthcare Professionals, the EWG requested a proposal on appropriate wording that would not cause further alarm to the patient. The EWG was concerned to strike the right balance between informing patients and worrying them.

9.7 The EWG agreed a discussion with the company should take place to review cases indicative of hypersensitivity and/or angioedema that have been received in the post-authorisation setting and to determine if updates to the product information are needed.

10. Update on anaphylaxis data for mRNA COVID-19 vaccines

10.1 The EWG heard a brief update to the Yellow Card data reported for the Pfizer/BioNTech vaccine.

10.2 The EWG heard that up to 25 January 2021, the MHRA has received a total of 90 reports with the preferred term (PT) anaphylaxis, 6 with the PT anaphylactoid reaction, and 2 each for anaphylactic shock and anaphylactoid shock following the Pfizer/BioNTech vaccine. A reporting rate of 1.8 cases per 100,000 doses is estimated in the UK based on these cases. Overall, spontaneous reporting in the UK has maintained a similar pattern of events with an onset largely within 15 minutes of vaccine administration and with no particular history of allergic reactions in the cases.

10.3 The EWG heard that although Moderna's COVID-19 vaccine is not yet available in the UK, a review of post marketing data from the US by the CDC provided an estimate of 2.5 cases per million doses of the Moderna vaccine. The CDC has estimated approximately 0.5 cases per 1 million doses with the Pfizer/BioNTech vaccine.

10.4 The EWG heard that this is lower than the estimates of UK rates for the Pfizer/BioNTech vaccine, and agreed, that this was due to the differences in the criteria for determining the rates, with the US analysis excluding a high number of cases by using the Brighton Collaboration criteria, and so any comparison should be treated with caution.

10.5 The EWG noted that anaphylaxis is already listed as an identified risk in the Moderna risk management plan (RMP) and therefore do not propose new safety advice.

10.6 The EWG reiterated that the data presented on anaphylaxis following the Moderna and Pfizer COVID-19 Vaccine does not indicate any new safety concerns with these products and that the current advice on anaphylaxis and allergic reactions are still supported by the available data for both these vaccines.

10.7 The EWG heard that the UK RMP for the Pfizer/BioNTech vaccine does not currently include anaphylaxis as an important identified risk, however this is included in the EU RMP which was authorised after the UK's authorisation of this vaccine.

10.8 The EWG discussed that the UK RMP should be updated to include anaphylaxis as an important identified risk, bringing the information in line with the warnings depicted in the SmPC and further bringing the information in line with the EU RMP.

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

None.

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

The next meeting is scheduled to take place on Thursday 4th February 2021 at 10:30.

The Meeting today started at 13:33 and ended at 17:32

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

NOT FOR PUBLICATION

COMMISSION ON HUMAN MEDICINES (CHM)

COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Thursday 4th February 2021** at **10:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan[1]
Professor N French
Professor D Goldblatt
Ms S Hunneyball[2]
Professor K Hyrich
Sir M Jacobs[2]
Professor P J Lehner
Dr S Misbah
Professor S Price
Dr A Riordan
Professor C Robertson
Professor P Shah
Professor T Solomon[3]
Dr R Thorpe
Mrs M Wang
Professor C Weir

Apologies

Professor H J Lachmann

Member of the CTBV Expert Advisory Group

Professor B K Park

Members of the CPS Expert Advisory Group

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

Invited Expert

[redacted][4]

Secretariat

[redacted]

MHRA Observers continued

[redacted] - LD
[redacted] - LD

[1] Joined during item 2
[2] Left after item 5
[3] Left during item 4
[4] Presented item 2 & left after this item

Professional Staff of MHRA Present

Principal Assessors[5]

Dr J Bonnerjea - LD
Dr P Bryan - VRMM

MHRA Presenters supporting specific items[5]

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

MHRA Observers

[redacted] - VRMM
[redacted] - LD
[redacted] - LD
Dr S Branch - VRMM
[redacted] - VRMM
[redacted] - VRMM
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[redacted] - LD - Medical Writer
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[redacted] - LD
[redacted] - VRMM
Ms N Rose - MHRA-NIBSC
[redacted] - LD
[redacted] - LD
[redacted] - VRMM
Mr P Tregunno - VRMM
[redacted] - Government Legal Team
[redacted] - MHRA-NIBSC

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

[5] supporting specific items

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 declared interests and other relevant interests for this meeting:

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

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

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

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

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

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

Professor 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.

Mrs Wang – Personal interests arising from being highly sensitive to insect stings, and plant products such as Hyacinth bulbs, which are recorded on Mrs Wang's medical records.

Professor Weir - NPNS - Imperial College and Other relevant interest arising from his department collaborates with Imperial College on a number of clinical trials.

CTBV

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

CPS

Mr V'lain Fenton-May – None
Professor Kevin Taylor – None
Dr Susannah Walsh – None

1.4 The Chair welcomed [redacted] from ZOE, Kings College London

2. ZOE App and suspected adverse events

2.1 The EWG heard from [redacted] on the preliminary analysis of the occurrence of adverse effects and reduction of SARS-CoV-2 positivity rate, based on the data provided by contributors to the ZOE/KCL COVID Symptom study. On 4th December 2020, questions on vaccination were made available to users of the app. Most of the ~4.5 million users are located in the UK. 1.5 million log data each week, and many of these have been reporting via the app since April 2020.

2.2 ~300,000 users had logged their vaccine; most were white and BAME populations were underrepresented. A high number of healthcare professionals reported regularly (45,000). Post vaccination PCR tests have been reported from 51,763 contributors while a much smaller proportion had antibody tests (1,654).

2.3 The first analysis focused on data from 40,000 mainly healthcare professionals who had received the Pfizer/BioNTech vaccine - at cut off ~23,000 first dose only (65%), and ~12,000 (35%) first and second dose. Local and systemic adverse effects were studied. Systemic effects were more frequent after the 2nd injection, (~11.1% reported at least one systemic adverse effect after the 1st dose versus ~19.7% same reporting measure after the 2nd dose). Systemic adverse effects were headache, fatigue, chills, shivering, diarrhoea, fever, arthralgia, myalgia, and nausea. The data were fairly consistent with the clinical trial data for the vaccine. Contributors who had COVID in the past were more almost twice as likely to have at least one systemic adverse effect (~33% vs ~19%). Younger users <55 years also reported more systemic effects (~25% vs ~13% in those >55 years), possibly due to a reduced immune response in older people. The most frequent adverse effects are fatigue and headache, and aftereffects tend to resolve after 2-5 days, although ~2% continued for longer.

2.4 Local adverse effects were pain that is localised, swelling, tenderness, redness, itch, warmth, proximal lymphadenopathy; these effects were short lasting (most lasting 3 days or less) and highly similar in both rate and type to those reported in the clinical trial. Local effects were more common after the 2nd dose. It should be noted that check box lists of adverse events were displayed to users, and the list was developed in collaboration with virologists and the Pfizer BioNTech clinical trial investigators. A free text box was also included under the category of other, to enable reporting of effects outside of the predefined list. Female contributors reported more adverse effects (both local and systemic).

2.5 The re-infection rates post Pfizer/BioNTech vaccination increased during the period 5-12 days after vaccination. The increase was suspected to be due to the window where there is no protection as the immune response has not had time to develop combined with a potentially higher risk of exposure, on travelling en route to and from vaccination centres / clinics, and possibly increased socialisation due to a false perception of immediate protection. After 12 days and adjusted for the background decrease in cases, an approximate reduction in infections in the vaccinated group of contributors of approximately 50% was observed.

2.6 Future analyses are planned to investigate similar parameters for the AstraZeneca vaccine and compare these to the Pfizer/BioNTech data. Questions to be explored included if past COVID may remove the need for a 2nd dose, the biological vaccine response in long COVID and responses in BAME vaccine recipients, to work with the MHRA to enhance reporting of rare side effects, and to explore the duration of protection through natural exposure and vaccine-based protection. In the invited experts closing remarks, attention was drawn to the limited NHS promotion of the app, for example at vaccination centres and other NHS platforms, despite Chief Medical Officer (CMO) support.

2.7 Questions and Answers

2.7.1 The Commission heard it will be explored if there is a relationship between the time interval from natural infection to vaccination, and if this affects the likelihood of developing systemic side effects. There is a hypothesis that vaccine recipients with a longer interval between natural infection and vaccination may experience reduced vaccination side effects, which may be attributed to waning immunity.

2.7.2 The Commission heard the vast majority of healthcare workers tested for COVID-19 post vaccination were symptomatic according to the app's symptom criteria which includes a greater list of symptoms compared with that used by Public Health England (PHE). The Commission noted that the post vaccination infection rate was similar to that observed in vaccine effect studies conducted in Scotland, and Professor Tim Spector requested access to any other relevant epidemiological data sets.

2.7.3 The Commission noted it may be beneficial on a precautionary basis, to calculate the number contributors that reported (resolved) infection prior to vaccination as a positive control when analysing the 5-12 day post vaccination infection data. If the proportion who had prior infection is high, there would be expected to be a degree of immunity, this could help to eliminate social factors and other routes of elevated exposure as causes.

2.7.4 The Commission heard messaging at the point of vaccination seems to focus on managing of common aftereffects, and perhaps, neglects to reinforce the message that no additional protection against infection will be acquired until at least 12 days after vaccination.

2.7.5 The Commission heard the Zoe app currently does not request information on use of analgesics including paracetamol by contributors to manage vaccine aftereffects, but this could be potentially added.

2.7.6 The Commission asked if any contributors have reported anaphylaxis or severe systemic reactions. No events have been seen so far, although the review of the other column is still incomplete. There is also another limitation that contributors may be unlikely to report severe systemic reactions due to their condition and perhaps due to the knowledge that the healthcare professional should report via the Yellow Card Scheme. Contributors might also report once they have recovered, so there could be a time lag. Data on localised allergic reactions is being collected and can be provided in due course. Professor Tim Spector was also keen for the MHRA to highlight any potential side of effects of special interest or rare side effects that could be investigated further using the app's data sets. Data from the CDC and MHRA indicate rates of anaphylaxis to be ~1 in 100,000 for PfizerBioNTech vaccine recipients.

2.7.7 The vaccinated cohort appear well motivated and drop-out rates from the app are low, users consistently and frequently engage with the app, and other materials on the affiliated website, e.g. a webinar with 100,000 attendees; frequent feedback also helps retain contributors. Complete data is preferred and generally contributors that drop-out are not included in the analyses.

2.7.8 The app includes a system to permit reporting on behalf of elderly relatives: ~300,000 users are in this group. The median age of contributors is ~55 years so the coverage of the JCVI priority list is relatively good, although a full proportional analysis is needed. The Commission heard that symptoms and severity of symptoms could be further defined / sub-divided in the app's checklist, where the MHRA feels it may be useful, e.g. in line with emerging signals to improve granularity of the data. The need to gather more detailed information needs to be balanced against the risk of dissuading users / lowering compliance if reporting takes too long, for example if symptom lists are too exhaustive. An alternative option would be to email all contributors reporting a specific symptom and ask them to provide a detailed narrative.

2.7.9 MHRA and [redacted] agreed that continued liaison between the VRMM and the King's College team is beneficial and should be continued, including to discuss data linkage.

2.7.10 The MHRA was asked to assist with facilitating promotion of the app through the NHS.

2.7.11 The Chair gave thanks [redacted] for the valuable contributions Kings College and ZOE are making to increase data collection and analysis to help further understanding of COVID-19.

3. Bell's palsy and myocarditis rapid cycle analysis and observed vs expected

3.1 The EWG discussed a paper which presented summaries of the most recent epidemiological analyses of the incidence of Bell's palsy and myocarditis or pericarditis following COVID-19 vaccination. The EWG heard updates on the observed vs expected analyses of Yellow Card reports and the rapid cycle analysis being conducted in the Clinical Practice Research Datalink (CPRD).

3.2 The analyses specific to Bell's Palsy were described and the EWG discussed the inconsistent results. In particular, they discussed the finding within the rapid cycle analysis which suggested a higher observed number of cases of Bell's Palsy in the 42 days following the first dose of the Pfizer/BioNTech vaccine than expected based on age-specific background risks of Bell's Palsy calculated in the CPRD primary care data.

3.3 The EWG agreed that there were limitations to the analyses and as such they did not provide evidence of an increased risk of Bell's Palsy and should be treated with caution. However, they were broadly supportive of the initiation of a more robust epidemiological study to further explore the issue. They noted that such a study would allow for more careful case definition and identification and advised that sensitivity analyses should be conducted around the risk window. The EWG agreed that monitoring of Bell's Palsy should also continue with further consideration of incidence rates following the second dose of the vaccine.

3.4 The analyses specific to myocarditis/pericarditis were also described and the EWG discussed the statistical signal of an increased incidence in the 42 days following the first dose of the Pfizer/BioNTech vaccine in the rapid cycle analyses. It was noted that this was based on a small number of cases.

3.5 It was agreed that this was likely to be a chance finding given the body of evidence but that monitoring of myocarditis should continue given the overlap with multisystem inflammatory syndrome seen predominantly in paediatric patients with COVID-19 infection.

4. Trends in reactogenic adverse reactions with the Pfizer and AZ vaccines

4.1 The EWG was presented with a summary of Yellow Card data for the Pfizer/BioNTech and AstraZeneca COVID-19 vaccines focusing on cases capturing one of the relevant serious criteria available; hospitalised, life threatening, fatal, disability/incapacitation and "other" medically significant such as affecting everyday activities. The meeting commented on how subjective these categories can be for recording the severity of reactions.

4.2 The meeting heard that a higher proportion of cases reporting any serous criteria was identified for the AstraZeneca COVID-19 vaccine compared to the Pfizer/BioNTech vaccine, and that this difference was largely related to the more moderate "other" serious criteria. The types of events most commonly reported for both of the COVID-19 vaccine related to reactogenicity side effects known to be associated with the vaccines. It was noted that a higher proportion of cases are reported in females compared to males, and the meeting commented that this has been seen with other vaccines too and the potential biases behind this were discussed.

4.3 Compared with Yellow Card data available on the flu vaccine for the past 10 years, there is higher proportion of serious reports for the flu vaccine compared to the COVID-19 vaccine. The nature of the events reported in the serious categories was similar between the flu vaccine and the COVID-19 vaccines. The frequency and nature of events reported for the Pfizer/BioNTech COVID-19 vaccine was also similar to data provided by the ZOE COVID Symptom Study and US data published by the CDC.

4.4 The meeting was presented with the reporting rates broken down by age groups based on usage data of both COVID-19 vaccines, which showed a higher proportion of serious events reported in younger age groups, particularly in the "other criteria" and largely representing reactogenicity events. Similarly, clinical trial data for both vaccines showed a higher proportion of reactogenicity events being reported in the younger age groups. In comparison with the flu vaccine data, there is not such a pronounced difference in younger age groups. The meeting discussed which reporting biases may be contributing to this difference.

4.5 The meeting was also presented with Yellow Card data suggestive of a higher proportion of serious events reported following the second dose of the Pfizer/BioNTech vaccine compared to that reported with any dose. This is similar to data from the clinical trials and that reported from the ZOE COVID Symptom Study and US data published by the CDC. There is limited data to conduct a similar analysis with the AstraZeneca vaccine; a higher frequency of events with the second was not observed in the clinical trials.

4.6 The meeting discussed the available data on use in those with prior-COVID-19 infection and it was noted by the meeting that the MHRA were engaged with PHE on how best to gather further data on this topic. The meeting also considered the need for a second dose of the COVID-19 vaccines in those with prior-COVID infection and that further data was needed before any conclusions could be drawn.

4.7 The meeting agreed with the conclusions presented in the paper and that the data did not indicate any new safety concern for either of the COVID-19 vaccines currently in use.

5. General safety update for the AZ vaccine

5.1 The meeting heard an overview of the safety of the AstraZeneca Covid-19 vaccine as described by Yellow Card reports. The meeting heard that up to the end of 31st January 2021, an estimated 3,098,605 doses of COVID-19 Vaccine AstraZeneca have been given

in the UK. Up to 28th January 2021, the MHRA has received a total of 9681 reports of suspected ADRs in association with COVID-19 Vaccine AstraZeneca.

5.2 The reactions reported most frequently are common reactogenicity reactions seen with all vaccines as well as in the AstraZeneca clinical trials. These terms, or associated umbrella terms are labelled in the product information.

5.3 63 fatal cases were received, with most occurring in patients aged 80+ and with underlying comorbidities.

5.4 The meeting heard that cases of Bell's Palsy and transverse myelitis, which are adverse events of special interest, had been received. These are being monitored closely and Observed vs Expected and Rapid Cycle analyses are also being performed.

5.5 Overall, the ADR data was broadly in line with the safety profile seen in clinical trials. Review of the cumulative data does not identify any new safety signals.

5.6 The EWG found the safety data reassuring.

5.7 The EWG commented regarding anaphylaxis that a recent case had been identified of a patient who experienced anaphylaxis with a biological medicine and had a strong reaction upon skin testing to both polysorbate and PEG.

5.8 Regarding transverse myelitis, the meeting commented that we may not see all cases of transverse myelitis reported via the Yellow Card Scheme and that these may be seen in hospital. Observed vs Expected and Rapid Cycle analyses will also be important to pick up additional cases, but hospital admission and discharge data could be important in identifying cases.

5.9 The meeting suggested that use of prophylactic paracetamol could be proposed to reduce the number of adverse events experienced. However, it was recalled that the data regarding use of prophylactic paracetamol in clinical trials was limited and this was only recorded in a small number of participants. This data therefore could not be used to recommend prophylactic use.

6. Verbal update on Yellow Card Vaccine Monitor

6.1 The EWG was provided with an update on enrolment of individuals to the Yellow Card Vaccine Monitor (YCVM), part of the MHRA pharmacovigilance surveillance strategy for the COVID-19 vaccines.

6.2 The EWG heard that individuals are recruited through the national call-recall process for vaccinations and receive a letter following the national call inviting them for vaccination. The EWG heard that many individuals also receive invitations through local call-recall processes that the MHRA is considering linking into.

6.3 The EWG heard to date approximately 120,000 invites to register with the YCVM platform have been posted with the aim of enrolling 10,000 individuals in total.

6.4 The EWG heard that approximately 8,000 individuals have registered with the YCVM platform to date. The EWG also heard that an equal proportion of men and women have registered and 92% are aged 70 years and over. The EWG noted the proportion of younger people registered should increase once the priority groups have been vaccinated.

6.5 The EWG heard that around 92% of individuals registered were of white British or white Irish ethnicity and that consideration is being given to increasing the representation of other ethnic groups.

6.6 The EWG heard that of the 8,000 individuals registered, approximately 4,000 have entered details regarding their first vaccine dose and that an equal proportion have received the Pfizer-BioNTech or Oxford AstraZeneca vaccines as their first dose.

6.7 The EWG heard that a small proportion of immunocompromised individuals have registered, and it is anticipated this number will increase as this group is called in for vaccination.

6.8 The EWG considered the importance of this data collection and promotion of the YCVM platform could occur at the point of vaccination and continue throughout the vaccination programme to maximise numbers contributing to the platform.

6.9 The EWG noted that epidemiological studies and rapid cycle analyses form will enable linkage to hospital admission data with the YCVM data important as an additional data source providing long-term follow-up.

7. Verbal update on Janssen Vaccine Quality issues

7.1 The Commission heard two rolling review cycles have been undertaken in order to review the data on the Janssen vaccine provided so far. The data reviewed was of high quality, and no unresolvable issues are currently envisaged by the quality assessment team. Certificates of Analysis for small commercial-scale process performance qualification (PPQ) batches are not expected until after the 22nd February 2021. The February data package is also expected to include details of manufacturing scale-up. Comprehensive comparability data for scaled-up supply is not expected until early March and is intended to be assessed by variation to the conditional marketing authorisation, if given. There are no concerns presently in relation to the finished product stability data, and preliminary data showed that the product is stable to at least 6 weeks at room temperature.

7.2 In terms, of resolvable issues, an out-of-date GMP certificate dated 2017 has been provided for the drug substance manufacturing site, likely due to COVID related delays to the next planned inspection. Some key release potency acceptance criteria are also wider than those specified for the clinical trial material, and therefore an in-depth clinical justification of the wider limits will be required. The company have requested that no questions are to be sent by the MHRA, until the MHRA have been sent the questions/assessment reports from the European Medicines Agency (EMA).

7.3 The Chair conveyed to members that data package would likely be available to be seen by the EWG by late February/early March 2021, depending on when the data have been submitted and assessed (and potentially when the EMA's assessment has been received).

8. Any Other Business

8.1 None.

9. Date and time of next meeting

The next meeting is scheduled to take place on Monday 15th February 2021 at 10:30.

The Meeting today started at 10:34 and ended at 12:51

[redacted]

19th July 2021

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

NOT FOR PUBLICATION

COMMISSION ON HUMAN MEDICINES (CHM)

COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Monday 15th February 2021** at **10:30** via videoconference

Participants Present

Members

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

Apologies

Professor T Solomon

Member of the CTBV Expert Advisory Group

Professor B K Park
Professor M Turner

Members of the CPS Expert Advisory Group

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

Invited Expert

[redacted][3]

Observers

[redacted]

Secretariat

[redacted]

[1] Left during item 9
[2] Left during item 8 & [3] supporting specific items

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD

MHRA Presenters supporting specific items[3]

[redacted] - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - MHRA-NIBSC
[redacted] - LD

MHRA Observers

[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - LD
Dr S Branch - VRMM
[redacted] - LD
[redacted] - MHRA-NIBSC
[redacted] - VRMM
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[redacted] - LD
[redacted] - MHRA-Policy
[redacted] - LD
Mr K McDonald - LD
Ms T Moore - IE&S
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - MHRA-NIBSC
Ms N Rose - MHRA-NIBSC
[redacted] - LD
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Key

LD = Licensing Division
NIBSC = National Institute for Biological Standards & Control
VRMM = Vigilance & Risk Management of Medicines
CTBV = Clinical Trials, Biologicals & Vaccines EAG
CPS = Chemistry, Pharmacy & Standards EAG
IE&S = Inspection, Enforcement & Standards

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 declared interests and other relevant interests for this meeting:

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

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

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

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

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

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

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

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

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

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

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

Professor Weir - NPNS - Imperial College and Other relevant interest arising from his department collaborates with Imperial College on a number of clinical trials.

CTBV

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

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

one of the manufacturing clean room suites at the Stevenage Centre. Professor Turner understands that this will be for contract AAV manufacture.

CPS

Mr V'lain Fenton-May – None

Mr Robert Lowe – None

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

Professor Kevin Taylor – None

Dr Susannah Walsh – None

1.4 Apologies were received from Professor Solomon for the meeting today.

1.5 The Chair welcomed [redacted] from PHE as an Invited expert for Item 2 - Update on Impact Surveillance. [redacted] left the meeting after his presentation.

1.6 The Chair also welcomed [redacted] of HSCNI and [redacted] of Public Health Wales as Observers for Items 4 & 5. The Observers left after item 5.

2. Update on Impact Surveillance

2.1 The EWG viewed slides and heard a presentation from Public Health England (PHE) on an update on Impact Surveillance. A presentation three weeks earlier consisted of analysis on Pillar 1 and Pillar 2 routine testing data. This update concerns data analyses from Pillar 1 and Pillar 2 data, SIREN (Sarscov2 Immunity and REinfection EvaluatioN) study data, the Severe Acute Respiratory Infection (SARI)-Watch surveillance system and the Royal College of GP (RCGP) Database.

2.2 Pillar 1 and Pillar 2 update

2.2.1 The EWG heard an update on the analysis of available Pillar 1 and Pillar 2 data; the data is linked to the National Immunisation Management Service (NIMS) database. The focus of the analysis was vaccine effectiveness (VE) for Pfizer and AstraZeneca (AZ) vaccines, rather than any impact analyses data.

2.2.2 The EWG heard that the Pillar update includes new data for AZ, the over 70s cohort population, analysis of cohorts with repeat testing and care home analysis.

2.2.3 In summary, PHE reported that VE against symptomatic diseases reaches 60-65% in the over 70s and ≤ 65 HSCW (health and social care workers) after the first Pfizer dose. There is a continued apparent reduction from day 35, but continued monitoring is required to discount any possible bias. After the second Pfizer dose, VE reaches approximately 85% in the over 70s and approximately 90% in < 65 HSCW. The VE of the AZ dose against symptomatic disease was shown to increase from 21 days.

2.2.4 EWG also heard that interim analysis of the data showed (i) preliminary evidence of VE against infection from Pfizer vaccine in HSCW (stronger evidence provided in the Siren data,

see below) and care home residents (ii) preliminary evidence of VE against infection from AZ in HSCW but not yet in care home residents (iii) Evidence of reduced mortality in vaccinated cases (Pfizer).

2.3 SIREN update

2.3.1 EWG heard that for this update the vaccination data sources were National Immunisation Management Service (NIMS) dataset and self-reporting via Siren questionnaires.

2.3.2 EWG heard that participants were assigned to cohort based on baseline antibody status (at 07 December 2020); positive cohort participants - antibody positive or evidence of infection and negative cohort – antibody negative and no previous positive test. The outcome for analysis was infection (positive Polymerase chain reduction test; PCR+) in the negative cohort.

2.3.3 EWG heard that this study had better defined cohorts of under 65 HSCW than that found in the Pillar cohorts.

2.3.4 The EWG heard that the Siren interim data showed vaccine effectiveness of 60-74% against infection at 21 days after a single dose of Pfizer vaccine in the negative cohort. The invited PHE expert indicated that future analyses may include symptomatic infection and hospitalisation.

2.4 Cohort analysis within the Royal College of General Practitioners (RCGP) Database

2.4.1 EWG heard that PHE conducted an analysis within the RCGP database, which is a General Practitioner (GP) cohort dataset. This database allows adjustment for more variables than is possible with the Pillar data, while still using the PCR-positive data that arise from the Pillar data. Initial analyses included the 80+ population, over the period 07/12/2020 – 24/01/2020 who tested PCR-positive and had a GP consultation with symptoms/clinical illness consistent with COVID-19 around the time the test was taken. This was compared against a Test-Negative Case Control (TNCC) data set.

2.4.2 PHE concluded that the results from analysis were broadly consistent with routine testing data. VE after one dose was 60-65% and 50% for the TNCC cohort. After two doses, vaccine effectiveness was 85% and 70-75% for the TNCC cohort.

2.4.3 The invited PHE expert indicated that future analyses would focus on VE within clinical risk groups.

2.5 SARI-Watch surveillance system

2.5.1 EWG heard that the Severe Acute Respiratory Infections (SARI)-Watch is the surveillance system for new Covid 19 hospitalisations.

2.5.2 EWG heard that analysis was restricted to elderly with Covid with symptoms. Hospitalisations were matched against the National Immunisation Management Service (for vaccination status with the Pfizer vaccine), age, sex, geographic region and period. The data was not adjusted for care home residents.

2.5.3 PHE reported that preliminary evidence shows that Pfizer vaccine is effective at preventing hospitalisation in patients in the 80+ age group (75%-80% reduction), compared to those that had not been vaccinated. It should be noted that the low number of hospitalisations seen immediately after vaccination is likely related to the deferral effect, where patients testing positive for Covid-19 or showing symptoms have their vaccinations deferred.

2.5.4 The invited PHE expert concluded overall that the preliminary evidence showed that the Pfizer vaccine was effective in preventing hospitalisations and that evidence through the Pillar 2 mortality analysis showed a lower risk of death in recipients of the Pfizer vaccine.

2.5.5 The PHE expert commented on the potential biases that cause the differences between real world data and trial data.

2.6 EWG discussion/comments

2.6.1 EWG asked whether the invited expert was able to link the efficacy data to variants. PHE stated that early data reflect the older variants and the majority of the data now emerging is against the newer variants. EWG heard that PHE does receive some data from the Lighthouse labs that would allow split along the lines of efficacy against older and newer variants. However, this sub-set of the data shows the same effect, but with wider confidence intervals.

2.6.2 EWG asked the PHE expert whether analysis of the Royal College of General Practitioners (RGCP) data was possible to look at effects on recipients of the vaccine who are on immunosuppressants. The invited expert indicated that this analysis would be conducted alongside other collaborators and result were expected soon.

2.6.3 EWG were interested in possible data to show whether protection is seen a few days after vaccination, which could be related to an adjuvant effect and could be very important to patients who are immunocompromised. The PHE expert thought that there is potential for a lot of bias in the day 0 to 3 data, but that interesting data regarding the severity of symptoms could be shown.

2.6.4 EWG asked for further information on the relationship between immunogenicity and the efficacy of the vaccines, given that some data show that immunogenicity (antibody levels) is lower in the over 65s. The PHE expert stated that they would like to see more antibody data in the over 65s before coming to any conclusions. However, the PHE expert stated that their efficacy results in the over 65s were higher than those seen in the Real-time Assessment of Community Transmission (REACT) study results.

2.6.5 EWG commented that it will be interesting to see the data for the end of February/start of March, i.e., when recipients who received their first dose at vaccine rollout will reach 12 weeks and receive their second dose.

2.6.6 EWG commented on parallel analyses conducted in Scotland and England, where the dataset reliably identified subjects that were known HSCW at time of test. Within this subset, the response was consistent with that presented by PHE over the interval 21 days- 6 weeks. As they have a fifth of the population, the dosing interval is wider in Scotland; however, the pattern is similar.

2.6.7 EWG stated that they looked forward to the next update.

3. Proposed statement on "flu like illness" for Pfizer/BioNTech and AstraZeneca COVID 19 vaccines – Verbal update

3.1 The meeting heard that flu like illness is a recognised side effect of the vaccines, and the EWG had previously discussed and agreed that further communication on this side effect was required to better inform patients on how this might present in patients. The EWG were presented with proposed wording to further characterise "flu like illness" in the information

for UK recipients and healthcare providers for the Pfizer/BioNTech and AstraZeneca COVID-19 vaccines, and for a similar statement to be included in the ADR data publication.

3.2 The EWG supported the inclusion of this statement and the EWG noted that it was important the information was worded in way that would be reassuring to recipients and that the advice is consistent with information provided in other patient leaflets on COVID-19 vaccination produced by the UK healthcare agencies. The EWG considered that the event of heart palpitations required further characterisation before it should be included in the product information for the vaccines.

4. Safety update on Pfizer/BioNTech COVID-19 vaccine

4.1 The EWG was presented with a second safety update for the Pfizer COVID-19 vaccine. The EWG was informed that the ADRs being reported for the vaccine were broadly in line with the known safety profile for the vaccine and that seen in the clinical trials. The EWG also heard that the signal of Bell's palsy has persisted in the observed/expected analysis and that the planned formal epidemiological study was progressing. The EWG were informed that the possible signal of myo/pericarditis which had been detected in the Rapid Cycle Analysis has continued to diminish and was likely a chance finding. The meeting discussed that there was a slightly lower reporting rate in the past month compared to previously and was reassured that promotion of the scheme was ongoing.

4.2 The meeting was presented with a summary of the anaphylaxis reports received through the Yellow Card scheme and related international data, and that the nature and frequency of events is similar to that reported previously for the Pfizer/BioNTech. The meeting discussed concerns from healthcare professionals and the JCVI COVID-19 subcommittee on the risk of transmission related to the 15-minute observation period which was introduced following initial reports of anaphylaxis with the Pfizer/BioNTech COVID-19 vaccine. The EWG acknowledged the practical constraints of the observation time and representatives from HSCNI and PHW noted that there was no direct evidence of increased COVID-19 transmission due to the waiting time. The EWG highlighted that there was limited data on the risk of anaphylaxis with the second dose. The meeting concluded that the 15-minute wait should remain in place until more data is available to support its removal.

4.3 The meeting concluded that of the data presented overall in the safety update that no new safety signal has been identified.

5. Review of fatal reports for the AstraZeneca and Pfizer/BioNTech COVID-19 vaccines

5.1 The EWG was presented with a paper which gave an overview of fatal reports received by MHRA to date. The paper presented cumulative vaccine exposure, broken down by age and discussed the analysis MHRA has performed on fatal reports, as well as international data available. The EWG noted that observed/expected analysis did not indicate an excess of deaths; however, it was acknowledged that these analyses are used with caution to assess mortality.

5.2 The meeting broadly found the data reassuring. It was noted that there was significant under reporting of fatalities to the Yellow Card Scheme and that there can be difficulty in interpreting the data where reports are sparse. The EWG discussed whether Hospital Episode Statistics data could be used to support Yellow Card data but noted that there is a 3 month lag to this data.

5.3 The EWG agreed with the conclusion that there was not a signal indicating an increased risk of death following vaccination.

6. Regulatory approach to new variants – feedback from international regulators' meeting

6.1 The EWG were informed about recent discussions held with other international regulators. While there is broad agreement about a more tailored approach to regulating SARS-Cov2 vaccine variants, it was highlighted that the draft MHRA guidance document required more discussion in its non-clinical and clinical sections. For the non-clinical section, experts emphasized the novelty of the coronavirus and the need, in principle, for a sufficiently large non-clinical database overall. It was appreciated, however, that the extent would depend on the knowledge already gained and the particular format of a given vaccine, and therefore agreed on an approach where absence of non-clinical data, including immunogenicity, will have to be justified by the Applicant. It was agreed that generation of non-clinical data should not delay the development and introduction of updated coronavirus vaccines. It was highlighted that SARS-Cov2 variants which are adapting to humans may be less pathogenic in animals, rendering animal challenge studies less straight-forward.

6.2 For the clinical part, the Expert Group noted that MHRA does not propose to ask for head-to-head non-inferiority studies on neutralising antibodies, but rather asks for studying humoral and cellular immune response (including neutralising antibodies) with the new variant, comparing with a panel of convalescent sera. Experts broadly agreed with this approach, in absence of knowledge of a meaningful non-inferiority margin.

7. Supply of AZ vaccine from SII

7.1 The EWG viewed slides and heard a presentation from MHRA concerning a paper assessment of an application under Regulation 174 (R174) to approve three named batches of ChAdOx1 nCov-19 vaccine from the Serum Institute of India (SII), a major facility in India, for use in the UK national vaccination programme. The assessment has been expedited to approve before the shelf-life expiry is reached.

7.1.1 The EWG heard that Covishield was developed in collaboration with Oxford University and AstraZeneca (AZ). The technology to manufacture this vaccine along with virus seed and cell banks were received from Oxford/AstraZeneca. The product has been approved in 10 countries and 34.5 million doses have been distributed worldwide by the end of January 2021.

7.1.2 The EWG heard that SII has provided MHRA with full Modules 1, 3 and 5 of the dossier, and some additional batch release data for the three named batches. The full-scale 2000 litre batches will be manufactured on two different lines in the SII facility.

7.1.3 The EWG also heard that AstraZeneca has transferred manufacturing process and key analytical methods for Covid-19 ChAdOx1 vaccine to SII. There have been some changes to manufacturing, however with no material effect to the product.

7.1.4 The EWG heard that manufacturing and testing of the seeds/banks appear largely acceptable, but some questions are raised re methods validation/missing reports. Questions have also been raised concerning testing for adventitious agents.

7.1.5 The EWG heard that the specifications for drug substance and drug product are almost identical to AZD1222. Data submitted confirm R174 batches conform to AZ R174 specifications (SII has provided a commitment to adhere to the AZ specifications previously approved as per R174). Analytical methods/validation were also assessed as generally acceptable.

7.1.6 The EWG heard that satisfactory stability data for 4 weeks at 2-8°C have been presented for the drug substance and inspection feedback confirms acceptable on-site procedures for storage and transportation within the facility. Currently limited stability data is available for the drug product; further stability data has been requested. The proposed shelf life is 6 months at 2-8°C The regulation 174 batches were manufactured in October 2020, and therefore, MHRA would require additional assurance over stability before these batches can be accepted with a > 6 -month shelf-life. The in-use shelf-life of 6 hours stored at 2 to 25°C is acceptable.

7.1.7 Concerning the dossier, MHRA concluded that subject to satisfactorily resolving the requests for further information (RFIs) the product demonstrates sufficient comparability to the Oxford/AZ vaccine, the manufacturing process is reproducible, and in control and the dossier provide sufficient data concerning safety of the product. However, additional stability data is required before an increased drug product shelf life can be assigned. Further, safety of the batches with regards to adventitious agents needs to be assured. The MHRA considered that if all RFIs are resolved (some immediately, some as a commitment), these R174 batches could be approved and could be labelled as AZ batches.

7.1.8 The EWG heard that SII is making/planning future changes to the manufacturing process, mainly related to changes in fermentation parameters (SII Process IV) and will make it more similar to the AZ Process IV. The process is currently undergoing validation with tentative completion late February 2021.

7.1.9 The EWG also heard the MHRA assessment of the interim report of the immunogenicity and safety bridging study performed in India (Interim CSR) submitted to support the application. EWG heard that safety data has been provided from 1600 subjects who received at least one vaccination with either Covishield (1200), placebo (300) or AZD1222 (100) in the immunogenicity and safety study. Reactogenicity was assessed in the same subpopulation as immunogenicity. The immunogenicity results indicate that Covishield can be considered noninferior to AZD1222 vaccine. In summary, there are no concerns about the safety of Covishield and its reactogenicity is broadly comparable to that of AZD1222.

7.1.10 MHRA requested whether EWG agrees that (i) the three named batches to be approved under R174, if RFIs are resolved and appropriate conditions are imposed (e.g. independent batch release, etc), (ii) that MHRA approves individual SII batches on the basis that they have consistent quality and production with the batch data obtained for the R174 batches, (iii) assuming the committee agrees to point (ii) would the committee wish to re-discuss regarding individual batches produced by the updated SII process (SII Process IV) before MHRA approved them.

7.2 EWG comments/discussion

7.2.1 The EWG asked the MHRA for an update concerning inspection of the facility. EWG heard that the MHRA-GMP inspection has been conducted and is to be concluded with the company imminently. No critical deficiencies had been raised and the conditions for supply would follow normal Marketing Authorisation Application routes (importation testing would be required and independent batch release by NIBSC would be specified in the conditions).

7.2.2 The EWG also requested an update from NIBSC regarding batch testing. EWG heard that NISBC had received samples of the R174 batches, and these were currently on test. NISBC assured the EWG that the same suite of testing as performed on the AZ vaccine would be applied to the R174 batches and the batches would also be tested against the AZ specifications (with respect to product appearance, the identity and the infectivity). Test results are expected later this week.

7.2.3 The EWG asked why these batches have become available, seeing that these batches are coming out of a geographical area which would be expected to have great need for these vaccines (India). The EWG was informed by MHRA-LD that the R174 batches were coming towards the end of their shelf life and run the risk of going out of date; it was considered that the UK, more so than others, have the logistics to deploy them quickly. NIBSC further commented that the MHRA had experience testing product from SII and results had been reassuring.

7.2.4 The EWG discussed the issue concerning the remaining shelf life on the product and concluded that the issue of deployment was outside the remit of the MHRA.

7.2.5 Concerning the quality data provided, EWG considered that overall, the quality aspects of the three discussed batches were acceptable once a small number of issues related to pathogen safety were satisfactorily resolved. These must be resolved before the batches are approved. The remaining concerns can be resolved as commitments. EWG was reassured, for the present time, that the clinical, immunogenicity and safety data is generally equivalent to the AZ vaccine.

7.2.6 The EWG endorsed the MHRA recommendations concerning approval of the R174 batches; once relevant quality issues are satisfactorily resolved EWG endorses the application being forwarded for CHM consideration for approval under R174. Further, EWG confirmed that there was no need for EWG to re-discuss individual batches produced by SII Process III or IV before MHRA approve them.

8. Updated efficacy analysis of AZD1222 vaccine and updated UK information for HCPs

8.1 The EWG was presented with an updated efficacy analysis based on the 07-12-2020 data cut off and which included all four studies (Cov001, -002, -003, and -005). This analysis will be presented in the updated UK Public Assessment Report (UKPAR) and updated Information for Healthcare Professionals (HCPs). The primary endpoint of vaccine efficacy was 66.7% (95%Confidence Interval [CI] 57.4, 74.0) with no severe cases/hospitalisations in the vaccinated participants. The efficacy with a dosing interval ≥ 12 weeks was 80.0% (95%CI 65.2, 88.5). Analyses incorporating both asymptomatic positive and symptomatic positive cases in the UK COV002 trial were further explained to show that the vaccine is reducing not only the proportion of symptomatic cases, but also the overall proportion of PCR-positive cases. This shows that the vaccine is reducing the transmission rate.

8.2 Apart from updated efficacy and immunogenicity data in the UK Information for HCPs, there will be changes to the safety data presented with the addition of anaphylaxis and diarrhoea in the list of Adverse Drug Reactions (ADRs) and corrections of frequency in a few reactogenicity ADRs. Slight differences in the safety sections with the EU-approved SmPC were highlighted, the main one being that in Section 4.4, the EU SmPC recommendation of close observation for at least 15 minutes following vaccination, in line with the other approved vaccines in the EU.

8.3 EWG comments/discussion

8.3.1 The EWG asked whether updated data was available from all studies on the median duration of follow-up following administration of the two vaccine doses. MHRA indicated that this information was currently awaited, as confirmation of the median duration of follow up had already been requested from AstraZeneca.

8.3.2 The EWG also raised concerns that the control arm of the study would have a diminishing number of subjects with time, as they are vaccinated in line with their national vaccination schemes. MHRA has confirmed that this is the case. The EWG asked for confirmation from

AZ of what they would be doing with their control arm in the future. MHRA confirmed that a protocol amendment to the UK studies had been approved to that effect.

8.3.3 One EWG member commented that anecdotal feedback received from patients would indicate that information being provided by health professionals to patients at the time of vaccination is inconsistent with scientifically established information, e.g. patients have reported being informed that vaccine effectiveness post vaccination is 2 weeks rather than 3 weeks. EWG recommended that MHRA liaise with the public health bodies to ensure clearer, consistent, unequivocal information is provided to patient concerning vaccination and vaccine effectiveness.

8.3.4 Overall, it was agreed that the UKPAR and the HCPs should be updated with the new information.

9. Analysis of ADZ1222 vaccine against new variants

9.1 The EWG was presented with recent results (submitted for publication) of AZD1222 vaccine against SARS-CoV-2 variants.

9.2 The first paper relates to the UK variant B.1.1.7. Vaccine recipients had neutralisation titres 9-fold lower against the B.1.1.7 lineage than against the Victoria lineage. However, the UK COV002 study showed an efficacy of 75% against the B.1.1.7 variant compared to 84% against the other variants to prevent symptomatic disease and an efficacy of 67% compared to 81%, respectively, to prevent any SARS-CoV-2 infection. An evaluation of viral load in the nasal swabs showed lower viral load in vaccinated participants compared to controls and in asymptomatic subjects compared to symptomatic subjects. Likewise, the duration of positivity of nasal swabs was shorter in vaccinated participants compared to controls and in asymptomatic subjects compared to symptomatic subjects. It was not different between the B.1.1.7 and non-B.1.1.7 variant cases.

9.3 The second paper relates to the South-African variant B.1.351. A [redacted] assay performed in 19 seronegative vaccinees showed that, out of 18 participants with neutralisation activity against B.1.1, 10 (56%) had undetectable neutralisation activity against the B.1.351 variant and the remaining eight showed a 2.5 to 31.5-fold relative reduction in neutralisation. The South-African COV005 study showed an overall efficacy of 22% whereas most cases (39/42) were due to the B.1.351 variant. In contrast, the efficacy after the first dose until 31.10.2020 (i.e., before circulation of the SA variant), a proxy for non-B.1.351 variant infection, was 75%, in line with the UK results.

9.4 EWG discussion/comments

9.4.1 The EWG considered that the data relating to the UK variant was reassuring. The EWG noted that whilst the data regarding the SA variant was more concerning, it is unknown yet whether the vaccine could still protect against severe disease. Given the age of the participants (median of 31 years), the SA trial is unlikely to address this question. The EWG also discussed the current thinking in relation to the role of T cells in the response to SARS-CoV-2, and in particular, that T cells may be more important in protection against severe disease. It has been proposed that T cell response may be preserved against variants due to cross-reactivity of T cell epitopes although what this means clinically is not yet known.

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

10.1 None.

11. Date and time of next meeting

The next meeting is scheduled to take place on Thursday 25th February 2021 at 12:30.

The Meeting today started at 10:33 and ended at 14:08

[redacted]

19th July 2021

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

COMMISSION ON HUMAN MEDICINES (CHM)

COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Thursday 25th February 2021** at **12:30** via videoconference

Participants Present

Members

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

Apologies

Professor P Shah

Member of the CTBV Expert Advisory Group

Professor B K Park
Professor M Turner

Members of the CPS Expert Advisory Group

Mr VI G Fenton-May
Mr R Lowe
Professor Y Perrie[3]
Professor K M G Taylor (Chair of CPS)
Dr S Walsh

Invited Expert

[redacted][4]

Secretariat

[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD

Presenters supporting specific items[4]

[redacted] - PHE
[redacted] - VRMM
[redacted] - LD
Dr P Bryan - VRMM
[redacted] - MHRA-NIBSC

MHRA Observers

[redacted] - VRMM
[redacted] - LD
Dr S Branch - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - VRMM
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[redacted] - MHRA-NIBSC
[redacted] - LD
Ms N Rose - MHRA-NIBSC
[redacted] - LD
[redacted] - VRMM
Mr P Tregunno - VRMM
[redacted] - MHRA-NIBSC
[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

[1] Left during item 3
[2] Joined during item 4
[3] Joined during item 3
[4] supporting specific items

1. Introduction and Announcement

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Professor Weir - NPNS - Imperial College and Other relevant interest arising from his department collaborates with Imperial College on a number of clinical trials.

CTBV

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

Professor Turner – NPNS interest. Professor Turner is a Non Executive Director (non-remunerated) on the Board of the Cell and Gene Therapy Catapult (CGT) until the end of March. CGT have been tasked by UK Government with re-purposing a factory in Braintree

to manufacture either a vaccine or a therapeutic mAb. No decision has been made as to whether or what product CGT Braintree may be asked to manufacture and that decision will be made by UK Government. Professor Turner does not believe that CGT Board will have any material input into the decision as to what product may be manufactured. Rentschler have signed a contract with the Cell and Gene Therapy Catapult (CGT) to rent one of the manufacturing clean room suites at the Stevenage Centre. Professor Turner understands that this will be for contract AAV manufacture.

CPS

Mr V'lain Fenton-May – None

Mr Robert Lowe – None

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

Professor Kevin Taylor – None

Dr Susannah Walsh – None

Invited Experts for this meeting

[redacted] – Other relevant interest – The Immunisation Dept at PHE does sell surveillance reports on Meningococcal and Pneumococcal vaccination and disease on cost recovery basis to GSK and Pfizer. [redacted] does not have any personal conflicts of interest.

[redacted] – None

1.4 Apologies were received from Dr Riordan for the meeting today.

1.5 The Chair welcomed [redacted] from PHE as an Invited expert for Item 2 - Update from PHE. [redacted] left the meeting after his presentation.

1.6 The Chair also welcomed [redacted], Consultant Haematologist and Professor of Lymphoma Biology, Kings College Hospital as an Invited expert for Item 4 - COVID-19 Vaccines and risk of immune thrombocytopenia. [redacted] participated for this item only.

2. Update from PHE on the effectiveness of vaccines (Pfizer and AZ)

2.1 The EWG heard an update from [redacted] of Public Health England on vaccine effectiveness data gathered following deployment of Pfizer/BioNTech and AstraZeneca vaccines. The facets of the presentation covered data collected from the following sources: routine testing, SIREN study, General Practitioner cohort study (from Royal College of GPs), hospitalisations, SARI watch, and vaccine impact data.

2.2 In summary, Pfizer vaccine effectiveness against symptomatic disease in older adults shows dose 1 reaches 60-70%, dose 2 reaches 85-90%. AZ vaccine effectiveness against symptomatic disease in older adults shows dose 1 reaches 60-75% and this has not yet

plateaued. The national data provide suggestive evidence of population level impact on hospitalisations and deaths.

2.3 The Chair noted it is reassuring that the results from England, Scotland and Israel on vaccine effectiveness show a great degree of consistency. The Chair also noted that extended interval data on the Pfizer vaccine from Scotland was an exception in that a decline in vaccine effectiveness with an increased interval between first and second doses was present in the data. The EWG noted the analysis plan for the dataset from Scotland will be honed to study the result. The present assumption that the result is not representative of a true effect, but rather an error due to the smaller sample size. The invited expert noted that the longer follow-up data (post 60 days second dose) shows that the Pfizer vaccine takes longer to generate effectiveness in the older subjects, and the uptrend in cases with a longer interval is too minor to produce any concerns. The Chair noted the recent data from the Real-time Assessment of Community Transmission (REACT-2) study show antibody levels are sustained after the first dose of the Pfizer vaccine to at least 36 days, further supportive of that vaccine efficacy reflects a sustained immune response, with no indication that protection is declining.

2.4 The EWG noted that outside of specific studies, systematic sequencing of samples from hospitalised cases in pillar 1 is not being undertaken. The EWG noted the measures to track potential escape variants in the UK datasets was currently limited. The EWG discussed the importance of enriching the sampling (viral genome sequencing) of vaccinated individuals admitted to hospital ("breakthrough cases"), in particular those with symptom onset beyond the date where protection from the vaccine is estimated to occur. Enrichment of sampling in this manner would likely serve to track potential vaccine escape variants of clinical concern more effectively. The invited expert agreed to refer the suggestion to PHE and noted that targeting severe populations (for example hospitalised individuals) would indeed, likely offer over advantages over the random sampling approach.

3. Marketing Authorisation requirements for new COVID-19 vaccines

3.1 Existing guidance on the development of new vaccines when effective vaccines are available and approved was presented. Three situations are possible. 1) There is an established correlate of protection. In that case, no comparative study to an approved vaccine is required. 2) A specific immune response is reasonably likely to predict protection. In that case, a comparative immunogenicity trial may be acceptable. The design of a non-inferiority immunogenicity trial was detailed, including its endpoints (neutralising/binding antibodies, T-cell response), its parameters (geometric mean titre, seroconversion rate), its non-inferiority margin. In addition, safety data (at least 3000 subjects) and post-approval effectiveness studies would be required. However, it was questioned whether this strategy is possible across different manufacturing platforms. 3) There is no approved vaccine of a similar platform. In that case, if a placebo-controlled trial is not feasible, a comparative efficacy trial is required (superiority or non-inferiority). It was questioned whether it might still be possible to justify an immunogenicity comparison between vaccines of "similar" platforms, e.g., inactivated vaccine vs subunit vaccine, and finally whether animal studies or human challenge studies might help support the choice of a comparator.

3.2 The EWG noted that new approaches to define correlates of protection are available which study more than a single antibody level, but comparison between trials is hindered by a lack of standardisation. Ratios of neutralising or binding antibodies to convalescent sera antibodies are being calculated to aid comparative analyses across trials. The EWG noted that the MHRA will most likely need to collaborate with international bodies to facilitate a broader understanding of, and to gather the information required to reliably define the correlates of protection.

3.3 The EWG noted correlates of protection are difficult to establish across different vaccine platforms. For viral vector and mRNA vaccines, in addition to inducing antibody responses these COVID-19 vaccines also provoke fairly potent T-cell responses, whereas theory suggests sub-unit vaccines may trigger lower levels of T-cell responses. The challenge will be to qualify the implications of such differences for immunity in vaccinated subjects and this may be an unrealistic goal.

3.4 The EWG noted standardised assays on variants could promptly be launched at NIBSC, and potentially could be used to assess immunity across vaccine platforms. The EWG heard that NIBSC are exploring using the international standard to compare neutralising assays across various platforms when challenged with different viral variants, but this work is presently hindered by the absence of normalisation of variants in the assays. Therefore, it cannot be ruled out that the intrinsic behaviour of the variant is responsible for any difference in the titres. One of the members of the EWG, offered to assist NIBSC to identify groups that could share provide relevant expertise on variant assays.

3.5 The MHRA informed the EWG that in the absence of correlates of protection, companies are seeking scientific advice from the MHRA with regard to their trial designs. The Chair signposted the trial design proposed by Valneva SE. The company are proposing an immunogenicity and safety trial of 4000 participants, 600 of which will have immunogenicity data collected, with efficacy as a secondary endpoint.

3.6 The EWG noted a method to evaluate a vaccine would be to study equivalent responses in convalescent sera. To benchmark vaccine efficacy, the vaccine should perform better in the same assay / assays when compared to sera of patients that have recovered from natural COVID-19 infection. The EWG noted neutralisation is only one component of the immune response but that T-cell responses are also likely to be important, and as such should also be evaluated. A member raised the data on variants from neutralisation activity compared to efficacy data from clinical trials, the correlation between the two appears clear. The expert also noted the currently emerging consensus is that T-cell responses are unlikely to contribute to protection in the immediate post-vaccination period but will be key for longer-term protection and potentially also in lowering the likelihood of progression to severe disease or death.

3.7 The EWG noted in the absence of correlates of protection, it is best to measure both antibody and T-cell responses as surrogate measures of efficacy.

3.8 The EWG noted that establishing robust measures of the durability of the immune responses caused by COVID vaccines is critical to understanding vaccine efficacy.

3.9 The Chair informed the panel that the EMA appear to be supportive of companies pursuing a non-inferiority approach to immunogenicity trial designs. The EWG statistical expert noted that ascertaining clinical meaning from a non-inferiority margin of a surrogate scale such as neutralising titres is challenging, however non-inferiority studies of other vaccines such as the flu vaccines could be used as an exemplar to follow. The statistical expert continued that more data would be needed for COVID-19 vaccine candidates and suggested that trial designs factor-in the gathering of data that would likely support the discerning of correlates of protection.

3.10 The EWG noted a potential future perspective is to test vaccine efficacy in human challenge models.

3.11 The MHRA informed the EWG that the rationale for the choice of the AZ vaccine as a comparator in the planned Valneva SE trial is not substantiated. The MHRA had also

considered whether a sub-unit vaccine may represent a better choice of comparator in the absence of any licensed vaccine using the same platform technology as Valneva.

3.12 The MHRA informed the EWG that at minimum a regulatory perspective is required on the choice of comparator ahead of the next scheduled meeting with Valneva. The Chair acknowledged that the company should justify the choice of comparator, the dose interval, and the trial age range / group (as the majority of the older population in the UK are, or will be vaccinated by the recruitment period), the company also need to be informed it will be mandatory to undertake a post-authorisation vaccine effectiveness study.

3.13 The MHRA informed the EWG that there are limited countries where placebo-controlled studies would be possible due to the varied national vaccination campaigns in progress.

3.14 The EWG were invited to consider the choice of comparator. The EWG noted that assessing the advantages and disadvantages of using comparators that utilise different platform technologies (from sub-unit vaccines, whole inactivated vaccines, mRNA, to vector vaccines) is problematic as none seem ideal, including sub-unit vaccines, and substituting comparators would not solve the issue. The EWG noted a paper comprising the views of regulators and scientists on non-inferiority challenges in different settings is expected to be published shortly. The Chair acknowledged that regulatory alignment on the global stage will be important in the near future, and it would be beneficial to promptly commence discussions with other regulatory bodies. In the immediacy, Valneva should justify their choice of comparator, including that it is a different platform technology and the proposed dosing interval.

4. COVID-19 Vaccines and risk of immune thrombocytopenia

4.1 The EWG heard reports of immune thrombocytopenia (ITP) for the Pfizer/BioNTech vaccine, AZ vaccine and the international data on the same topic for the Moderna vaccine which is not currently used in the UK. The reports were heard in the context of vaccination coverage in the UK, which at the time of the meeting, it was estimated that over 10 million doses of the Pfizer/BioNTech vaccine have been administered in the UK as of 21 February 2021 and over 8.4 million doses of the AstraZeneca COVID-19 vaccine have been administered in the UK as of 21 February 2021.

4.2 Pfizer/BioNTech have also reviewed events of immune thrombocytopenia in the context of observed vs expected analyses for international usage of their vaccine and did not identify an increased rate in excess of that expected. The meeting also heard that a review by the US Centre for Disease Control (CDC) covered data to 27th of January 2021 and also did not identify a signal of ITP.

4.3 The EWG focused on two key questions a) if the vaccine is causally related to de novo cases of ITP, and b) If there is a signal to suggest the vaccine could exacerbate pre-existing ITP.

4.4 The EWG noted that diagnosis of ITP requires a thorough clinical assessment; however the details within the reports are varied in terms of the level of assessment of the patient as undertaken by the healthcare professionals. The EWG discussed the limited influence that one particular case should have on the considerations, because this patient's low haemoglobin was suggestive of other haematological disease. This case aside, overall the number of plausible ITP cases appears sufficient to justify continued monitoring.

4.5 The EWG discussed the biological plausibility of the potential signal. The EWG noted that vaccines used in other diseases have been causally linked with cases of thrombocytopenia (TP); in some of these instances the adjuvant has been theorised to be responsible, but the identification of TP cases across different vaccine preparations and technologies somewhat

challenges this view. The EWG also noted that COVID-19 infection can also cause thrombocytopenia not only by means of increased platelet turnover, but direct platelet infection by SARS-CoV-2. Therefore, concomitant COVID-19 infection needs to be thoroughly evaluated as potential confounding factor. It was confirmed that the majority of the reports state 'negative' for concomitant COVID-19. In summarising remarks, the EWG noted it was plausible that ITP could potentially be associated with each of the three vaccines discussed.

4.6 The EWG noted the number of ITP cases likely represents a borderline signal with the Pfizer/BioNTech and the Moderna vaccine, and perhaps a more likely signal for the AZ vaccine. Further details of individual cases are required, and any new reports need to be carefully evaluated and incorporated to on-going analyses. Mechanistic data could also be used to interrogate the likelihood of a causal relationship. At present, the EWG noted that the level of information and the proportionately low number of cases of TP preclude making any robust judgements on causality.

4.7 On the topic of exacerbation of pre-existing ITP as potential side effect triggered by the vaccine, the EWG considered that viral infections can lead to flare ups in patients with ITP. Mixed outcomes are also reported with other vaccines in the literature, with some studies suggesting a causal link to the vaccine and others not. It was also considered by the EWG that unvaccinated patients who have a sub-clinical IPT may advance to clinically diagnosable IPT more rapidly following vaccination. The EWG noted a proposed mechanism involved the downstream processes of inflammation in response to vaccination, leading to up-regulation of pre-existing types of autoantibodies. The EWG determined that it was plausible that the time of onset to ITP could potentially be accelerated due to use of COVID-19 vaccines but that an association with the vaccines could not currently be established.

4.8 The EWG noted the detailed narrative regarding the case of fatal cerebral venous sinus thrombosis (CVST) in a 32 year old patient, and that there was no evidence of confounding. The EWG noted thrombotic events or bleeding is rare in cases of ITP, but bleeding can occur in cases of wet ITP. Further information on this case, and any other similar cases, should be obtained as follow-up.

4.9 The EWG noted a number of reports of ITP and thrombocytopenia do not appear to include any confounding factors and which decreased the likelihood these reports represent a chance finding.

4.10 The EWG considered the proposed follow up forms to gather additional information on these cases, and systemic lupus should be added to the list of other potential causes of TP.

4.11 The EWG discussed whether vulnerable patient groups, in particular patients with auto-immune disease, would be more susceptible to ITP. The meeting considered that this could be plausible but there is no evidence to suggest that this is the case at the moment. Monitoring platelet counts in the period prior to vaccination in patients with auto-immune disease was not recommended by the EWG, as there is presently only a potential signal, and also because results would be difficult to interpret especially when considering that some immune conditions can cause low-platelets, e.g. lupus. The EWG agreed the topic of vulnerable patients including those with auto-immune diseases, should be revisited in the near future /when further data may have become available. The EWG discussed ITP in the paediatric population and confirmed that if the vaccination schedule is broadened to include children, there will be a need to rapidly monitor and review potential haematological signals in children, particularly as 40% of ITP cases occur in children mostly under the age of 10 years.

4.12 The EWG noted the need to conduct very in-depth assessments of individual cases that include no apparent confounding factors and communicate with other international regulators to gain further insights, and establish a basis for a coordinated regulatory response.

4.13 The EWG noted future studies should explore platelet activation in vaccinated patients, and although initiating these studies falls outside of the MHRA's purview, the EWG could form a recommendation to researchers.

4.14 The EWG considered that initiation of risk minimisation for ITP would be premature at this stage and the addition of warnings on ITP in the product information for the vaccines would be (currently) unfounded and may only unnecessarily contribute to vaccine hesitancy.

4.15 The EWG concluded that cases of immune and non-immune thrombocytopenia should continue to be monitored.

5. Update on COVID-19 vaccine AstraZeneca safety

5.1 The EWG heard an update on safety data for the AstraZeneca vaccine up to 19th February 2021. 41,157 reports of suspected ADRs in association with COVID-19 Vaccine AstraZeneca had been received in the context of roughly 8 million doses given. The most frequently reported reactions were consistent with expected reactogenicity reactions and were present in the product information. 227 fatal cases had been received, the majority of which were in patients aged over 80 years. An update of cases received for adverse events of interest Bell's palsy and transverse myelitis was provided. Analysis of individual cases as well as epidemiological analysis did not indicate a signal.

5.2 The EWG discussed cases reporting transverse myelitis and the plausibility of cases where patients reporting the condition with very quick recovery, without input from a healthcare professional. The EWG considered these cases to be less plausible to be true transverse myelitis than those where medical review and treatment have been sought.

5.3 The EWG discussed the importance of acquiring more information on the reported cases to allow further assessment of cases although the difficulties in obtaining this with established follow up measures were acknowledged.

5.4 The EWG advised that no regulatory action was required currently but further information for assessment was required.

6. Review of potential risk of encephalitis with Pfizer/BioNTech and AstraZeneca COVID-19 vaccines

6.1 The EWG heard an overview of an ongoing report regarding a recipient of the AstraZeneca Covid-19 vaccine who experienced encephalopathy, multi-organ failure and paralysis with an onset between 24-48hours post vaccination. The patient had a complex medical history, significant for reactions to viral and bacterial infections as well as a previous reaction to a vaccine.

6.2 A review of cases of encephalopathy and encephalitis and related terms reported to the Yellow Card database was presented, to a data lock point of 15th February 2021 and from clinical trials with the Astra Zeneca and Pfizer vaccines.

6.3 The EWG noted that as per the product information, a previous reaction to a vaccine (other than a prior COVID-19 vaccine) does not contraindicate use of any COVID-19 vaccine. A

search of the Yellow Card database for other cases mentioning previous reactions to vaccines found only reports of reactogenicity type reactions to the COVID-19 vaccines.

6.4 The EWG discussed the most recent information regarding the index case and commented on the complexity of the patient's medical history.

6.5 The EWG commented on previous reports of fatal reactions to the use of adenoviral vectors used therapeutically (rather than as a vaccine) and stated that it was important to be clear that these events are not similar to the events being discussed currently and that the adenovirus vectors used in these therapies were live adenovirus vectors, rather than a replication-deficient adenovirus vector, as used in COVID-19 vaccine AstraZeneca.

6.6 The EWG concluded that more information was needed on this case, however it was not possible to establish causality with vaccination for this patient and that there wasn't wider evidence of similar reactions currently. The EWG considered there is no need for any updates to the product information or communications at this time.

7. Core Risk Management Plan for COVID-19 vaccines – requirements for update following strain

7.1 The EWG heard MHRA proposal to principles and requirements of an updated pharmacovigilance system and core Risk Management Plan for COVID-19 vaccines strain variations and agreed of the principles laid down in the proposal.

7.2 Update on the Guideline

7.2.1 MHRA-NIBSC updated the EWG on recent revisions of the guideline that were made in consultation with stakeholders and other regulators. Experts approved all proposals made and strongly encouraged timely publication.

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

8.1 None.

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

The next meeting is scheduled to take place on Tuesday 2nd March 2021 at 11:30.

The Meeting today started at 12:32 and ended at 15:00.

[redacted]

19th July 2021

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

COMMISSION ON HUMAN MEDICINES (CHM)

COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Tuesday 2nd March 2021** at **12:30** via videoconference

Participants Present

Members

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

Apologies

Professor S Price
Professor B K Park (Member of CTBV EAG)

Member of the CTBV Expert Advisory Group

Professor M Turner

Members of the CPS Expert Advisory Group

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

Invited Experts presented Item 2[2]

[redacted]

Invited Experts for Items 2 & 5

[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted] - LD (& for CHM)

Presenters supporting specific items[3]

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

MHRA Observers

[redacted] – VRMM
[redacted] - VRMM
[redacted] - LD
Dr S Branch - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
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[redacted] – VRMM
[redacted] - Devices
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - MHRA-NIBSC
Ms N Rose - MHRA-NIBSC
[redacted] - MHRA-NIBSC
[redacted] - LD
[redacted] - VRMM
[redacted] – Government Legal Team
[redacted] - MHRA-NIBSC
[redacted] - LD
[redacted] - LD
Dr K Wydenbach - LD

Observers

[redacted] (also participated in item 5)

[redacted]

Secretariat

[redacted]

23rd July 2021

[1] Joined during item 5
[2] Left after this item
[3] supporting specific items

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

1. Introduction and Announcement

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

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

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

1.3 Participants declared interests and other relevant interests for this meeting listed at **Annex II** to the minutes.

1.4 Apologies were received from Professor Price and Professor Park for the meeting today.

1.5 The Chair welcomed the following invited experts who presented item 2 - Analyses from REACT 2 study on vaccines. The experts left after the presentation of this item:

[redacted]

1.6 The Chair welcomed the following invited experts who participated for item 5 - Vaccination during Pregnancy & Breastfeeding.

[redacted], MD PRCOG

[redacted]

[redacted] **(also observed item 2)**
[redacted]

[redacted] **(also observed item 2)**
[redacted]

1.7 The Chair welcomed the following Observers who observed the meeting today and will be observing future meetings on the safety items:

[redacted]
Locum Consultant in Health Protection
Public Health Agency

[redacted] OBE - **Apologised**
[redacted]

[redacted]
Public Health Scotland

[redacted]

[redacted] MB ChB. FRCGP. FIMC (RCSEd), DUMC
[redacted]

2. Analyses from REACT 2 study on vaccines

2.1 The EWG viewed slides and heard a presentation by Imperial College London experts on the results of real-time assessment of community transmission 2 (REACT-2) programme, round 5, carried out on 26 January - 8 February 2021. REACT 2 is a community survey of adults in England that measures the prevalence of antibodies using the self-administered lateral flow immunoassay (LFIA) test. The survey comprised 172,099 participants, with valid immunoglobulin G (IgG) results from 154,417. The survey questionnaires collected demographic details, as well as clinical and COVID-19 vaccination histories.

2.2 The EWG heard a report on the overall prevalence of positivity for SARS-CoV-2 IgG antibodies in the community in vaccinated and unvaccinated individuals, the impact of vaccination on antibody status, and confidence in vaccination across the population. The EWG heard that antibody responses were detected after vaccination with Pfizer/BioNTech or AstraZeneca vaccines. However, the analysis was limited to those who received the Pfizer/BioNTech vaccine due to insufficient data for comparison with the AstraZeneca vaccine.

2.3 The EWG heard that antibodies to SARS-CoV-2 spike (anti S) protein and neutralisation were detected using the [redacted] (threshold value for positivity AU/ml). The results demonstrated the detection of antibodies on the LFIA correlated well with the threshold for neutralisation of live virus in in-vitro assays.

2.4 The EWG noted that the findings from REACT 2 study indicated higher prevalence of antibodies (37.9%) in the vaccinated population compared to the unvaccinated population (9.8%), which resulted from natural infections. The EWG heard that high level antibody positivity was seen following two doses of Pfizer/BioNTech vaccine across all age groups, with slightly higher levels in the younger population. It was also noted following a single dose of Pfizer/BioNTech vaccine high levels of antibody positivity were detected in those with previous infections compared to those with no history of COVID-19. The EWG heard that following a single dose of Pfizer/BioNTech vaccine lower antibody positivity was seen with increasing age. A high response was noted in those with previous or suspected COVID-19 across all age groups. The results on post vaccination indicated that the antibody response peaks around 30 days for all age groups.

2.5 The EWG heard that the uptake of vaccination by age was the highest in those aged 80 years and over (93.9%), followed by those aged 75-79 (64.9%). The data analysed also reported that 68.9% of healthcare workers and 59.7% of care home workers had received the vaccination. Further data was also received on 17,000 people who had reported having received one or two doses of the vaccine.

2.6 The EWG heard that confidence in the vaccine program was high with 92% of people being vaccinated or agreed to accept the offer. It was reported that vaccine confidence varied with age and ethnicity, with lower confidence in the higher prevalence groups (young people and those of Black or Asian ethnicity). It was noted that the reasons behind vaccine hesitancy were mainly related to the safety of the vaccine. Particular concerns were also identified around pregnancy, fertility, and allergies in all age groups.

2.7 The EWG heard the status and details of future plans, these included analysis of ongoing data, further modelling and comprehensive review of data, continuing to analyse digital images of completed LFIA tests, and conclusion of the pending rounds of REACT and linking the antibody results to cases, hospitalisations and mortality. The group are also awaiting confirmation that the blood testing services of [redacted] can be used to mount a larger scale analysis of the older cohort using [redacted] with the aim of subsequently linking results to clinical and hospital data.

2.8 The EWG asked whether qualitative or further quantitative assessments are being performed on the images. The EWG heard that the images are being read and checked by multiple individuals. However, a new method for automated reading is being developed and will be available in the future.

2.9 The EWG enquired if the apparent lower antibody response with age, may instead be due to an inadequate sensitivity or levels beyond the limit of quantification of the assay. The EWG heard that this was highly unlikely, because when using the same assay in older participants, post second dose, a far higher level of antibody was noted.

2.10 The EWG also heard that use of the [redacted] intends to focus on the older cohort and the assay should be capable of better characterisation of antibody responses when used in conjunction with a standard laboratory rush assay.

2.11 The EWG asked the invited experts about the binding kinetics of antibodies that have been afucosylated. The invited experts expressed a need to review the data on this topic before a response can be given.

2.12 The EWG enquired whether the WHO international standard will be used to calibrate the assay to an international unit to allow comparisons across other data sets. The external experts commented that calibration of assay quantification was based on previous inhouse

assays and information from published papers, and this was then aligned to [redacted]

2.13 The EWG asked the external experts whether people had reported of COVID-19 after receiving the vaccine and if this could be linked to the lateral flow positivity threshold. The expert stated that there are more data from previous study (REACT 1) which is under investigation. Further data are also being collected to link to the subsequent post vaccination hospitalisation, data on positivity and mortality.

3. COVID-19 Vaccine Moderna post authorisation study protocols: Post Authorisation Safety in the US and Observational Pregnancy Outcome Study

3.1 The EWG heard that Moderna had submitted protocols for a post authorisation safety surveillance (PASS) study to be conducted in the US, and for a pregnancy registry, to be conducted in centres in the US and in certain EU countries. The EWG heard that the US PASS proposes to further characterise the safety concerns of long-term safety and anaphylaxis with their COVID-19 vaccine, as included in the Risk Management Plan. The EWG noted that neither of the studies were proposed to be conducted in the UK, and that the protocols would be subject to approval by other regulators such as the US FDA and the EMA.

3.2 The EWG noted that the study design was a retrospective observational cohort study which will be conducted using a large US healthcare database. The EWG also heard that the study objectives were to estimate background rates for adverse events of special interest (AESI) prior to and during the pandemic, and since introduction of COVID vaccines, assess observed versus expected rates for AESIs and to estimate the relative risk for AESIs which meet prespecified evaluation threshold using a self-controlled risk interval (SCRI) analysis. The EWG noted that the proposed study timelines may be subject to change depending on protocol approval by various regulators, although interim updates are proposed every three months.

3.3 The EWG were informed that the MHRA intended to send some questions to the company for consideration, in relation to the power of the study to identify or exclude levels of risk for any AESI studied; also the design of the SCRI analyses will need to be AESI-specific and that use information on the UK deployment of the Moderna vaccine should be used to inform useful stratifications of data in the UK to understand the safety profile in the UK vaccinated cohort.

3.4 The EWG heard that a prospective, observational pregnancy exposure registry is proposed to collect primary data in the US and several EU countries from pregnant women who have received Moderna COVID-19 vaccine, and their healthcare providers. The EWG noted that the study proposes to estimate the proportion of major congenital malformations in the infants of women exposed to Moderna's vaccine and compare the proportion of major congenital malformations with the prevalence of birth defects in the general population in the EU and US (using European Surveillance of Congenital Anomalies [EUROCAT] and Metropolitan Atlanta Congenital Defects Program [MACDP], respectively. The EWG also noted the study also proposes to evaluate other adverse outcomes of pregnancy, and infant outcomes such as minor malformations.

3.5 The EWG agreed with the MHRA's assessment of the protocols and the proposed list of questions for the company. The EWG also recommended asking for some more specific details on other criteria for performing the SCRI analysis in the US PASS. Regarding the pregnancy registry, the EWG proposed asking the company to discuss the representativeness of the data collected in the pregnancy registry, and also whether the

choice of external comparators for the US and EU may introduce bias due to variations in the way that outcome data are collected.

4. COVID-19 Vaccine Moderna post authorisation study protocol: Safety and Immunogenicity of Moderna in Immunocompromised Patients

4.1 The EWG heard that a draft protocol for post authorisation study to characterise the use of SARS-CoV-2 mRNA-1273 vaccine in the subgroup of immunocompromised patients was submitted by Moderna. The protocol concerns a phase III, open-label, clinical trial comparing the safety and immunogenicity of the vaccine in uncomplicated solid organ transplant patients and healthy controls, aiming to monitor participants for 12 months after vaccination. The primary objectives are to evaluate safety and reactogenicity and to evaluate serum neutralising antibody response 28 days after first and second doses. Secondary objectives include evaluation of immune response persistence for a year and describing the incidence of COVID-19 in solid organ transplant (SOT) patients compared to healthy participants.

4.2 The EWG noted that the safety endpoints were assessed by clinical review of relevant parameters including adverse events (AEs), serious adverse events (SAEs), medically attended AEs (MAAEs), any reported adverse events of special interest (AESIs), and a biopsy-proven organ rejection.

4.3 The EWG heard the proposed humoral and cellular immunogenicity response endpoints and safety analyses are acceptable.

4.4 The MHRA has requested clarification from the company on the statistical comparison of the antibody responses of the transplant patients and the healthy participants, and on the method of selecting the antibody threshold from pivotal study mRNA-1273-P301.

4.5 The EWG heard that a request has been made for the company to confirm whether the subset of participants for exploratory cellular immunogenicity responses include both SOT recipients and healthy participants, to enable comparison. Justification was also requested to establish whether the sample size is large enough to achieve the aims of the study.

4.6 The EWG discussed further questions the MHRA will potentially raise with the company. The EWG noted that the immunocompromised subjects proposed in the study are uncomplicated SOT patients. The EWG was asked to comment whether the study population reflects the broader immunosuppressed population, if not, to comment on further suggestions for which other subgroups may be recruited and any potential recruitment sources.

4.7 The EWG agreed with the MHRA assessor that the patient population is very restrictive and is not representative of the wider immunosuppressed population. The EWG advised that the company's post authorisation study should include patient groups with both primary and secondary antibody deficiency, bone marrow transplant recipients, patients on immunosuppressant therapy, and patients with autoimmune disease or inflammatory disease. The EWG also recommended that an adequate sample for each of these groups can be obtained from the relevant scientific, or professional societies. The EWG also recommended having a broad spectrum of patients in these groups, including patients with combined secondary defects in terms of T-cell defects as well as antibody deficiency.

4.8 The EWG also heard about the company's proposal to measure cellular immunogenicity endpoints relating to B-cells and T-cells in a subset of participants at 7 days post second dose. Advice was sought from EWG whether the timing for sample collection is optimal.

4.9 The EWG noted in the phase I study conducted by Moderna, sample collection occurred at 14 days after the second dose, to align with the period for generation of T-cell response. At a minimum, it would be beneficial for the company to include a 14-day time point to allow comparison between the phase I immunogenicity data and the forthcoming post authorisation study data.

4.10 The EWG confirmed that the proposal for evaluation of more general safety endpoints as well as transplant rejection was generally acceptable. The EWG advised the MHRA to encourage the company to consider new data emerging and work closely with academic groups to produce a better-informed study protocol.

4.11 The EWG endorsed the list of questions to the company.

5. Vaccination during Pregnancy & Breastfeeding

5.1 The EWG heard that current COVID-19 vaccine trials within the UK do not allow inclusion of pregnant women but that there are plans from several companies to address this. Pfizer have announced a trial in pregnant women to compare the data to that from their pivotal trial, but as yet this will not involve the UK. Janssen have been in communication with the Clinical Trials Unit (CTU) and submitted an updated protocol for review for their planned phase II trial. The trial will evaluate women in the 2nd and 3rd trimester for safety and immunogenicity as well as parameters in the neonates. The CTU has also heard about a possible trial evaluating the deployed vaccines in pregnant women at 13 to 24 weeks gestation. The design will be similar to another ongoing trial of deployed vaccines but focusing on the doses and prime-boost regimen.

6. Any Other Business

6.1 None.

7. Date and time of next meeting

The next meeting is scheduled to take place on Tuesday 9th March 2021 at 15:30.

The Meeting today started at 11:31 and ended at 13:56.

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Annex I

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

Chair and Members

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

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

Invited experts

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

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

Observers

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

Annex II

The following participants declared interests and other relevant interests at the meeting today:

Apologies were received from Professor Price and Professor Park for this meeting.

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

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

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

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

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

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

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

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

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

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

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

Mrs Wang – Personal interests arising from being highly sensitive to insect stings, and plant products such as Hyacinth bulbs, which are recorded on Mrs Wang's medical records.

Professor Weir - NPNS - Imperial College and Other relevant interest arising from his department collaborates with Imperial College on a number of clinical trials.

CTBV

Professor Turner – NPNS interest. Professor Turner is a Non Executive Director (non-remunerated) on the Board of the Cell and Gene Therapy Catapult (CGT) until the end of March. CGT have been tasked by UK Government with re-purposing a factory in Braintree to manufacture either a vaccine or a therapeutic mAb. No decision has been made as to whether or what product CGT Braintree may be asked to manufacture and that decision will be made by UK Government. Professor Turner does not believe that CGT Board will have any material input into the decision as to what product may be manufactured. Rentschler have signed a contract with the Cell and Gene Therapy Catapult (CGT) to rent one of the manufacturing clean room suites at the Stevenage Centre. Professor Turner understands that this will be for contract AAV manufacture.

CPS

Mr V'lain Fenton-May – None

Mr Robert Lowe – None

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

Professor Kevin Taylor – None

Dr Susannah Walsh – None

Observers for this meeting

[redacted]

COMMISSION ON HUMAN MEDICINES (CHM)
COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Tuesday 9th March 2021** at **15:30** via videoconference

Participants Present

Members

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

Apologies

Mr R Lowe
Professor C Robertson
Professor P Shah

Member of the CTBV Expert Advisory Group

Professor M Turner

Members of the CPS Expert Advisory Group

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

Observers

[redacted]

Secretariat

[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted] - LD (& for CHM)

Presenters supporting specific items

[redacted]

MHRA Observers

[redacted]
Dr S Branch - VRMM
[redacted]
Dr P Bryan - VRMM
[redacted]
Dr S P Lam - LD
[redacted]
Ms N Rose - MHRA-NIBSC
[redacted]
Mr P Tregunno - VRMM
[redacted]
Dr K Wydenbach - LD

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

[redacted]

13th April 2022

1. Introduction and Announcement

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

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

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

1.3 Participants declared interests and other relevant interests for this meeting listed at **Annex II** to the minutes.

1.4 Apologies were received from Professors Robertson, Shah and Mr Lowe for the meeting today.

1.5 The Chair welcomed the following observers invited to observe the safety items discussed at the meeting today:

[redacted]

[redacted]
Public Health Scotland

[redacted] Public Health Wales

[redacted]

2. Moderna dosing interval

2.1 The EWG heard the Moderna COVID-19 vaccine was authorised under Regulation 174 of the HMRs 2012 on 08 January 2021. On 31 December 2020, in response to a DHSC request for specific guidance on an extended dosing interval, EWG and CHM advised that the recommended dosing interval should be at least 28 days. But, in subsequent discussions the manufacturer did not agree, and the product information for HCPs states that it is recommended to administer the second dose 28 days after the first dose and refers to

section 5.1 which provides an outline of the data on efficacy after the first dose and information about the dosing interval in the trial which was up to 42 days.

The EWG was reminded of the efficacy seen after 1 dose of Moderna and after 1 dose of Pfizer-BioNTech, as they are both mRNA vaccines with similar results in their clinical trials. Effectiveness data after one dose were presented mainly for the Pfizer-BioNTech vaccine.

2.2 The EWG were asked to consider, if a dosing interval of 'at least 28 days' for the Moderna vaccine could still be recommended, based on the currently available data.

2.3 The EWG noted recent discussions on the topic of vaccine dosing interval in the medical literature. The EWG noted an interval of 'at least 28 days' would be consistent with the outcome of the previous EWG discussion on the 31 Dec 2021, and the decision to make the specific recommendation of 'up to 12 weeks' is within JCVI's purview. The evidence on mRNA vaccine efficacy post first dose is reassuringly high ~80-90%. The real-world vaccine effectiveness data from Scotland, and Canada is also very encouraging, although the recent rate of infection in Canada has been lower. The EWG also noted the need to be consistent with the dosing interval between the two mRNA vaccines, or to be able to factually describe the basis for any inconsistencies, given the platforms are very similar.

2.4 The EWG noted that the most recent evidence available strengthens rather than undermines the rationale for an interval of at least 28 days. The EWG noted there is a reasonable basis to support extending the dose interval to at least 28 days. The precise implementation of the interval e.g. possibly to 12 weeks, in order to optimise population coverage falls within JCVI's purview.

2.5 The EWG noted the Pfizer and Moderna platforms use very similar but not identical technologies, and therefore, any comparison needs to be precisely constructed / grounded in science. Another caveat is that the landscape may change depending on the emergence of variants and as the present understanding of the disease matures.

2.6 The EWG noted it was of great benefit that high levels of efficacy have been shown against the primary virus, but as mentioned previously variants remain a potential concern. The scientific rationale that led to the extension of the AZ vaccine interval was based on fairly limited data, but this rationale was shown to be correct when cross-referring to real-world data. Therefore, applying the same thought process to the Moderna vaccine would not be unreasonable, but would need to be supported by immunogenicity data / other trial data such as the Oxford Vaccine Group heterologous prime-boost COVID-19 vaccination trial (Com-COV).

2.7 The EWG noted there is a need for more comparative immunogenicity data, but data emerging on the correlates of protection is promising for both for binding antibody to spike and viral neutralisation. The identical testing platforms are being used to test sera from cohorts of Moderna vaccine recipients and Pfizer vaccine recipients. The early comparative results show immunogenicity three weeks after one dose to be similar. The EWG noted that the recommended dosage of Moderna dose is larger than that of Pfizer/BioNTech.

2.8 The EWG asked about the process to handle the potential amendment to return the vaccine interval to that originally endorsed by the EWG. The Chair explained that the present meeting represents the first stage, the collation of the views of the expert committee, which will be followed by a CHM meeting, where a recommendation may be given. The recommendation will enable the MHRA to approach DHSC with the position of the CHM, and a discussion with the manufacturer will follow to reconcile the product information with an extended dosing

interval. A dosing interval of at least 28 days should permit the JCVI greater flexibility to facilitate wider Moderna first dose vaccine coverage.

2.9 The EWG requested information on the approach taken by the Canadian regulatory authority. The EWG heard a form of emergency-use authorisation has been granted and currently reflects the 28-day interval, reflecting an off-label approach that has been taken for the roll-out. The EWG noted that the dose interval of 4 weeks selected in the trials, was not based on exploratory clinical data.

2.10 The Chair concluded that the EWG share the perspective that the available data continue to support a dosing interval of at least 28 days for the Moderna vaccine, and that dosing interval recommendations should be consistent across both mRNA vaccines (Moderna and Pfizer/BioNTech).

3. Covid-19 Vaccines – Risk of Seizures

3.1 The EWG was informed of a cluster of 4 cases of seizures in patients with epilepsy who developed pyrexia and seizures within a few hours of receiving the AstraZeneca COVID-19 vaccine. The EWG noted that seizures/convulsions are included in the list of adverse events of special interest (AESI) for all COVID-19 vaccines and as such are closely monitored by the MHRA and the vaccines' authorisation holders. The EWG heard that although vaccines in general are not known to be causally associated with seizures in adults, seizures are included as an AESI as a precaution, because of the known but uncommon risk of febrile seizures in children following some immunisations.

3.2 The EWG considered an assessment of clinical trial data and individual case reports of seizure-related events reported via the UK Yellow Card Scheme for the Pfizer-BioNTech and AstraZeneca COVID-19 vaccines. For the Moderna vaccine, only clinical trial data and data from non-UK cases reported to the MHRA by the vaccine authorisation holder were considered; UK specific post-marketing data are not currently available as this vaccine has not yet been deployed in the UK.

3.3 The EWG agreed that the currently available data do not provide any evidence of a causal association between the COVID-19 vaccines and onset of seizure events in people without a prior history of seizure.

3.4 The EWG also agreed that the currently available data do not suggest a direct vaccine-specific increased risk of seizure and the COVID-19 vaccines in people with epilepsy or history of seizure.

3.5 The EWG discussed the small number of cases of seizure in people with a prior history of seizure reported alongside other known side effects of the COVID-19 vaccines. The EWG noted that intercurrent illness, feeling generally unwell, fever and fatigue can be triggers for seizures in some people with epilepsy and that some people do experience flu-like symptoms within 1-2 days of COVID-19 (and other) vaccinations. The EWG heard that the International League Against Epilepsy currently advises that fever developing after a COVID-19 vaccination could lower the seizure threshold in some people and that antipyretics, such as paracetamol, taken regularly after vaccination will minimise this risk.

3.6 The EWG noted that the UK information for the COVID-19 vaccines includes advice that, if required, paracetamol may be used after vaccination to provide symptomatic relief from post-vaccination adverse reactions and that advice about the use of paracetamol is also provided in the Green Book. The EWG agreed that there was no evidence available on whether

prophylactic paracetamol would reduce the risk of seizures in people with epilepsy following COVID-19 vaccination.

3.7 The EWG advised that based on the data currently available no updates to the product information for the COVID-19 vaccines are required, but that the risk of seizures should continue to be kept under close review.

4. Potential risk of Guillain-Barré syndrome GBS with Pfizer/BioNTech and AstraZeneca COVID-19 vaccines

4.1 The EWG was provided with an overview of Yellow Card reports of Guillain-Barré syndrome (GBS), an Adverse Event of Special Interest, up to and including 3 March 2021 with the Pfizer, AstraZeneca and Moderna vaccines. Clinical trial data and company data from Summary Monthly Safety Reviews were also provided.

4.2 The EWG heard epidemiological analysis which involved ecological, observed vs expected and rapid cycle analyses.

4.3 The EWG commented on the importance of following up GBS reports to gain sufficient detail to understand whether the cases meet the Brighton Collaboration Criteria for true Guillain-Barré syndrome.

4.4 The EWG and invited observers discussed ways to encourage healthcare professionals to provide more detail in Yellow Card reports and respond to follow up requests, including communicating with royal colleges and similar bodies, as well as medical directors of trusts.

4.5 The EWG noted that it was important to promote thorough reporting for all adverse events, rather than specific ones in order to avoid stimulating reporting and creating biases within the Yellow Card database.

4.6 The EWG stated that there was the potential of an increased signal of GBS, particularly with the AstraZeneca vaccine and that reports of GBS should be closely monitored but that a formal epidemiological study was not yet indicated at this stage.

5. Review of safety data for use of COVID-19 vaccines in patients with neuromuscular disorders

5.1 The EWG heard background information about a case of a patient with a neuromuscular disorder who had died shortly after receiving the AstraZeneca vaccine, as well as reports of patients with neuromuscular disorders experiencing more severe myalgia and creatinine kinase increases after vaccination with the Pfizer and AstraZeneca vaccines.

5.2 The EWG was provided with an overview of clinical trial data, Yellow Card reports and international reports regarding patients with underlying neuromuscular disorders who reported an aggravation of the underlying disease or renal damage, as well as reports of severe muscle damage in recipients regardless of their underlying disease status.

5.3 The EWG noted that the effects reported were broad but that no clear signal of vaccine association could be seen in the data.

The EWG requested that where possible, further details should be obtained for the most serious cases.

The EWG commented that creatinine kinase increases were difficult to interpret without knowing what the patient's baseline levels are.

5.4 The EWG concluded that these types of report should be kept under close monitoring but that no regulatory action was required at this stage.

6. Yellow Card Vaccine Monitor: Verbal Update

6.1 The EWG was provided with an update on enrolment of individuals to the Yellow Card Vaccine Monitor (YCVM), part of the MHRA pharmacovigilance surveillance strategy for the COVID-19 vaccines.

6.2 The EWG were reminded that individuals are recruited through the national call-recall process for vaccinations and receive a letter following the national call inviting them for vaccination.

6.3 The EWG heard that approximately 17,000 individuals have registered with the YCVM platform to date. Around 13,500 individuals have submitted data on their vaccination, of which around 5,700 individuals have submitted adverse reactions amounting to 11,500 adverse drug reactions reported to the YCVM.

6.4 The EWG also heard that a slightly higher proportion of women have registered compared to men, and women were also more likely to report an ADR.

6.5 The EWG heard that around 90% of individuals registered were of white British or white Irish ethnicity. The EWG considered the need to increase ethnic diversity and heard that engagement with the national call-recall process could increase ethnic diversity in specific areas.

6.6 The EWG heard that the top ten ADRs reported by vaccine type were consistent with the known short-term reactogenic effects of the COVID-19 vaccines.

6.7 The EWG considered that the presentation of data from the YCVM could be amended with stratification based on patient characteristics as opposed to the vaccine type in future updates to the EWG.

7. Any Other Business

7.1 None.

8. Date and time of next meeting

The next meeting is scheduled to take place on Thursday 18th March 2021 at 10:30.

The Meeting today started at 15:33 and ended at 17:24.

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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).

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

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

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

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

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

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

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

Mrs Wang – Other relevant interest arising from family with several rare diseases and conditions, some of which result in epileptic fits as a consequence.

Professor Weir - NPNS - Imperial College and Other relevant interest arising from his department collaborates with Imperial College on a number of clinical trials.

CTBV

Professor Turner – NPNS interest. Professor Turner is a Non Executive Director (non-remunerated) on the Board of the Cell and Gene Therapy Catapult (CGT) until the end of March. CGT have been tasked by UK Government with re-purposing a factory in Braintree to manufacture either a vaccine or a therapeutic mAb. No decision has been made as to whether or what product CGT Braintree may be asked to manufacture and that decision will be made by UK Government. Professor Turner does not believe that CGT Board will have any material input into the decision as to what product may be manufactured. Rentschler have signed a contract with the Cell and Gene Therapy Catapult (CGT) to rent one of the manufacturing clean room suites at the Stevenage Centre. Professor Turner understands that this will be for contract AAV manufacture.

CPS

Mr V'lain Fenton-May – None

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

Professor Kevin Taylor – None

Dr Susannah Walsh – None

Observers for this meeting

[redacted] – [redacted]

[redacted]

[redacted] – [redacted]

[redacted] – [redacted]

COMMISSION ON HUMAN MEDICINES (CHM)

COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Wednesday 17th March 2021** at **15:00** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan
Mr VI G Fenton-May
Professor N French
Professor D Goldblatt
Ms S Hunneyball
Sir M Jacobs
Professor H J Lachmann
Professor P J Lehner
Mr R Lowe
Dr S Misbah
Professor Y Perrie
Professor S Price
Dr A Riordan
Professor T Solomon
Professor K M G Taylor
Dr R Thorpe
Professor M Turner
Dr S Walsh
Mrs M Wang
Professor C Weir

Apologies

Professor K Hyrich
Professor C Robertson
Professor P Shah

Invited Experts

[redacted]

Observers

[redacted]
Professor W S Lim
[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted] - LD (& for CHM)

Presenters supporting specific items

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

MHRA Observers

Ms R Arrundale - MHRA-Policy
[redacted] - Directorate
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - LD
Dr S Branch - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - MHRA-NIBSC
[redacted] - VRMM
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[redacted] - LD
[redacted] - LD
[redacted] - VRMM
[redacted] - LD - Medical Writer
[redacted] - LD
[redacted] - LD
[redacted] - MHRA-NIBSC
[redacted] - LD
Dr J Raine - MHRA CEO
Ms N Rose - MHRA-NIBSC
[redacted] - VRMM
[redacted] - LD
[redacted] LD
[redacted] - VRMM
Mr P Tregunno - VRMM

[redacted]

[redacted] - LD
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - VRMM
Dr K Wydenbach - LD

Secretariat

[redacted]

[redacted]

22nd June 2021

Key
LD = Licensing Division
NIBSC = National Institute for Biological Standards & Control
VRMM = Vigilance & Risk Management of Medicines
Directorate = Director of Operational Transformation
MHRA CEO = Chief Executive

1. Introduction and Announcement

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

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

1.3 Participants declared interests and other relevant interests for this meeting at **Annex II** to the minutes.

1.4 Apologies were received from Professors Hyrich, Robertson and Shah for this meeting.

1.5 The Chair welcomed the following invited experts for the meeting today:

[redacted] Professor of [redacted] University of Oxford

[redacted] Imperial Healthcare College NHS Trust

[redacted] at Oxford University Hospitals

[redacted] at University Hospital Birmingham

[redacted] University College London Hospitals

According to the Conflict of interest Policy invited experts are permitted to participate in discussions and do not contribute to conclusions and recommendations. At the chair's discretion, Professor Scully, Dr Cooper and Dr Lester was permitted to participate by answering specific questions from the chair, but not raise spontaneous comments or questions.

1.6 The Chair welcomed the following Observers for the meeting today:

[redacted] Public Health England

[redacted]
Immunisation, Hepatitis, Blood Safety and Countermeasures Response
National Infection Service
Public health England

[redacted]

[redacted]
Professor of Primary Care and Director of Graduate Studies
[redacted]

[redacted]
Locum Consultant in Health Protection
Public Health Agency

[redacted]
Public Health England

[redacted], NIHR Health Protection Research Unit in Immunisation
London School of Hygiene & Tropical Medicine

[redacted]
Public Health Scotland

Professor Wei Shen Lim
COVID-19 Chair for JCVI

[redacted]
Public Health England

[redacted] Public Health Wales

[redacted]
Clinical Workstream [redacted]
National COVID-19 Vaccination Programme
NHS England and NHS Improvement (National)

[redacted]
Immunisation, Public Health England

2. Review of venous thromboembolism and thrombosis with thrombocytopaenia reported following vaccination with AstraZeneca COVID-19 vaccine

2.1 Introduction

2.1.1 The Chair welcomed the invited experts in haematology to the ad hoc Expert Working Group which had been convened to advise on reports of venous thromboembolism and thrombosis with thrombocytopaenia following vaccination with the AstraZeneca COVID-19 vaccine.

2.1.2 The Chair indicated that there were three questions to consider:

a. Is there an increased risk of peripheral VTE associated with the Pfizer and AZ vaccines?

b. Is there an increased risk of thrombocytopaenia with the Pfizer and AZ vaccines?

c. What is the expert view on cases of thrombosis with thrombocytopaenia associated with the AZ vaccine?

2.2 Peripheral Venous thromboembolism

2.2.1 The meeting heard data presented by MHRA and Public Health England in relation to peripheral venous thromboembolic events. Combined epidemiological evidence from multiple data sources including the MHRA's Yellow Card database, CPRD and the Secondary Uses Service consistently indicate that the incidence of venous thromboembolic events is not at a higher level than expected when compared to historical background rates and when other risk factors such as underlying conditions were taken into account. The Group concluded following discussion that the available data indicate there was no signal of these events occurring with either COVID-19 vaccine currently deployed in UK, Pfizer/BioNTech and AstraZeneca COVID-19 vaccine.

2.3 Immune thrombocytopaenia

2.3.1 Observed/ expected analyses indicate the number of observed spontaneous reports of ITP received through the Yellow Card scheme remains substantially below the expected.

2.4 Thrombosis with thrombocytopaenia

2.4.1 There were no cases noted for the Pfizer vaccines. Case report details were presented for the Astra Zeneca vaccine. The meeting noted a small cluster of 7 thrombotic events (5 CVST and 2 PE) occurring in conjunction with thrombocytopenia predominantly in younger patients (range 19-73, mean 41.7, median 32 years) following vaccination with AstraZeneca COVID-19 vaccine. This was agreed to be a challenging issue to investigate: due to the combination of events, it would extremely be difficult to evaluate this using epidemiological analyses alone, and detailed examination of the clinical characteristics of the cases would be needed.

2.4.2 The meeting heard evidence relating to a signal of thromboembolic events occurring with thrombocytopaenia that had been raised by the EMA following suspension of the AstraZeneca vaccine in several EU member states including Ireland, Norway, Iceland, Austria, Estonia, Lithuania, Luxembourg, Italy, Latvia, and most recently, France, Spain and Germany. There appeared to be a pattern of Cerebral Venous Thrombosis with thrombocytopaenia. Some cases were apparently confounded, e.g. by concomitant hormonal oral contraceptives. There were 5 cases in Norway (4 CVST plus 1 portal venous

thrombosis, three of whom were on Oral Contraceptives or Nuvaring) and 7 cases in Germany all in young women (three with potential risk factors for thrombosis, oral contraceptives, unspecified genetic disorder and pre-existing thrombophilia with von Willebrand disease type 1, Factor V Leiden mutation and anticardiolipin antibody).

2.4.3 The meeting noted anecdotally that there were likely other similar cases that had not yet been received by the MHRA. Experts agreed there was a need to rapidly gather data on these cases, including previous COVID-19 infection, with clinical input from a panel of clinical experts as the data emerged to keep pace with the dynamic nature of the signal. It would also be helpful to put out a call for reporting via the British Society for Haematology, not only of cases occurring in relation to the vaccine but also those which occur naturally.

2.4.4 Experts noted that the co-existence of a prothrombotic state with thrombocytopaenia is rare. Although this is seen to occur rarely with certain conditions, at present it is unclear if a causal association exists with the vaccine. Nevertheless, given the close temporal association and the rare nature of the event, the meeting concluded this should be promptly evaluated further as a signal.

2.4.5 To date, thrombosis occurring with thrombocytopenia has not been noted with the Pfizer vaccine from UK Yellow Card reports. The Centres for Disease Control's rapid cycle analysis for events of venous thromboembolism, pulmonary embolism and disseminated intravascular coagulation has not identified a statistically significant increased risk for any of these events for the mRNA vaccines in use in the USA (Pfizer and Moderna).

2.4.6 Immune thrombocytopenia can occur with vaccines, for example, it has been noted to be associated with the MMR vaccine at a risk of approximately 1 per 25,000. Further literature analyses of the occurrence of thrombocytopaenia together with thrombosis for any vaccine needs to be undertaken.

2.5 Conclusion

2.5.1 The Group agreed that there was no evidence of an increased risk of peripheral venous thromboembolism. The group also agreed that the evidence did not support an increased risk of thrombocytopaenia alone.

2.5.2 Although the numbers of cases of thrombosis with thrombocytopaenia were small, the Group advised that since this was a very serious condition further information should be rapidly gathered.

2.6 Advice

2.6.1 The meeting advised that the benefit-risk of the vaccine was still positive overall, although it may vary in different age groups and clinical vulnerability. Further data on the risk of COVID-19 stratified by age needs to be evaluated (not only with respect to mortality, but also hospitalisation) to provide a better assessment of benefit-risk in different age groups.

2.6.2 The meeting agreed on the further next steps:

a. To work with expert haematologists on a proforma to rapidly gather more relevant clinical details on cases of thrombosis with thrombocytopaenia

b. To work with a panel of experts to obtain expert review of cases, understand their nature and whether there is a causal association.

c. To work with clinical groups including the British Society for Haematology to encourage pro-active reporting of cases to the Yellow Card scheme in as much

detail as possible. This would include reporting of COVID-19 serology, and also of similar events not associated with vaccination.

d. Along with experts, to carefully establish appropriate risk minimisation strategies to enable patients and non-specialists to be able to detect the occurrence of these events at an early stage.

e. Ongoing review at a rapid pace to be discussed with the Expert Working Group at subsequent meetings.

2.7 Communications

2.7.1 The meeting noted that public messaging around the signal would need to be very carefully handled to maintain public confidence.

3. Any Other Business

None.

4. Date and time of next meeting

The next meeting is scheduled to take place on Thursday 18th March 2021 at 10:30.

The Meeting today started at 15:01 and ended at 17:10.

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Annex I

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- May not currently be or have previously been involved in the development of COVID-19 vaccines

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

Invited experts

- 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

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Observers

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

Annex II

The following participants declared interests and other relevant interests at the meeting today:

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

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

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

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

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

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

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

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

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

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

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

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

Professor Turner - NPNS interest. Professor Turner is a Non Executive Director (non-remunerated) on the Board of the Cell and Gene Therapy Catapult (CGT) until the end of March. CGT have been tasked by UK Government with re-purposing a factory in Braintree to manufacture either a vaccine or a therapeutic mAb. No decision has been made as to whether or what product CGT Braintree may be asked to manufacture and that decision will be made by UK Government. Professor Turner does not believe that CGT Board will have any material input into the decision as to what product may be manufactured. Rentschler have signed a contract with the Cell and Gene Therapy Catapult (CGT) to rent one of the manufacturing clean room suites at the Stevenage Centre. Professor Turner understands that this will be for contract AAV manufacture.

Professor Weir - NPNS - Imperial College and Other relevant interest arising from his department collaborates with Imperial College on a number of clinical trials.

Invited Experts for this meeting

[redacted]

Observers for this meeting

[redacted] - None

[redacted] - None

[redacted] - None

[redacted]

[redacted] – None

Professor Lim - NPNS interest as the institution he works for (Nottingham University Hospitals NHS Trust) has received unrestricted investigator-initiated research funding from Pfizer for an unrelated prospective population-based cohort study of pneumococcal pneumonia in which WSL is the Chief Investigator.

[redacted]

[redacted]

[redacted]

[redacted] – None

[redacted] – None

[redacted] – None

COMMISSION ON HUMAN MEDICINES (CHM)
COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Thursday 18th March 2021** at **10:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan
Mr VI G Fenton-May
Professor N French
Professor D Goldblatt
Professor K Hyrich
Sir M Jacobs
Professor P J Lehner
Mr R Lowe
Dr S Misbah
Professor Y Perrie
Professor S Price
Professor C Robertson
Professor P Shah
Professor T Solomon
Professor K M G Taylor
Dr R Thorpe
Professor M Turner
Dr S Walsh
Mrs M Wang
Professor C Weir

Apologies

Ms S Hunneyball
Professor H J Lachmann
Dr A Riordan

Invited Experts – Presenters of Item 2

[redacted]

Observers

[redacted]

Secretariat

[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD

Presenter supporting specific item

[redacted]

MHRA Observers

[redacted] - LD- Medical Writer
[redacted] - LD- Medical Writer
[redacted] - LD
Dr S Branch - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - VRMM
[redacted] - MHRA-NIBSC
[redacted] LD
[redacted] - LD
[redacted] LD
[redacted] - LD
Ms N Rose - MHRA-NIBSC
[redacted] LD
[redacted] - LD
Mr P Tregunno - VRMM
[redacted] - MHRA-NIBSC
[redacted] - LD
[redacted] - LD

[redacted]

19th July 2021

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

1. Introduction and Announcement

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1.3 Participants declared interests and other relevant interests for this meeting at **Annex II** to the minutes.

1.4 Apologies were received from Professor Lachmann, Dr Riordan and Ms Hunneyball for this meeting.

1.5 The Chair welcomed the following invited experts for the meeting today:

Dr [redacted]
Consultant Epidemiologist, Public Health England

Dr [redacted]
Institute of Health Informatics

Dr [redacted]
Public Health Registrar at UCL

1.6 The Chair welcomed the following Observers for the meeting today:

Dr [redacted]
[redacted], Public Health England

Dr [redacted]

Dr [redacted]
HSCNI

Dr [redacted]
Public Health Scotland

Dr [redacted]
Public Health England

Dr [redacted]
[redacted] Public Health Wales

Dr [redacted] MB ChB, FRCGP, FIMC (RCSEd), DUMC
Clinical Workstream – [redacted]
National COVID-19 Vaccination Programme
NHS England and NHS Improvement (National)

2. Vivaldi Project

2.1 The EWG viewed slides and heard a presentation by Birmingham University/University College London (BHU/UCL) experts on the findings of the Vivaldi Project. The Vivaldi project is an ongoing prospective cohort study of staff and residents 65 years and over in care homes in England that analyses vaccine effectiveness against Polymerase Chain Reduction (PCR)-positive SARS-CoV-2 infection.

2.2 The EWG heard that analysis data are sourced from NHS Foundry (Pillar 1 and Pillar 2 for PCR testing data, and the National Immunisation Management Service [NIMS] database for vaccination). The primary outcome was any new PCR-positive SARS-CoV-2 infection, excluding any PCR+ within 90 days of a prior PCR positive (and start of time at risk delayed until 90 days had elapsed). The analysis period was 08 December 2020 to 09 March 2021 (the date of first vaccination in the resident cohort being the start date of analysis). Vaccination status was defined as a time varying exposure extending from unvaccinated, and day intervals up to 48^{+} days.

2.3 The EWG heard that the cohort for analysis was 10,101 residents (with a median age of 86). 88% of the cohort had received their first vaccine (2/3 Oxford/AstraZeneca and 1/3 Pfizer), with 11% of vaccinees having a prior infection. Only 6% had received their second dose; hence this cohort was not considered in this vaccine effect analysis.

2.4 The majority of the PCR testing in the analysis was Pillar 2 testing (99.4%) with only 0.7.% symptomatic at the time of testing. The median PCR results per month (1.6. PCR^{+} results) were predominately from Pillar 2 testing (84.7%), with only 7.6% symptomatic at time of testing. Based on this analysis data, the overall crude infection rate was 21.2/10,000 person day (95% Confidence Interval [CI] 20.1, 22.3). Overall, there was 52% PCR positives, with cycle threshold of less than 25 (Ct <25).

2.5 The EWG heard that analysis based on adjusted hazard ratios shows an early protective effect that may be due to the deferral effect with active outbreak, with a true protective effect likely from Day 28 for both vaccines. It was noted that the early deferral effect was greater with the AstraZeneca vaccine than with Pfizer; the expert explained that it was not clear as to why this was and suggested that it may be linked with the time of deployment of the two vaccines and the type of homes where they were deployed. Based on the results of the analysis of vaccination effect by prior exposure (infection), it is unclear as to whether vaccination is providing any protection beyond that gained from prior infection.

2.6 The EWG heard that future analyses will include sensitivity analyses and further exploration of Ct values data, further analyses of serology data from pre-and post-vaccination samples, vaccine effectiveness against hospitalisation due to COVID-19, vaccine effect after second

dose of vaccine, incorporating estimates of care home seroprevalence prior to vaccination into care home level analyses, and incorporating staff vaccination coverage estimates into future models.

2.7 The EWG asked for clarification as to the reason for the small number of residents (3 residents out of 631; 0.5% of the cohort) having different first and second vaccines. The external expert explained that this was unclear; however, this is as the NIMS records indicate.

2.8 The EWG asked the external experts whether vaccine protection in this cohort was being seen at 28 days, later than in other studies, due to the older population and the slower ability to mount an immune response in this population. The experts stated that the reasons were unclear. However, they explained that mainly Pillar 2 testing was analysed where the subjects were likely asymptomatic, while the outcome in the trials was symptomatic infection, although these trials looked at some asymptomatic cases as well. External experts also commented that the onset of symptomatic disease appears slightly later in the elderly population than the younger age groups, around 21 days versus 14 days. It was agreed with the EWG that this was consistent with data that has already been published.

2.9 The EWG questioned whether the stratification of data by care home should be carried out to reflect the status of other residents in the care home. However, the external experts explained that in the majority of cases the vaccination is carried out too rapidly within a single care home for this effect to be analysed and adjusted for through this type of stratification.

2.10 The EWG asked whether the invited experts could provide an explanation for reported deaths in unvaccinated care home residents only, in terms of survivor bias. The invited experts commented that potential biases (e.g. decisions as to which residents are vaccinated or are hospitalised due to end of life care) make it difficult to analyse the outcomes of hospitalisation and death; however, a sensitivity analysis is planned to exclude those who were never vaccinated, but were at the home at the time vaccination was occurring within the care home.

2.11 The EWG commented that they are looking forward to the analysis on the impact of the second dose. The external expert confirmed that analysis would be conducted on the second dose once the data is available.

3. Pfizer/BioNTech COVID-19 Vaccine – Risk of severe cutaneous adverse reactions (SCAR)

3.1 The EWG was informed of two reports of Toxic Epidermal Necrolysis (TEN) in which the suspected reaction occurred following vaccination with the Pfizer-BioNTech COVID-19 vaccine, one of them fatal, and one case of Stevens-Johnson syndrome (SJS). The EWG noted that SJS and TEN are variants of the same condition distinct from erythema multiforme with an incidence of about 1-2 cases per million population per year. The EWG was reminded of clinical and histopathological features of this condition.

3.2 The EWG considered an assessment of clinical trial data and individual case reports received via the UK Yellow Card Scheme for the Pfizer-BioNTech vaccine concerning Severe Cutaneous Adverse Reactions (SCARs), including cases of SJS/TEN.

3.3 The EWG agreed that the currently available data do not provide evidence of a causal association between Pfizer-BioNTech vaccine and SJS/TEN, and in the fatal case presented concomitant medication could have also triggered the reaction. In all three cases, the onset of symptoms was inconsistent with a vaccine related effect. In addition, the clinical and histopathological features reported in these cases did not meet all the diagnostic criteria for

SJS/TEN with regard to both clinical and histopathological features. The EWG also noted that the number of cases does not exceed the background rate expected for this disease given over 10 million doses of vaccine were administered.

3.4 The EWG agreed that the review of other bullous and erosive skin conditions reported via the Yellow Card scheme did not identify any further possible cases of SJS/TEN and considered no other cases of Severe Cutaneous Adverse Reactions included in the review raised a concern.

3.5 The EWG noted that reviews of less serious skin hypersensitivity reactions (including rash, urticaria, pruritus) and delayed hypersensitivity reactions (including those starting at the injection site) are ongoing in parallel and agreed these should be discussed at the meeting only if a concern emerged.

3.6 The EWG advised that based on the data currently available no update to the product information is required, but that the risk of severe cutaneous adverse reactions should continue to be kept under review.

4. Any Other Business

4.1 None.

5. Date and time of next meeting

The next meeting is scheduled to take place on Wednesday 24th March 2021 at 13:30.

The Meeting today started at 10:31 and ended at 11:28.

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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.

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

Professor Turner - NPNS interest. Professor Turner is a Non Executive Director (non-remunerated) on the Board of the Cell and Gene Therapy Catapult (CGT) until the end of March. CGT have been tasked by UK Government with re-purposing a factory in Braintree to manufacture either a vaccine or a therapeutic mAb. No decision has been made as to whether or what product CGT Braintree may be asked to manufacture and that decision will be made by UK Government. Professor Turner does not believe that CGT Board will have any material input into the decision as to what product may be manufactured. Rentschler have signed a contract with the Cell and Gene Therapy Catapult (CGT) to rent one of the manufacturing clean room suites at the Stevenage Centre. Professor Turner understands that this will be for contract AAV manufacture.

Mrs Wang - Other relevant interests arising from being highly sensitive to insect stings, and plant products such as Hyacinth bulbs, as recorded on Mrs Wang's medical records. The family of Mrs Wang lives with several rare diseases and conditions, some of which result in epileptic fits.

Professor Weir - NPNS - Imperial College and Other relevant interest arising from his department collaborates with Imperial College on a number of clinical trials.

Observer declared interest for this meeting

Dr [redacted]

COMMISSION ON HUMAN MEDICINES (CHM)
COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Tuesday 23rd March 2021** at **15:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan[1]
Mr VI G Fenton-May
Professor N French
Professor D Goldblatt
Ms S Hunneyball
Professor K Hyrich[2]
Sir M Jacobs
Professor H J Lachmann
Professor P J Lehner
Mr R Lowe
Dr S Misbah
Professor Y Perrie
Professor S Price
Dr A Riordan
Professor C Robertson
Professor T Solomon
Professor K M G Taylor
Dr R Thorpe
Professor M Turner
Dr S Walsh
Mrs M Wang
Professor C Weir

Apologies

Professor P Shah

Invited Experts

[redacted] (presenter of specific item)

[redacted]

Observers

[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD

Presenter supporting specific item

[redacted] - VRMM
[redacted] - VRMM

MHRA Observers

Ms R Arrundale - MHRA-Policy
[redacted] - VRMM
[redacted] - LD
Dr S Branch - VRMM
[redacted] - MHRA-NIBSC
[redacted] - VRMM
[redacted] – MHRA-Policy
[redacted] - VRMM
[redacted] - VRMM
[redacted] - MHRA-NIBSC
[redacted] - COMMS
[redacted] - VRMM
[redacted] - VRMM
[redacted] - VRMM
Dr J Raine - MHRA CEO
Ms N Rose - MHRA-NIBSC
[redacted] - VRMM
[redacted] - VRMM
Mr P Tregunno - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - VRMM

Secretariat

[redacted]

[redacted]

4th February 2022

Professor W S Lim

[redacted]

Professor Van-Tam

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

[1] left during item 8
[2] joined during item 7

1. Introduction and Announcement

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

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

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

1.3 Participants declared interests and other relevant interests for this meeting listed at **Annex II** to the minutes.

1.4 Apologies were received from Professor Shah for this meeting.

1.5 The Chair welcomed Invited Expert, Dr [redacted], [redacted] of Public Health England who presented item 7 - Vaccine benefit by age group and analysis of risk of events of thrombosis with thrombocytopenia at the meeting today.

1.6 The Chair welcomed the following Invited Haematology Experts for the meeting today:

Dr [redacted] **-** Imperial Healthcare College NHS Trust
Dr [redacted] **-** [redacted]
Dr [redacted] **-** Oxford University Hospitals
Dr [redacted] **-** University Hospital Birmingham
Professor [redacted], University of Oxford
Professor [redacted] **-** University College London Hospitals
Dr [redacted] **–** [redacted]

1.7 The Chair welcomed the following Observers for the meeting today:

Professor Jonathan Van-Tam - Deputy Chief Medical Officer
[redacted] **-** Public Health England **(**Scientific Secretariat to JCVI)
Dr [redacted] **-** Public Health England (Head of JCVI Scientific Secretariat)
Professor [redacted]
Dr [redacted] **-** HSCNI
Dr [redacted] **-** HSCNI
Dr [redacted] **-** LSHTM
Dr [redacted] **ry -** PHS
Professor Wei Shen Lim - COVID-19 Chair for JCVI
Dr [redacted] **-** Public Health England
Dr [redacted] **-** PHW
Dr [redacted] **-** NHS England & NHS Improvement
Dr [redacted]

Ms [redacted] **-** Public Health England
Dr [redacted] Public Health England
Dr [redacted] **-** Imperial College London

2. Minutes of EWG meeting of 17th March 2021

2.1 The minutes were subject to one comment on the reporting rate being addressed. This comment was actioned. The amendment was revisited by the Chair who then approved the minutes as a true and accurate record of the proceedings on 22nd June 2021.

3. Update on communications since 17 March 2021

3.1 MHRA had published a statement on 18 March which communicated the findings of the EWG so far, that the currently available evidence does not suggest that blood clots in veins (venous thromboembolism) are caused by COVID-19 Vaccine AstraZeneca, and that a further, detailed review into a very rare and specific type of blood clot in the cerebral veins (sinus vein thrombosis) occurring together with lowered platelets (thrombocytopenia) is ongoing. The EWG was informed that the MHRA advice remained that the benefits of the vaccines against COVID-19 continue to outweigh any risks and that the public should continue to get their vaccine when invited to do so.

3.2 The meeting heard an update on the PRAC review of thrombocytopenia and thromboses, and subsequent communications from the EMA. The meeting also heard that pending further review, PRAC had recommended introducing warnings in the product information for AstraZeneca COVID-19 vaccine to inform of a potential risk of DIC or CVST with thrombocytopenia. The meeting was given an overview of several media articles reporting on studies performed in Germany and Norway, which discuss potential mechanisms for the reported events. It was highlighted that there was no peer reviewed published evidence to date. It was also commented that a collection of cases may be published in the Lancet shortly. The experts noted that while there was a difference in wording between the communications released by the EMA and MHRA, both had stated in press briefings that no causal association with the AZ vaccine had been confirmed.

4. Update on COVID-19 Vaccine AstraZeneca and risk of thromboembolic events with concurrent thrombocytopenia

4.1 The EWG were presented with a summary of the cases available to date of thromboembolic events with concurrent thrombocytopenia following vaccination with AZ, both from the UK and worldwide. A potential case definition was also presented to the EWG.

4.2 Experts commented that many of the cases lacked important information for assessment but noted that the overall benefit:risk of the vaccine was still considered positive for the entire currently vaccinated population. The age groups reported in the cases were considered, and it was noted that older patients may present with different thromboses (such as PE and cardiac) due to variable risk factors. The experts noted that a number of cases in their records had tests for antibodies against heparin/platelet factor 4 (anti-PF4 antibodies) carried out, and that a number of these were positive. There was a discussion of the potential mechanism, including if it could be related to the spike protein which would not be specific to AZ. The EWG advised caution in assuming a link to the vaccine without establishing a mechanism as this had led to erroneous associations in some past cases.

4.3 The possible case definition was discussed, and it was proposed that this could be graded into three categories of diagnostic certainty in a similar way to Brighton Collaboration criteria: possible cases which report thrombosis alongside thrombocytopenia; probable cases which

also report D-dimer >4000 and confirmed cases which also include identified anti-PF4 antibodies. The experts suggested that platelet functional test should be considered in cases with strong clinical correlation if anti-PF4 testing was ambiguous.

4.4 The meeting considered whether there could be any relation to vaccine storage or delivery issues; the MHRA confirmed that there was no evidence to support this at present and also no evidence of a batch-related issue.

5. Updated proforma for case report collection – for agreement

The EWG were provided an overview of the proforma developed between MHRA and haematology experts to aid in gathering important case details on reports submitted to the MHRA. The EWG agreed that this could be refined and that comments should be provided to the MHRA so a final version could be agreed.

6. Risk management proposals including draft treatment guideline

6.1 The meeting considered what information could be gathered to further define risk factors in cases and potentially determine at risk groups. The MHRA also summarised future plans for a call to reporting of cases of interest and collaboration with PHE on data collection including serological testing. The meeting also heard of considerations for studies which could be conducted to further assist in the investigation of this potential risk.

6.2 The meeting discussed the lack of risk factors in many of the cases and highlighted that cases in older patients may not have raised suspicion to trigger full investigation and reporting of the events.

6.3 It was also considered what advice could be provided to advise patients on when to seek help, particularly around symptoms of headache and bruising. It was considered that advice to professionals on treatment protocols should be co-ordinated with NHSE and devolved administrations and ensure that it reaches key stakeholders in a co-ordinated way, while avoiding causing unnecessary concerns on the use of the vaccine.

7. PHE: vaccine benefit by age group and analysis of risk of events of thrombosis with thrombocytopenia

7.1 The meeting was presented with updated analysis from PHE of the events of interest associated with the AZ and Pfizer vaccine in the UK. The presentation highlighted that there was no indication of a raised risk of thromboembolic events with either of the vaccines and of the new terms included there were small numbers of events identified. There was no increased risk identified with the exception of 'Intracranial and intraspinal phlebitis and thrombophlebitis' for which there was indication of a small increased risk for AZ in the under 65 year age group; it was noted that unadjusted confounding could be present and that the numbers were small.

7.2 PHE also presented an analysis of the benefit of COVID-19 vaccination. It was shown that younger age groups required higher number of vaccinations to reduce deaths, hospitalisation and long-COVID, and that this effect of age was less pronounced for hospitalisation and long-COVID prevention. It was also noted that risk factors within age groups could impact this effect. A risk analysis of MHRA cases of CVST and CVST concurrent with thrombocytopenia was also provided, and showed that if causality was assumed, there would be a lower number of doses of AZ needed in the younger age group for an event of CVST with thrombocytopenia to occur, compared with older age groups.

7.3 The EWG discussed the uncertainties of the risk analysis and that due to the rarity of the events, these estimates would likely have wide confidence intervals. The EWG commented that an accurate number of cases is also unknown. The meeting highlighted that a case definition would assist in investigating this further.

8. AstraZeneca: presentation from company on cases received, potential mechanisms and discussion on studies planned

The Chair welcomed the following representatives from AstraZeneca for the meeting today:

8.1 AstraZeneca presented a summary of the cases they had received to date. The meeting heard that the majority of cases were female and younger age, and where dose was reported, these were all first dose. Many of the cases had important information missing. AstraZeneca provided an overview of potential mechanisms and discussed whether these would be specific to the AstraZeneca vaccine and its vector or common to all COVID-19 vaccines and associated with the spike protein. AstraZeneca commented on the challenges of epidemiological study of the combined event of thromboses with thrombocytopenia and stated that the company was engaged with NHSE to develop a protocol to study the potential association further.

8.2 The EWG discussed whether there would be any differences in the spike protein in the AZ vaccine compared to that produced with other vaccines. The company also confirmed to the meeting that no invitro assays had been conducted at present and that it was in contact with international investigators regarding cases too.

9. Next steps / Recommendation

9.1 The EWG discussed the information presented at the meeting. Members commented that the cases lacked significant information at present, that there was insufficient evidence to establish causality at present, and that the events that have been reported are rare. The EWG highlighted that information needed to be gathered on possible risk factors in cases.

9.2 The meeting also noted that there had been potential cases of thromboembolic events with thrombocytopenia reported with the Pfizer vaccine and that this information was important to consider. The meeting concluded that details on these reports should be obtained and presented for further discussion could be given at the next EWG meeting (24 March 2021).

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

None.

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

The next meeting is scheduled to take place on Wednesday 24th March 2021 at 13:30.

The Meeting today started at 15:32 and ended at 19:01.

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

Annex I

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

Chair and Members

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

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

Invited experts

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

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

Observers

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

Annex II

The following participants declared interests and other relevant interests at the meeting today:

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

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

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

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

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

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

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

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

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

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

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

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

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

Professor Turner - NPNS interest. Professor Turner is a Non Executive Director (non-remunerated) on the Board of the Cell and Gene Therapy Catapult (CGT) until the end of March. CGT have been tasked by UK Government with re-purposing a factory in Braintree to manufacture either a vaccine or a therapeutic mAb. No decision has been made as to whether or what product CGT Braintree may be asked to manufacture and that decision will be made by UK Government. Professor Turner does not believe that CGT Board will have any material input into the decision as to what product may be manufactured. Rentschler have signed a contract with the Cell and Gene Therapy Catapult (CGT) to rent one of the manufacturing clean room suites at the Stevenage Centre. Professor Turner understands that this will be for contract AAV manufacture.

Mrs Wang - Other relevant interests arising from being highly sensitive to insect stings, and plant products such as Hyacinth bulbs, as recorded on Mrs Wang's medical records. The family of Mrs Wang lives with several rare diseases and conditions, some of which result in epileptic fits.

Professor Weir - NPNS - Imperial College and Other relevant interest arising from his department collaborates with Imperial College on a number of clinical trials.

Invited Haematology Experts for this meeting

[redacted]

[redacted]

[redacted]

Dr Will Lester - PNS in Pfizer and Sanofi – no interests were declared in relation to vaccines

[redacted]

[redacted]

[redacted]

[redacted] - None

Observers for this meeting

[redacted]

[redacted]

[redacted]

Professor Wei Shen Lim - NPNS arises from the institution (Nottingham University Hospitals NHS Trust) where Professor Lim works has received unrestricted investigator-initiated research funding from Pfizer for an unrelated prospective population-based cohort study of pneumococcal pneumonia in which Professor Lim is the Chief Investigator.

[redacted]

COMMISSION ON HUMAN MEDICINES (CHM)
COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Wednesday 24th March 2021** at **13:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer[1]
Professor G Dougan[1]
Mr VI G Fenton-May
Professor N French
Professor D Goldblatt
Ms S Hunneyball
Professor K Hyrich
Sir M Jacobs
Professor H J Lachmann
Professor P J Lehner
Mr R Lowe
Dr S Misbah
Professor Y Perrie
Professor S Price
Dr A Riordan
Professor T Solomon
Professor K M G Taylor
Dr R Thorpe
Professor M Turner
Dr S Walsh
Mrs M Wang
Professor C Weir

Apologies

Professor C Robertson
Professor P Shah

Secretariat

[redacted]

Key
LD = Licensing Division
NIBSC = National Institute for Biological Standards & Control
VRMM = Vigilance & Risk Management of Medicines
MHRA CEO = Chief Executive
IE&S = Inspection, Enforcement & Standards
Comms = MHRA Communication

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD

Presenter supporting specific item

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

MHRA Observers

[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
Dr S Branch - VRMM
[redacted] - LD
[redacted] - MHRA-NIBSC
[redacted] - LD
[redacted] - MHRA-Policy
[redacted] - LD
[redacted] - Comms
Dr SP Lam - LD
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - VRMM
[redacted] - IE&S
[redacted] - LD
Dr J Raine - MHRA CEO
Ms N Rose - MHRA-NIBSC
[redacted] - MHRA-NIBSC
[redacted] - LD
[redacted] - LD
Mr P Tregunno - VRMM
[redacted] - LD
[redacted] - MHRA-NIBSC
[redacted] - LD
Dr K Wydenbach – LD

[redacted]
4 February 2022

[1] left during item 5

1. Introduction and Announcement

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

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1.3 Participants declared interests and other relevant interests for this meeting listed at **Annex II** to the minutes.

1.4 Apologies were received from Professors Robertson and Shah for this meeting.

2. Minutes

2.1 Minutes of EWG Meeting on Wednesday 13th January 2021

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

2.2 Minutes of EWG Meeting on Monday 18th January 2021

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

3. Update on cases of thromboembolic events with thrombocytopenia occurring with Pfizer and Astra-Zeneca COVID-19 vaccines

3.1 At the meeting on 23 March 2021, the EWG had noted that there had been potential cases of thromboembolic events with thrombocytopenia reported with the Pfizer vaccine. The MHRA confirmed that to date no UK cases of thromboembolic events with thrombocytopenia had been received following Pfizer COVID-19 vaccination but that one non-UK case of cerebral venous sinus thrombosis (CVST) with concurrent thrombocytopenia in association with the Pfizer vaccine had been reported. The EWG heard that the MHRA was seeking urgent clarification from the European Medicines Agency regarding other potential cases of thromboembolic events with thrombocytopenia occurring with the Pfizer vaccine.

3.2 The EWG heard that since their previous meeting on 23 March 2021, the MHRA had received details of cases of thromboembolic events with concurrent thrombocytopenia following vaccination with AstraZeneca COVID-19 vaccines from haematology experts. Following this, the MHRA were now reconciling such cases with Yellow Card reports on the MHRA database, where this was possible given the limited information in some reports. The EWG noted that there were now over 30 cases of thromboembolic events with thrombocytopenia with AstraZeneca, including cases with and without reported possible confounding factors.

3.3 The EWG highlighted that the background rate of thromboembolic events with thrombocytopenia is not known. The EWG discussed possible ways to obtain further information about the background rate including the feasibility of using laboratory, radiological, or the UK Biobank databases. The EWG considered that one approach would be to identify cases with a clinical diagnosis of CVST (and related terms) and then look at platelet counts to identify if any of these cases occurred with concurrent thrombocytopenia.

3.4 The EWG discussed anti-PF4 antibodies which had been reported in some of the cases of thromboembolic events with thrombocytopenia following AstraZeneca COVID-19 vaccination. The EWG considered anti-PF4 antibodies might not be the only identifying factor in such cases and that was important to know the background incidence of anti-PF4 antibodies in general and in people who had received a COVID-19 vaccine.

3.5 The EWG noted that the cases of CVST with thrombocytopenia that had been reported with AstraZeneca COVID-19 vaccine included cases without pre-disposing factors for CVST. The EWG commented that this was unusual in comparison with previously published reports of CVST in which most patients had a predisposing risk factor for this event.

3.6 The EWG noted that the need for any updates to the product information for AstraZeneca COVID-19 vaccine would be considered at a future meeting when more data would be available including further information on any additional cases in association with the Pfizer COVID-19 vaccine.

4. Novavax NC AR Sequence 1

4.1 The EWG heard the Matrix M1 adjuvant proposed for use in this vaccine has not been used in any vaccines authorised in UK or EU, but may be included in a Hepatitis vaccine in the US (yet to be fully confirmed): it has been used in other vaccines the company has in development. The EWG noted the review of the toxicology data for this adjuvant will need to be particularly in-depth, as human use is relatively recent. The EWG noted that the toxicity studies provide sufficient pharmacological and immunological data to support use of the vaccine in principle, notwithstanding the need for a comprehensive characterisation of the Matrix M1 adjuvant. The EWG also noted the available literature on the Matrix M1 adjuvant does not cover all aspects necessary to assure safety, and therefore additional supportive data will be required from the company. The EWG heard a parallel assessment is being undertaken by the EMA. The EWG noted that the company should be asked whether they intend to supply further data on the Matrix M1 adjuvant.

4.2 The EWG noted that glycosylation of antigens in some circumstances can block access to epitopes, [redacted]. The EWG heard the [redacted] The FluBlok vaccine also uses a baculovirus expression system resulting in glycosylated antigens and this product is widely authorised.

4.3 The EWG noted that the Novavax vaccine is clearly immunogenic, and T-cell responses are well balanced if slightly skewed [redacted] The challenge data in macaques showed sub-genomic SARS-CoV-2 RNA to be undetectable in vaccinated animals, a similar result was noted in non-clinical (NC) studies of the Moderna Vaccine. The AstraZeneca vaccine, however, did not completely eliminate virus in the nose. It is not yet known if the Novavax NC challenge data will translate to reduced transmissibility or perhaps superior efficacy in clinical trials.

4.4 The EWG Novavax data package on immunology was comprehensive, but the EWG noted that the previous application data packages for other, since authorised vaccines, additionally included studies of T-cell exhaustion, although, as of yet, this data has not proved useful.

4.5 The Chair explained that the clinical package is expected to be received shortly, and the data on variants will be a key aspect of the assessment process.

4.6 The EWG heard the Phase I/II data is expected within 2 weeks, and the phase III clinical study is expected to be submitted mid-April. The Chair confirmed that the EWG should be approached for advice on a rolling basis, in line with receipt and review of each data package, rather than the EWG advising on the entire clinical dossier.

4.7 The Chair asked about the mechanism underpinning the differential Th responses to alum adjuvant and Matrix M1. The MHRA noted that the means by which alum induces a Th2-favoured response is not known, but it is reliably established that it does.

4.8 The EWG endorsed the proposed list of questions, also seeking to clarify of there is commercial human use of the M1 matrix adjuvant. The MHRA confirmed the questions will be issued to the company with a deadline of four weeks for response. The company have already indicated that they intend to submit additional NC data to MHRA. It is hoped that these two components (responses, new data) can be brought to the EWG at a future meeting, in early May.

5. Novavax Quality Update

5.1 The EWG were provided with an overview of the manufacturing development. The EWG noted the [redacted] may be complicated by the [redacted] The forms need to be appropriately controlled, [redacted]. The EWG also noted the batch of product used in the clinical trial may not show an appropriate level of similarity to the batches created at production scale. The [redacted] issue should be considered a matter of [redacted] The potential for [redacted] to affect clinical outcomes needs to be investigated and understood. The EWG noted the [redacted] will also affect the [redacted] of the product and could impact [redacted]. The EWG noted that the heterogeneous nature of the product may be unavoidable; however, theoretically suitable antibody selection for the potency assay could qualify the product to a level that is satisfactory for authorisation. Ultimately, the company need to demonstrate that [redacted] of their product does not affect function.

5.2 The EWG endorsed the summary on [redacted] as detailed in the paper prepared by the assessment team. On a related topic, the EWG heard the [redacted] is proposed to demonstrate the potency of commercial batches but is intended for use outside of the release specification.

5.3 The EWG noted the revised [redacted] should be qualified for the purposes of release testing and used to replace the [redacted] The release specification limits also need to be configured to include both an upper and lower limit.

5.4 On a separate topic, the EWG noted that the absence of a signal of coagulopathy in the pre-clinical studies was reassuring. However, if cases of coagulopathy were to appear within the clinical trial, it will need to be established if the phospholipid content of the formulation could be a contributory factor. Currently, the literature on anti-phospholipid in humans shows auto-phosphatidylcholine antibodies can be produced by humans, but these do not appear to be pathogenic.

5.5 The MHRA confirmed meetings have recently occurred weekly with the company, the latest update is that PPQ batches are to be expected mid-April – May. The company are also participating in a rolling review (emergency use) application with the FDA.

6. Janssen update on the 'Reliance Procedure

6.1 The EWG heard that the Janssen Covid-19 vaccine is the first application in the UK with a single dose regimen. It received Emergency Use Authorisation (EUA) in the US on 27 February 2021 and the EMA issued a Conditional Marketing Authorisation (CMA) on 11 March 2021. The CMA submission to the MHRA followed later. The EWG were advised that a Regulation 174 request has not been received from DHSC and that this procedure would follow the EU Decision Reliance Procedure (but with an expedited timetable).

6.2 The EWG noted that the assessment for this regulatory route focuses on 'GB specific considerations' with points raised only if they are considered 'decision critical' meaning any concern which, if not addressed satisfactorily, changes the benefit risk from positive to negative.

6.3 The EWG heard that the complete data package is expected for the Reliance procedure shortly, and that this item will be brought back to the EWG once the assessment team has completed their assessment. It was noted by the assessors that, subject to review of the complete submission, no decision critical points are anticipated. The EWG heard that whilst there were no cases of anaphylaxis up to the data cut-off, there was a report of a delayed hypersensitivity reaction in a subject with angioedema and urticaria several days after vaccination. There was also a late breaking case of anaphylaxis that met the Brighton Collaboration Case Definition after the data cut-off. The EWG heard that the EMA have included a recommendation in the product information that individuals are observed for 15-minutes post vaccination to monitor for potential allergic / hypersensitivity reactions. This is in-line with the recommendations for all COVID-19 vaccines approved by the EMA to date.

6.4 The EWG noted the company are undertaking a second pivotal efficacy trial with two doses, whereas the present data package is based on a single dose pivotal trial. The EWG asked what the outcomes for 'the first' CMA would be, if the two-dose trial subsequently shows better efficacy, and/ or increased durability of immune response. The EWG heard when comparing data from single and two-dose studies in hamsters no differential response was seen. The MHRA assessor noted that if a Regulation 174 authorisation were to be conferred for the single dose, and subsequently greater benefit is shown in the two-dose trial, this may complicate aspects of vaccine policy and roll-out. Particularly, the issue how to manage the time interval for those who have had one dose under the initial regulation 174. However, the single dose vaccine meets the regulatory requirements.

6.5 The MHRA assessment team also confirmed that the data currently available show efficacy up to 2 months post dose and persistence of immunogenicity up to 3 months with the single dose. Longer follow-up data will be provided post-approval.

6.6 The MHRA assessor informed the EWG that 95% of subjects developed neutralising antibodies against the adenoviral vector after a single dose. Available data are limited, but presently show little correlation between levels of antibody against SARS-CoV-2 after the second dose and levels of neutralising antibody against the vector after the first dose. The second dose approximately doubles levels of neutralising antibodies against SARS-CoV-2, but this would need to be balanced against risks of development of neutralising antibodies against the adenoviral vector after the first dose.

6.7 The EWG noted the ongoing signal of rare cases of thrombosis with thrombocytopenia with COVID-19 vaccines. The EWG heard that unlike the AZ vaccine, the Spike protein in the

Janssen vaccine is [redacted]. The EWG noted that 2.5 million doses of the Janssen vaccine have been administered in the US and requested that this data is explored for signals of thrombosis with thrombocytopenia. The MHRA assessment team will also confirm whether or not the EMA have requested the company to submit a protocol for a post-authorisation study in relation to coagulopathy.

6.8 The EWG enquired about the justification of non-COVID-19 vaccine controls in forthcoming studies. The MHRA confirmed that in the Janssen one-dose trial, following the EUA in the US, all subjects on placebo will be offered the vaccine and encouraged to remain in the study for follow-up. The Chair noted the regulatory landscape in terms of clinical trials for future COVID vaccines will likely be adapted to our increased understanding of COVID-19 vaccines, and immunogenicity studies will likely be used to replace trials once a high coverage of the population has been reached.

7. Any Other Business

None.

8. Date and time of next meeting

The next meeting is scheduled to take place on Wednesday 31st March 2021 at 11:30.

The Meeting today started at 13:32 and ended at 15:47.

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

Annex I

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

Chair and Members

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

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

Invited experts

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

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

Observers

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

Annex II

The following participants declared interests and other relevant interests at the meeting today:

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

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

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

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

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

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

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

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

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

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

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

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

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

Professor Turner - NPNS interest. Professor Turner is a Non Executive Director (non-remunerated) on the Board of the Cell and Gene Therapy Catapult (CGT) until the end of March. CGT have been tasked by UK Government with re-purposing a factory in Braintree to manufacture either a vaccine or a therapeutic mAb. No decision has been made as to whether or what product CGT Braintree may be asked to manufacture and that decision will be made by UK Government. Professor Turner does not believe that CGT Board will have any material input into the decision as to what product may be manufactured. Rentschler have signed a contract with the Cell and Gene Therapy Catapult (CGT) to rent one of the manufacturing clean room suites at the Stevenage Centre. Professor Turner understands that this will be for contract AAV manufacture.

Mrs Wang – Other relevant interests arising from being highly sensitive to insect stings, and plant products such as Hyacinth bulbs, as recorded on Mrs Wang's medical records. The family of Mrs Wang lives with several rare diseases and conditions, some of which result in epileptic fits.

Professor Weir - NPNS - Imperial College and Other relevant interest arising from his department collaborates with Imperial College on a number of clinical trials.

COMMISSION ON HUMAN MEDICINES (CHM)
COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Wednesday 31st March 2021** at **11:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan[1]
Mr VI G Fenton-May
Professor N French[2]
Professor D Goldblatt
Ms S Hunneyball[3]
Professor K Hyrich
Sir M Jacobs
Professor H J Lachmann
Professor P J Lehner
Mr R Lowe
Dr S Misbah
Professor Y Perrie
Professor S Price
Dr A Riordan
Professor C Robertson
Professor T Solomon
Professor K M G Taylor
Dr R Thorpe
Professor M Turner
Dr S Walsh
Mrs M Wang
Professor C Weir

Apologies

Professor P Shah

Invited Experts

[redacted]

Observers

[redacted]

Professor W S Lim

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD

Presenter supporting specific item

[redacted]

MHRA Observers

[redacted]
Dr S Branch - VRMM
[redacted]
Dr J Raine - MHRA CEO
Ms N Rose - MHRA-NIBSC
[redacted] - MHRA-NIBSC
[redacted]
Mr P Tregunno - VRMM

Secretariat

[redacted]

Key
LD = Licensing Division
NIBSC = National Institute for Biological Standards & Control
VRMM = Vigilance & Risk Management of Medicines
MHRA CEO = Chief Executive
Comms = MHRA Communications

[redacted]

[1] joined during item 3
[2] joined during item 2
[3] joined during item 5

4th February 2022

1. Introduction and Announcement

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

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

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

1.3 Participants declared interests and other relevant interests for this meeting listed at **Annex II** to the minutes.

1.4 Apologies were received from Professor Shah for this meeting.

1.5 The Chair welcomed Invited Experts, Professor [redacted], Professor of [redacted] who presented item 2 and left after this item. Dr [redacted] Public Health England joined and presented item 6.

1.6 The Chair welcomed the following observers:

[redacted] – NHS England
[redacted] PHS
[redacted] – PHW
[redacted] Miller – PHE
[redacted] – NHS England
[redacted] – PHE
[redacted] – PHE
Professor Wei Shen Lim – JCVI

2. Vaccine Safety Study

2.1 The EWG viewed slides and heard a presentation by researchers at the University of Edinburgh on the studies conducted in Scotland using a nationwide platform called EAVE (early assessment of antivirals and vaccine effectiveness) II. EAVE II was originally created to respond to the N1H1 (swine flu) pandemic, and is used to link data to monitor, understand and mitigate the effects of a pandemic. The aim of EAVE II is to create a national, real-time prospective cohort, using Scotland's health data infrastructure to investigate the effectiveness and safety of vaccines and treatments.

2.2 The EWG heard that the objectives were i) to investigate the impact of the first dose of vaccine on COVID-19 hospitalisations, ii) to estimate the frequency and characterise severe COVID-19 events i.e.COVID-19 hospitalisations and deaths after 14 days post first dose, and iii) to investigate the association between first doses of vaccines and vascular adverse

events, specifically venous thromboembolic disease and cerebral sinus venous thrombosis (CSVT), haemorrhage, and thrombocytopenia and idiopathic thrombocytopenia (ITP).

2.3 The EWG heard that a prospective cohort study was conducted using the EAVE II database comprised of linked vaccination, primary care, real-time polymerase chain reaction (RT-PCR) testing, hospitalisation and mortality records of 5.4 million people in Scotland. A time-dependent Cox model and Poisson regression models were fitted to estimate effectiveness against COVID-19 related hospitalisation (defined as 1-adjusted Hazard Ratio) following the first dose of the Pfizer/BioNTech and AstraZeneca vaccines.

2.4 The EWG noted that the overall vaccine effect in relation to risk of hospitalisation was assessed across all age groups. The findings of the study for both vaccines showed reduced risk of hospitalisation amongst the vaccinated (with a vaccine effect of 70% at 21-34 days post-vaccination) compared to the unvaccinated individuals. It was noted that limited data was analysed for the AstraZeneca vaccine beyond 28 days post-vaccination, but the data showed some effect of a comparable order of magnitude to the clinical trials. The EWG also heard that the results of the vaccine effect were similar in those aged 80 years and over with a vaccine effect of 60-90%.

2.5 The EWG heard that the national data demonstrated correlation between a single dose of the Pfizer/BioNTech and AstraZeneca vaccines and reductions in the risk of COVID-19 related hospitalisations in Scotland.

2.6 The EWG heard the details of a second ongoing prospective cohort study which investigated the effect of Pfizer/BioNTech and AstraZeneca vaccines 14 days after the first dose to second dose or end of study. The analysis period was between 08 December 2020 to 08 March 2021.

2.7 The EWG heard that the results showed that out of 1,679,756 individuals that were given the first dose of either vaccines, 481 were hospitalised and 260 died of COVID-19. The EWG heard based on the data from distribution of incidents, the majority of deaths occurred with the Pfizer/BioNTech vaccine which was targeted to people in care homes, whereas the AstraZeneca vaccine was given to over 80 year olds who were largely living in the community.

2.8 The EWG heard the interim analysis based on adjusted rate ratios shows higher risk of severe outcomes (hospitalisation or death) in males (with 33% increase) and in the older population aged 80 and over. It was also noted that other characteristics such as presence of comorbidity, higher deprivation, smoking status and no previous COVID-19 infection also influenced the risk ratio of both vaccines.

2.9 The EWG was also presented with details of a third ongoing study to investigate the association between first doses of vaccines and vascular adverse events. The EWG noted that an incident case-control study nested within the prospective cohort study was undertaken on data from consultations requested during a period from 8 December 2020 to 14 March 2021. The EWG heard that very few CSVT events (16 cases) were reported, with less than 5 events amongst individuals vaccinated with the Pfizer/BioNTech or AstraZeneca vaccines. It was reported that most of the events were in unvaccinated individuals. The EWG noted that further analysis will be performed once more data is collected.

2.10 The EWG heard that a seasonal pattern was not associated with the number of consultations; however, an increase in the number of consultations for ITP was observed in 2021.

2.11 The EWG heard that the observed and expected number of events, post vaccination, in the incident case-control study showed no evidence of an increased risk of venous thromoboembolic disease (excluding CSVT), haemorrhage and thrombocytopenia. However, the observed number of ITP events in those vaccinated with AstraZeneca vaccine was higher compared to the expected number of events in those aged 60-79.

2.12 The EWG heard that the preliminary results suggested that there is a signal for ITP with 0.82 cases per 100,000 doses of vaccine. It was also noted that due to the lag of discharge of data, analysis may be incomplete as this is reliant only on the GP data. Further analysis will be carried out to investigate whether the ITP is the causal risk with the AstraZeneca vaccine.

2.13 Discussion/Comments

2.13.1 The EWG asked whether the 260 cases that died were confirmed COVID-19 deaths based on death certificate data. The investigator stated that the deaths mainly occurred in elderly patients who tested positive for COVID-19 and died within 28 days of contracting COVID-19. The association of deaths with COVID-19 was also confirmed from the death certificates.

2.13.2 The EWG questioned whether genomic sequencing of virus had been conducted on samples obtained from the 260 who had died and whether this data could be linked to different variants of concern. The investigator stated that work is in progress, whereby a systematic genome sequencing of the positive cases is conducted, and the potential vaccine failures are linked to the genome data in order to identify variants.

2.13.3 The EWG asked whether smoking was independent of the other risk factors such as comorbidity, sex and deprivation. The investigator stated that smoking was an independent factor.

2.13.4 The EWG enquired whether differences were seen in mortality between individuals admitted from care homes versus from the community, and whether an indication of exposure to higher viral load in care homes was seen which had contributed to hospitalisation and death. The EWG heard that initially there were difficulties obtaining the necessary data to explore this question, but recently this has changed, and the relevant research may soon be possible.

2.13.5 The EWG asked whether analysis of data after 21 days, where immunity appears, or 28 days post vaccination will be undertaken. The investigators confirmed that data analysis following 21 and 28 days post vaccination will be undertaken, and the results will be provided to the MHRA.

2.13.6 The EWG inquired if there was a correlation between obesity and death. The investigators confirmed correlation between obesity and death when presented as a single factor, however, obesity is dominated by the other factors when present with comorbidities.

2.13.7 The EWG noted that natural ITP events are more common in those aged 60 and over. However, data analysed confirmed that more events of ITP were observed than expected in those aged 60-79 with the AstraZeneca vaccine. It was not possible to compare the data for those aged 40 and under due to limitations of the dataset.

2.13.8 The EWG asked that if there is a possibility of tracking the ITP patients aged 60-79 years to confirm that the diagnosis was correct and measure the anti-PF4 antibody in those patients. The EWG heard that it is problematic to link data to these patient records as they are anonymised in line with the privacy agreements on GP data.

2.13.9 The EWG noted both ITP and heparin induced thrombocytopenia (HIT) syndrome are both autoimmune conditions affecting the platelets. However, in classic ITP the most commonly elevated antibodies against platelets are glycoprotein IIb-IIIa or Ib-IX, whereas in HIT syndrome antibodies against platelet factor 4 (PF4) are elevated. The EWG noted additional information is needed to understand the pathogenesis of ITP and HIT and to evaluate potential relationships between them. The EWG also noted that ITP is a complex diagnosis that can be difficult to validate.

2.13.10 The EWG asked if there was a possibility of the ITP cases were also previously diagnosed (prior to vaccination) and if the reduction in platelets was exacerbated rather than initiated by the vaccine. The investigators stated that a special permission is required to retrace these patients and perform further analysis. The EWG advised that these issues need further investigation as it is known that ITP can be affected by a precipitant. The possibility that the case reports reflect previously undiagnosed and/or subclinical clinical ITP also needs to be explored.

2.13.11 The EWG were informed by the MHRA that analysis on hospital episode statistics (HES) data were conducted to investigate the ecological analysis of ITP pre-pandemic and during the pandemic. The EWG heard that data from Public health England showed a marked reduction in ITP cases during the pandemic compared to pre-pandemic levels. CPRD continues to conduct sequential monitoring for ITP which identified an excess number of ITP cases with the AstraZeneca vaccine in younger patients. The MHRA noted the source of the large difference in the underlying baseline rate of ITP in previous years versus during the pandemic need to be investigated. The EWG noted it may be useful to undertake a self-control case series analysis of the CPRD data to mitigate against changes in baseline rates.

2.13.12 The EWG suggested that further analysis is required to confirm the ITP signal with the AstraZeneca vaccine.

3. Risk of anaphylaxis with Pfizer/BioNTech COVID-19 vaccine and review of the recommended observation time

3.1 The EWG noted that Pfizer/BioNTech COVID-19 vaccine UK product information (PI) currently advises that those with known hypersensitivity to any of the vaccines ingredients should not receive the vaccine, and that appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction. Close observation for at least 15 minutes is also recommended. This issue has been previously considered twice in January by the EWG when the current wording to the PI was endorsed. The EWG heard that the total number of doses administered for this vaccine to 24th March 2021 is 10.9 million first doses and 2.5 million second doses. The MHRA has received a total of 256 reporting PTs of anaphylaxis or the related terms (reporting rate of 1.9 cases per 100,000 doses) and among them 87 cases were identified as being possibly or probably meeting levels 1-3 diagnostic criteria of the Brighton collaboration criteria (reporting rate of 0.65 cases per 100,000 doses). Around 60% of anaphylaxis cases were reported to occur within 15 minutes after vaccination.

3.2 The EWG agreed that the current PI is appropriate and agreed on the need to keep the recommendation for 15 min observation time. Although better evidence on possible transmission occurring in vaccination centres is welcomed, it is at present difficult to attribute a possible increased risk of contracting Covid19 to the waiting time alone, without also considering all other steps involved in the vaccination process (for example travel to the vaccination centre on public transport). The EWG discussed the need to maintain public confidence in the program and the fact that a change in recommendations could generate confusion in the public and loss of confidence if supervision is withdrawn and an incident occurs.

4. Safety of COVID-19 Vaccines in Pregnancy

4.1 The EWG noted that limited information is available for use of COVID-19 vaccines in pregnancy and so are not currently recommended for use during pregnancy but may be given to front-line healthcare workers and pregnant women with underlying health conditions that place them at greater risk of severe illness.

4.2 Yellow card reports have been received for both the Pfizer-BioNTech and Oxford-AZ vaccines (n=89 and 114 respectively), with most reports related to vaccination occurring early in pregnancy.

4.3 Reports of first trimester miscarriage have been received for both vaccines, both with and without other reactions to the vaccine being reported for the same cases. Based on the number of reports received, the rate of miscarriages for the Oxford-AZ vaccine (23%) is similar to the 25% background rate expected in the UK, whereas the reporting rate for the Pfizer-BioNTech vaccine is currently higher (54%). The EWG noted that data on numbers of vaccinations administered to pregnant women are not yet available to give an accurate estimate of miscarriage rates and that data from the USA for this and the Moderna vaccine has shown a lower miscarriage rate than expected from background.

4.4 A few reports of preterm deliveries following third trimester vaccination have been received but pregnancy outcomes for the majority of 2nd and third trimester vaccines are not yet known.

4.5 The EWG noted that pregnancy carries an elevated risk of blood clots due to hypercoagulability especially in later pregnancy and postpartum. One case of deep vein thrombosis in a leg had been reported following a third trimester vaccination which was being treated according to standard obstetric practice.

4.6 Overall, the EWG considered that the current data are limited but do not raise any particular safety concerns.

4.7 The EWG noted that randomised controlled trials in pregnant women are proposed for the Pfizer-BioNTech vaccine and for the Janssen vaccine (not yet authorised in the UK) whilst an observational cohort study is proposed to investigate safety of the Oxford-AZ vaccine in pregnancy.

5. Discussion on update of thromboembolic events associated with thrombocytopenia reported following COVID-19 vaccination

5.1 The EWG was presented with an update on the issue of thromboembolic events with thrombocytopenia; a review of cases of thromboembolic events associated with thrombocytopenia following vaccination with COVID-19 Vaccine AstraZeneca; a review of cases of thromboembolic events associated with thrombocytopenia following vaccination with other COVID-19 vaccines and a presentation of epidemiological data.

5.2 The EWG heard an updated summary of actions regarding the issue of thromboembolic events and thrombocytopenia, which included:

- temporary suspension of use in people aged less than 55 years in Canada by the Public Health Authority,
- a recommendation by the German Standing Committee on Vaccination (STIKO)

- MHRA's statement on 18th March which communicated the Expert Working Group (EWG) advice that the available evidence currently does not suggest blood clots in veins (venous thromboembolism) are caused by COVID-19 Vaccine AstraZeneca, and that a further, detailed review into a very rare and specific type of blood clot in the cerebral veins (sinus venous thrombosis) occurring together with lowered platelets (thrombocytopenia) is ongoing.
- EMA made a similar statement on 18th March with a decision to update the product information while further investigations were ongoing.

5.3 The EWG was presented with some background information and background rates of thromboembolic events, cerebral venous sinus thrombosis (CVST) specifically, and thrombocytopenia. It was noted that both thrombosis and thrombocytopenia are known to occur in COVID-19 infection - occasionally with mild disease and even after recovery from acute infection. There is also a correlation of these events with severe disease and death.

5.4 The EWG heard that cases reported to MHRA have been evaluated and validated using the WHO-UMC causality assessment system and the case definition which had been established by the EWG and invited haematology experts. The case definition is as follows:

- Confirmed case: Venous/ arterial thrombosis + Platelet count < 150 + D-dimer > 4000 + anti-PF4 antibodies
- Probable: Venous/ arterial thrombosis + Platelet count < 150 + D-dimer > 4000
- Possible case: Venous/ arterial thrombosis + Platelet count < 150
- Unlikely: Criteria met for any of the above BUT alternative diagnosis more likely to explain event.
- Criteria not met: only one or none of the criteria met

A summary of the outcomes of case validation and adjudication was presented, with case details and the validation results provided as an annex in advance of the meeting. Summary details of reported sex and a breakdown of reported ages per classification category were also presented.

5.5 The EWG noted the invited haematology expert's considerations from the adjudication of cases and the difficulties in evaluating the data due to insufficient information in some reports such as the sequence of events (and therefore ability to discern whether cases were predominantly thrombotic or haemorrhagic). The EWG noted the expert's comment that some cases were atypical in that they reported CVST with haemorrhages (which was uncommon), and also that haemorrhage would be unusual if the events are due to a HITT-like mechanism. However, neurologists felt that haemorrhage does occur in patients with CVST even in the absence of thrombocytopenia.

5.6 The EWG discussed the case definition and concluded that it was appropriate and is currently broad enough to capture possible cases and that it can be narrowed and refined as we learn more. The EWG commented that both venous and arterial thromboembolic events should be included in the case definition and that there was not a need to specify a time to onset until a proposed mechanism is better understood.

5.7 The EWG commented that a better understanding of the rate of PF4 antibody positivity in the vaccinated population in general and in people who had had a COVID-19 infection would be valuable. Public Health England informed the EWG of plans underway to gather data on background presence of antibodies to PF4 using samples from older vaccine recipients, unvaccinated individuals and convalescent samples.

5.8 The EWG noted recent literature which quoted the background rate of CVST as 15 per million per year, with 5% mortality. The number of cases and those that were fatal were therefore of significance. The EWG considered that there may be more reporting of such events in younger age groups as they may be less recognised, diagnosed and investigated in older people. In the elderly, symptoms may be ascribed to an ischaemic stroke without undertaking a CT venogram potentially underestimating the incidence of CVST in the elderly. The EWG also considered that differences in the deployment strategies between the AstraZeneca and Pfizer vaccines may affect reporting of potential cases, as elderly people in care homes mostly received the Pfizer vaccine.

5.9 The EWG heard that work was ongoing with collaboration between neurologists and haematologists to establish background rates using neurology and radiology centre data on CVST events and linking it to records of the patients' platelet counts.

5.10 The EWG discussed possible mechanisms for the events reported. A HITT-like mechanism has been proposed by international research groups, due to the presence of anti-PF4 antibodies in some affected patients. It was noted that PF4 can be stimulated by inflammatory responses and that there were likely many conditions that can stimulate PF4, with tuberculosis being one example. The EWG commented that it could be associated with the PF4 antibodies plus a currently unknown other factor(s). Nevertheless, the EWG noted that it could take a long time to identify a mechanism.

5.11 The EWG considered that the onset times of the reports showed a temporal association with vaccination. However, they noted that the pattern seen in onset times could be due to a healthy vaccinee effect following vaccination and then fewer cases with longer onset times due to a lack of longer follow-up time after vaccination and a detection bias in cases with longer onset times.

5.12 The EWG concluded that while there was a temporal association between vaccination and the reported events, the mechanism had not been confirmed and thus a causal association with the AstraZeneca vaccine could not be established. The EWG considered that useful information could be gleaned from data from 2nd doses; however, there currently was not sufficient 2nd dose data to analyse any potential risks.

5.13 The EWG heard that no UK cases of thromboembolic events with thrombocytopenia had been reported for the Pfizer vaccine. However, one case had been reported in Italy (of cerebral venous thrombosis with thrombocytopenia), as well as a Slovenian report of M2 branch thrombus with a low platelet count and an Italian case of pulmonary embolism with thrombocytopenia. Non-UK cases were also validated with the criteria described above. MHRA highlighted a US publication of a series of cases reporting thrombocytopenia within 2 weeks of vaccine with mRNA COVID-19 vaccines. Two cases reported thrombotic events with thrombocytopenia following Pfizer vaccine. MHRA also reported on 1 case from clinical trials and another from post-marketing use of the Janssen vaccine in the US.

5.14 The EWG was presented with statistics on the cumulative exposure to the AstraZeneca and Pfizer vaccines, broken down by age, followed by estimates of the incidence rates of CVST with thrombocytopenia and as well as for all thromboembolic events with thrombocytopenia, broken down by age and gender.

6. An updated epidemiological analysis of the risks of thromboembolic events and potential further study

6.1 The EWG heard the MHRA review of an analysis from PHE of the events of interest associated with the AZ and Pfizer vaccine from hospital admissions data in the UK. The presentation highlighted that there was no indication of a raised risk of thromboembolic

events with either of the vaccines. There was no increased risk identified with the exception of 'Intracranial and intraspinal phlebitis and thrombophlebitis' for which there was indication of a small increased risk for AZ in the under 65 years age group; it was noted that unadjusted confounding could be present and that the numbers were small. The EWG was also informed about an analysis of the benefit of COVID-19 vaccination based on a PHE review. The number of cases of hospitalisation, death and long-COVID prevented per 1 million vaccinations per age group was presented, along with the number of cases and fatal cases of thromboembolic events expected to be reported per 1 million doses.

6.2 The EWG were also presented with opportunities for further epidemiological analysis.

6.3 When discussing the benefit risk in different age groups, the EWG again commented that there could be under reporting of events in elderly people due to a less thorough investigation of neurological symptoms. That being said, the EWG noted that the age distribution seen is typical for CVST events in the non-vaccinated population.

6.4 The EWG discussed whether risk mitigation was needed due to the presence of an alternative vaccine where these events are not seen at the same level, however it was agreed that risk benefit evaluations should be made without consideration of other vaccines.

6.5 The EWG considered that the overall risk of thrombosis with thrombocytopenia remains low but there is concern of significant harm for individual patients. In younger age groups, the risk of COVID-19 and associated complications might not be as high and so the benefit risk from the vaccine in these groups may be different to older groups. It was however noted that while Long COVID is still not well understood, this is an important risk in young people and a potential decrease in this risk would be an additional benefit of vaccination.

6.6 The EWG was not able to identify any specific risk factors but did note that cases with confounding factors should be further investigated to determine if there are any specific populations at risk.

6.7 The EWG concluded that based on current data it not possible to establish an age group where the benefit risk was negative but recognised that irrespective of causality, early identification of such events and correct treatment were needed.

6.8 The EWG commented that the gender bias usually seen with CVST has not been established in the reported cases, which could also suggest a causal link. It was agreed that simple and clear messaging on warning signs is needed so that cases could be identified early, reported in detail and managed clinically.

6.9 The EWG was presented with an overview of planned and ongoing pregnancy studies for the Pfizer and AstraZeneca vaccine, as well as initiated paediatric studies.

6.10 The EWG heard that there was clear support from the Paediatric Medicines Expert Advisory Group for vaccine studies in children with careful evaluation of safety in this population. The EWG considered it reasonable to suggest that children will be at lower risk of these events as thromboembolic risk factors are much lower in children and also there were no documented cases of HITT in children.

6.11 The EWG concluded that paediatric and pregnancy trials should not be stopped at this point, but there needs to further evaluation of the pregnancy trials, and pregnancy exposure to date.

6.12 The EWG advised that the benefit/risk is still overwhelmingly positive, however younger age groups may have risk minimisation needs. Further work is needed on case definition and

case ascertainment will be important. Understanding the background rate of these thromboembolic events with concurrent low platelets will be critical as it is not currently clear if or how much higher above background rates these events are currently occurring. Better mechanistic data is needed to establish causality. Currently a temporal association is seen with vaccination, but causality has not been established.

6.13 The EWG considered it important to communicate what is currently understood about these events with clear, simple messaging in order that vaccine recipients can be appropriately informed. The EWG highlighted the two important audiences for communications; the general population and the healthcare professionals in order to minimise misinformation and establish MHRA evidence as the single point of truth.

6.14 The EWG supported the co-ordination with the EMA and WHO, and to consider lessons learnt from previous high-profile vaccine communications.

6.15 Regarding the content of communications, the EWG advised that the benefits of vaccination should be emphasised in order to contextualise this small potential risk. Information about the potential risk should be provided in absolute terms, with the uncertainties stated. The upper estimate of the risk should be presented, compared to the potential risks from COVID-19 infection.

6.16 The EWG advised that communications should avoid segmenting young vs old or by gender as there are currently too many uncertainties. It should be made clear that it remains a dynamic situation which is still under extensive investigation and advice might change as evidence emerging.

7. Any Other Business

7.1 None.

8. Date and time of next meeting

The next meeting is scheduled to take place on Tuesday 6th April 2021 at 12:30.

The Meeting today started at 11:32 and ended at 14:42.

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Annex I

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

Chair and Members

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

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

Invited experts

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

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

Observers

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

Annex II

The following participants declared interests and other relevant interests at the meeting today:

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

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

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

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

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

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

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

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

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

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

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

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

Professor Robertson - Other relevant interest arising from presenting a vaccine safety study alongside Professor Sheikh of Primary Care Research and Development to the EWG on behalf of the EAVE II and DaC-VaP Collaborators.

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

Mrs Wang - Other relevant interests arising from being highly sensitive to insect stings, and plant products such as Hyacinth bulbs, as recorded on Mrs Wang's medical records. The family of Mrs Wang lives with several rare diseases and conditions, some of which result in epileptic fits.

Professor Weir - NPNS - Imperial College and Other relevant interest arising from his department collaborates with Imperial College on a number of clinical trials.

Observers

Dr [redacted] **-** [redacted]

Professor Wei Shen Lim - NPNS arises from the institution (Nottingham University Hospitals NHS Trust) where Professor Lim works has received unrestricted investigator-initiated research funding from Pfizer for an unrelated prospective population-based cohort study of pneumococcal pneumonia in which Professor Lim is the Chief Investigator.

COMMISSION ON HUMAN MEDICINES (CHM)
COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Tuesday 6th April 2021** at **12:00** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan
Mr VI G Fenton-May
Professor N French
Professor D Goldblatt
Ms S Hunneyball
Professor K Hyrich
Sir M Jacobs
Professor H J Lachmann
Professor P J Lehner
Mr R Lowe
Dr S Misbah
Professor Y Perrie
Professor S Price
Dr A Riordan
Professor C Robertson
Professor T Solomon
Professor K M G Taylor
Dr R Thorpe
Professor M Turner
Dr S Walsh
Mrs M Wang
Professor C Weir

Apologies

Professor P Shah

Observers

[redacted]
Professor W S Lim
[redacted]

Secretariat

[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD

Presenter supporting specific item

[redacted]

MHRA Observers

[redacted]
Ms R Arrundale - MHRA-Policy
[redacted]
Dr S Branch - VRMM
[redacted] - Comms
Dr SP Lam - LD
[redacted] - LD
Dr J Raine - MHRA CEO
[redacted] - MHRA-NIBSC
[redacted]

[redacted]

4th February 2022

Key

LD = Licensing Division
NIBSC = National Institute for Biological Standards & Control
VRMM = Vigilance & Risk Management of Medicines
MHRA CEO = Chief Executive
Comms = MHRA Communications

1. Introduction and Announcement

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

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

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

1.3 Participants declared interests and other relevant interests for this meeting listed at **Annex II** to the minutes.

1.4 Apologies were received from Professor Shah for this meeting.

1.5 The Chair welcomed the following observers:

[redacted] Statistician, Public Health England

[redacted] Joint Committee on Vaccination and Immunisation, Public Health England

[redacted] NHS England [redacted] for COVID-19 Immunisation [redacted]

Professor Wei Shen Lim
Chair of COVID-19 Subcommittee at JCVI

[redacted] Public Health England

[redacted] Public Health Scotland

[redacted] Public Health England

[redacted] Vaccine Preventable Disease Programme at Public Health Wales

[redacted]
National COVID-19 Vaccination Programme

[redacted]
Public Health England

[redacted]
Public Health England

1.6 The Chair welcomed the following representatives from AstraZeneca:

[redacted] Late Respiratory & Immunology

[redacted] Clinical Development, Immunology

[redacted] Clinical lead

[redacted] Medical and Payer Evidence Strategy, Respiratory and Immunology

[redacted]
Professor of Haemostasis and Thrombosis, [redacted]

[redacted] Pharmacovigilance [redacted]

[redacted] Regulatory Affairs

[redacted] Medical Officer

[redacted]
Regulatory Affairs [redacted]

[redacted] Regulatory Science [redacted] Inflammation Autoimmune, Infection & Vaccines

[redacted] Pharmacovigilance [redacted]

[redacted] Patient Safety

2. Presentation from AstraZeneca

2.1 The company gave a presentation on the global reports of thromboses with concurrent thrombocytopenia. The company highlighted that the vast majority of cases had come from the UK and EU, and that there had been a significant rise in reporting following media interest. It was commented that CVST represented a significant number of the cases of thromboembolism reported, and the cases showed a trend towards younger age groups and females. The meeting was informed that a number of the cases had significant missing data which limited assessment.

2.2 The company presented their observed-expected analysis using a large US insurance claims database to calculate the background incidence of CVST, CVST with thrombocytopenia and any large thromboses with thrombocytopenia within a 14-day risk window. ICD10 codes had been selected which were considered to most closely relate to events reported in such cases. It was noted that the use of the US claims database had a number of limitations including a larger representation of the younger population and those who were insured which may not represent the population as a whole. The analysis showed that for thromboses with thrombocytopenia, there was a higher observed rate than expected in the younger age groups and that this imbalance was not seen in the older age groups (50+ years), and this was similar in the UK and EU data. Similarly, for CVST alone, there was a higher reporting rate in the observed cases than expected for those aged less than 60 years, but no increased incidence detected in those over 60 years old. It was noted by the company that confidence intervals were wide, and the number of cases was small.

2.3 The company concluded that the benefit risk balance for the vaccine remained positive. The company stated that they were working on epidemiological analysis alongside investigation into the mechanism of the events in association with the vaccine.

2.4 The EWG agreed that a consistent definition to use globally could be preferable, including which risk window should be considered. The company noted that there is a natural background incidence of anti-PF4 antibodies in the population regardless of heparin exposure and without thrombus associated, at around 3-5%. Analysis of sera from sample study participants was underway by the company to investigate the prevalence of anti-PF4 antibodies. The company confirmed that they were not aware of any cases occurring after the second dose.

2.5 The company confirmed that the study in adolescents had been paused for recruitment following a data monitoring board discussion.

2.6 The EWG commented how unusual it was to have a large usage of the vaccine in India and yet only 2 cases outside of Europe. The company confirmed that they were working with the Serum Institute of India to engage with national reporting work in India.

2.7 AstraZeneca representatives were asked to leave the meeting before the next presentation.

3. Thromboembolic events with thrombocytopenia - update on cases

3.1 The EWG was presented with an update of the Yellow Card data on cases of thromboembolism and thrombocytopenia up to the data lock point of 31 March 2021. It was reported that the majority of cases related to CVST alongside thrombocytopenia, but other thromboembolic events had also been reported, and that a higher proportion of CVST cases were fatal compared to other thromboembolism events. The EWG heard that the quality of cases had greatly improved since the introduction of the Yellow Card proforma with specific questions on tests and investigations.

3.2 Incidence rates of the events by age group were also presented to the meeting, alongside epidemiological data on the vaccine's impact on reducing COVID-19 cases, long COVID, hospitalisations, ICU admissions and deaths. Modelling data was also provided showing the impact of a hypothesised 10% slower roll out of the vaccine on the predicted cases in the UK.

3.3 The EWG discussed the incidence rates by age for both CVST and non-CVST events and fatalities. It was commented that the case numbers were low considering the usage. Differences compared to the company analysis of benefit risk were highlighted and this could be due to different calculations on the expected impact of the vaccines in preventing cases globally. The EWG noted that the data had consistently showed a higher incidence in younger individuals in both the MHRA and company data. The EWG concluded that it was important to communicate on the available evidence in the younger age groups and allow informed consent, but that an age cut off for usage would not be proposed at present from a regulatory perspective.

4. Proposed revisions to product information

4.1 The EWG was presented with proposed product information statements which had been compiled following discussion at CHM. The EWG agreed with the proposed contraindication wording for patients with previous major thrombotic event with thrombocytopenia. The EWG discussed the proposed warnings and description of symptoms. and generally agreed that the information proposed was appropriate. There was discussion on the time frame for the symptoms of concern and it was agreed not to be restrictive on this. The EWG considered a statement on the causal relationship should be maintained with consideration to the wording to reflect current evidence levels.

4.2 Advice on use in pregnancy was also discussed, noting the lack of data in this area and the desire not to restrict options for pregnant women when the risk factors were unclear. The EWG concluded that the current statement should be retained with a linking statement to the information in 4.4 and 4.8.

4.3 The draft statement for section 4.8 was presented and the limitations of the frequency definitions used were discussed as the "very rare" category did not clearly indicate the rarity of the events.

4.4 The EWG was informed that statements for the patient information leaflet would be drafted once the healthcare professional information had been confirmed and that lay members would have the opportunity to input on this.

5. Any Other Business

None.

6. Date and time of next meeting

The next meeting is scheduled to take place on Monday 12th April at 11:00.

The Meeting today started at 12:01 and ended at 14:38.

Annex I

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

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Observers

Professor Wei Shen Lim - NPNS arises from the institution (Nottingham University Hospitals NHS Trust) where Professor Lim works has received unrestricted investigator-initiated research funding from Pfizer for an unrelated prospective population-based cohort study of pneumococcal pneumonia in which Professor Lim is the Chief Investigator.

[redacted] **-** Lapsed and NPNS - Regarding companies to declare interests for, prior to joining Public Health Scotland, [redacted] worked for a company that provided epidemiological services to the pharmaceutical industry. Whilst working there, [redacted] supported respiratory vaccine development activities at Janssen (Johnson & Johnson). [redacted] has now left that role.

[redacted] - Other relevant interests in Pfizer & GSK- The Immunisation and Countermeasures Division has provided vaccine manufacturers (including Pfizer and GSK) with post-marketing surveillance reports on pneumococcal and meningococcal infection which the companies are required to submit to the UK Licensing authority in compliance with their Risk Management Strategy. A cost recovery charge is made for these reports.

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COMMISSION ON HUMAN MEDICINES (CHM)
COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Monday 12th April 2021** at **11:00** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor G Dougan
Mr VI G Fenton-May
Professor N French
Professor D Goldblatt
Ms S Hunneyball[1]
Professor K Hyrich
Sir M Jacobs
Professor H J Lachmann
Professor P J Lehner
Mr R Lowe
Dr S Misbah
Professor Y Perrie
Professor S Price
Dr A Riordan
Professor C Robertson[2]
Professor T Solomon
Professor K M G Taylor
Dr R Thorpe
Professor M Turner
Dr S Walsh
Mrs M Wang
Professor C Weir

Apologies

Professor J Breuer

Observers

[redacted]

Secretariat

[redacted]

[1] Left for 30 mins and returned during item 2
[2] Joined during item 2

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD

Presenter supporting specific item

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

MHRA Observers

[redacted] - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - LD
Dr S Branch - VRMM
[redacted] - LD
[redacted] - MHRA-Policy
[redacted] - VRMM
[redacted] - Comms
[redacted] - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - LD
Mr P Tregunno - VRMM
[redacted] - LD

[redacted]

22nd July 2022

Key
LD = Licensing Division
VRMM = Vigilance & Risk Management of Medicines
Comms = MHRA Communications

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1.3 Participants declared interests and other relevant interests for this meeting listed at **Annex II** to the minutes.

1.4 Apologies were received from Professor Breuer for this meeting.

1.5 The Chair welcomed the following observers:

Professor [redacted]

Dr [redacted]

Dr [redacted]
Public Health Scotland

Dr [redacted]
Public Health England

Dr [redacted] Public Health Wales

Dr [redacted] MB ChB, FRCGP, FIMC (RCSEd), DUMC
Clinical Workstream – [redacted]
National COVID-19 Vaccination Programme

2. Update on COVID-19 Vaccines and risk of thromboembolic events with concurrent thrombocytopenia

2.1 The VBR EWG was presented with the latest data on thromboembolic events with thrombocytopenia associated with the COVID-19 Vaccines up to a data lock point of 5 April 2021. A summary of regulatory actions taken by the MHRA and EMA since the last VBR EWG meeting on 6 April 2021 was also presented.

2.2 A summary of the case reports associated with the AstraZeneca COVID-19 Vaccine was presented along with summary tables of co-morbidities and concomitant medication for the 19 confirmed cases with thrombocytopenia associated with CVST or non-CVST events. It was noted that 5 were obese, 4 cases had no reported co-morbidities or concomitant medication, 1 had been treated for hypothyroidism and the majority were Caucasian. No apparent risk factors were identified. The overall fatality rate has decreased to 22% but it was not clear if this reduction reflected reporting of less serious cases or improved patient management. The EWG also noted that a possible pregnancy case has been reported along with a single case following a second dose of the vaccine. Approximately 1 million second doses of the AstraZeneca COVID-19 Vaccine have been administered mainly to older people in the UK to date.

2.3 The UK and foreign cases associated with the Pfizer, Moderna and Janssen COVID-19 vaccines were summarised using the same case definition. It was noted that the Janssen paediatric trial has been suspended because of issues related to reactogenicity and that the initial marketing authorisation for this product is currently under MHRA evaluation via an EE reliance procedure.

2.4 For the AstraZeneca COVID-19 Vaccine, the EWG heard that there had been no significant change to the overall incidence or fatality rates of CVST with thrombocytopenia since the last meeting. An increase in the estimated incidence of CVST+ other site thromboembolic events with thrombocytopenia had been seen since the last data lock point, although the confidence intervals were overlapping. The difference was driven by events in vaccinees aged between 50 and 70, which corresponds with the ages currently being targeted for vaccination. No change was seen in the fatality rate for CVST+ other site thromboembolic events.

2.5 The EWG was presented with an updated evaluation of events of interest after COVID-19 vaccines using first episodes in the SUS database linked to National Immunisation Management System by NHS number. The adjusted risk of CVST in the 15-39 age group was increased, particularly in the defined risk window of 4 to 13 days after immunisation with the AstraZeneca COVID-19 Vaccine. Two cases of disseminated intravascular coagulation have also occurred in the same age group following vaccination with the Pfizer vaccine but this only provides weak evidence of an association. Cases of thrombocytopenia are not reliably identified using this data.

2.6 Three cases of capillary leak syndrome (CLS) associated with the AstraZeneca COVID-19 vaccine were also presented. It was noted that CLS is a very rare, relapsing-remitting disorder of unknown aetiology and that 2 cases had such a prior history, making any causality assessment difficult. The EWG concluded that this signal should be closely monitored.

2.7 The EWG concluded that it was not possible to evaluate individual risk-benefit profiles for sub-populations of healthy people and patients with comorbidities in the age-stratified data presented but the overall benefit-risk balance for the AstraZeneca COVID-19 Vaccine

remained positive. It also advised the MHRA to continue closely monitoring these events associated with COVID-19 vaccines, particularly following second doses.

3. Third update on the Safety Data for the Pfizer/BioNTech COVID-19 Vaccine

3.1 The EWG was provided with a verbal update on the cumulative safety data for the Pfizer/BioNTech COVID-19 Vaccine, up to a data lock point of 6 April 2021. The EWG was informed of the current usage data for first and second doses of the Pfizer/BioNTech COVID-19 vaccine in the UK, up to the 4 April 2021.

The EWG heard that the nature of the Yellow Card reports was similar to that previously presented for the Pfizer/BioNTech vaccine. A slight decrease in the reporting rate was noted which may suggest increased awareness of common side effects experienced after receiving the Pfizer/BioNTech vaccine as the vaccination campaign progresses. The EWG heard that the most frequently reported events were consistent with previous safety updates and those observed in clinical trials, and that the reporting was noted to be largely related to typical reactogenicity events, and that this was true for both first and second doses.

Higher proportions of reports in females and in those under the age of 55 years was noted for both first and second doses; higher reporting in females has previously been discussed at the EWG as potentially caused by underlying reporting biases in spontaneous reporting systems, in combination with a higher proportion of female vaccinees in the health and social care work force population prioritised by the vaccine campaign.

3.2 The EWG heard that caution should be used in interpretation of the UK Yellow Card dose data, as dose number is not a mandatory reporting field and routine collection of these data was introduced from February 2021.

The EWG were also informed of data from international regulators, which included similar reactogenic events after the second vaccine dose, and an increased frequency of events after the second vaccine dose compared to the first dose which is similar to that seen in clinical trials.

3.3 The EWG were also provided with an update of the adverse events of special interest which are currently under review for the Pfizer/BioNTech vaccine. These included fatal cases, anaphylaxis, Bell's palsy, Guillain-Barré syndrome and cardiac adverse event reports including myocarditis and pericarditis.

The EWG were informed of trends in the data from the UK vaccination programme and new data from international regulators. The EWG heard of potential confounding factors were described in the data, such as age, plausibility of time to onset, variable reporting terms, reporter's opinion of causality and significant comorbidities.

The EWG was informed of ongoing epidemiological studies and analysis, including rapid cycle analysis and mortality stratified by frailty index, that seeks to identify any emerging signals and trends in reporting data for the Pfizer/BioNTech vaccine.

3.4 The EWG discussed the data available regarding fatal anaphylactic reactions, Guillain-Barre and Bell's palsy.

The EWG commented that tryptase laboratory test values should be interpreted with caution and requested that further details on the anaphylaxis reports be provided when available.

The EWG discussed the cases of Guillain-Barré and Bell's palsy, including epidemiological evidence that the background population rate of Guillain-Barré during the pandemic has

reduced and that Guillain-Barré has been associated with COVID-19 infection. The EWG recommended that safety data for Bell's palsy in relation to the Pfizer/BioNTech vaccine and Moderna vaccine should continue to be monitored, and suggested sources of safety data from epidemiological studies and the NHS.

The EWG also requested that cases of exposure during breast-feeding be presented in future updates on reproduction issues.

3.5 The EWG concluded that no new safety concerns had been identified and therefore no further regulatory action was required based on the data presented.

4. Any Other Business

None.

5. Date and time of next meeting

The next meeting is scheduled to take place on Friday 23rd April at 14:00.

The Meeting today started at 11:01 and ended at 12:24.

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

Annex I

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

Chair and Members

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

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

Invited experts

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

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

Observers

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

Annex II

The following participants declared interests and other relevant interests at the meeting today:

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

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

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

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

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

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

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

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

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

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

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

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

Mrs Wang – Other relevant interests arising from being highly sensitive to insect stings, and plant products such as Hyacinth bulbs, as recorded on Mrs Wang's medical records. The family of Mrs Wang lives with several rare diseases and conditions, some of which result in epileptic fits.

Professor Weir - NPNS - Imperial College and Other relevant interest arising from his department collaborates with Imperial College on a number of clinical trials.

Observers

Professor [redacted] - NPNS - University of Oxford employee (with no involvement in research or clinical trials related to Oxford AZ vaccine)
[redacted]

Dr [redacted] - Lapsed and NPNS - Regarding companies to declare interests for, prior to joining Public Health Scotland, [redacted] worked for a company that provided epidemiological services to the pharmaceutical industry. Whilst working there, [redacted] supported respiratory vaccine development activities at Janssen (Johnson & Johnson). [redacted] has now left that role.

Dr [redacted] - Other relevant interest in Pfizer & GSK- The Immunisation and Countermeasures Division has provided vaccine manufacturers (including Pfizer and GSK) with post-marketing surveillance reports on pneumococcal and meningococcal infection which the companies are required to submit to the UK Licensing authority in compliance with their Risk Management Strategy. A cost recovery charge is made for these reports.

COMMISSION ON HUMAN MEDICINES (CHM)
COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Monday 19th April 2021** at **17:15** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Mr VI G Fenton-May
Professor N French
Professor D Goldblatt
Ms S Hunneyball
Professor K Hyrich
Sir M Jacobs
Professor H J Lachmann
Professor P J Lehner
Mr R Lowe
Dr S Misbah
Professor Y Perrie
Professor S Price
Dr A Riordan
Professor T Solomon
Professor K M G Taylor
Dr R Thorpe
Professor M Turner
Dr S Walsh
Mrs M Wang

Apologies

Professor G Dougan
Professor C Robertson
Professor C Weir

Observers

[redacted]
Professor W S Lim
[redacted]

Secretariat

[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted]

Presenter supporting specific item

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

MHRA Observers

[redacted] - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - LD
[redacted] - Comms
Dr S Branch - VRMM
[redacted] - LD
[redacted] - MHRA-NIBSC
[redacted] - MHRA-Policy
[redacted] - VRMM
[redacted] - VRMM
[redacted] - VRMM
Dr SP Lam - LD
[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
Ms N Rose - MHRA-NIBSC
[redacted] - LD
[redacted] - LD
Dr K Wydenbach - LD
[redacted]

4th February 2022

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

1. Introduction and Announcement

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

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

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

1.3 Participants declared interests and other relevant interests for this meeting listed at **Annex II** to the minutes.

1.4 Apologies were received from Professors Dougan, Robertson and Weir for this meeting.

1.5 The Chair welcomed the following observers:

Mr

Dr
Public Health England

Professor

Professor Wei Shen Lim
Chair of JCVI

Dr

Dr
Public Health Scotland

Dr
Public Health Wales

Dr
National COVID-19 Vaccination Programme

2. Update on COVID-19 Vaccines and risk of thromboembolic events with concurrent thrombocytopenia

2.1 The VBR EWG was presented with the latest data on thromboembolic events with thrombocytopenia associated with the authorised COVID-19 Vaccines up to a data lock point of 14 April 2021. The data lock point for the Janssen vaccine was 12 April 2021. A summary of regulatory actions taken by the MHRA, EMA and FDA since the last EWG meeting on 12 April 2021 was also presented.

2.2 Recent published case series and a case of secondary immune thrombocytopenia following the AstraZeneca COVID-19 Vaccine were also presented.

2.3 An overview of the case reports associated with the AstraZeneca COVID-19 Vaccine was presented along with a summary table of reported second dose cases. The result of PF4 antibody testing is awaited in one probable second dose case and 4 others were considered unlikely on the basis of medical co-morbidities. The overall fatality rate has decreased to 19%.

2.4 The UK and foreign cases associated with the Pfizer, Moderna and Janssen COVID-19 vaccines were summarised using the same case definition. It was noted that PF4 antibodies were detected in a Janssen clinical trial case. The EWG recommended that all suspected cases associated with other COVID-19 vaccines should be tested for PF4 antibodies to further characterise the risk and potentially clarify any causal mechanism(s).

2.5 The estimated number of second AstraZeneca COVID-19 vaccine doses administered has significantly increased to 2.3 million whilst the number of first doses has increased slightly, in line with the current deployment programme. Age-stratified estimated case incidence rates for CVST and CVST plus non-CVST events were presented. The incidence rate following a second dose, based on a single probable case, was 0.4 (0.01, 2.4) per million compared to an overall incidence rate of 7.9 (6.8, 9.2) per million for first/unknown doses. The overall CVST incidence for first/unknown doses has increased from 2.4 to 3.6 per million doses and that for CVST and non-CVST has increased from 4.9 to 8.0 per million doses, although the overall fatal incidence rate for CVST and non-CVST cases after the first/unknown dose has increased from 1.2 to 1.7 per million. This small increase in the fatality rate is not statistically significant. The risk estimates were then compared with the expected benefits of the vaccine in age subgroups.

2.6 Proposed triggers for regulatory action were presented and the EWG considered the following 3 questions:

2.6.1 Question 1: based on the evidence presented does the EWG consider the benefit-risk balance remains favourable for all patients and for all age groups?

The EWG advised that the overall benefit-risk profile of the AstraZeneca COVID-19 Vaccine remains positive. However, the benefits of immunisation in individuals aged under 30 years is more equivocal and may begin to be outweighed by the potential risks should the incidence rate further increase, although the benefit risk was also considered dependent on the status of the COVID-19 pandemic, its severity and impact on hospitalisation. The EWG also advised that the benefit-risk ratio for those aged 30 – 39 remained positive, although this requires close attention given the apparent increased number of cases. However, the EWG considered that no further regulatory action was warranted at this stage.

2.6.2 Question 2: Does the EWG consider there might be an increased risk for the second dose of the vaccine?

The EWG advised that the estimated point estimate for the incidence of thromboembolic events with thrombocytopenia associated with the second dose is only based on a single patient. Many people receiving their second doses have not entered the known risk period or will still be in it, so an absence of cases provides little reassurance. Overall, there is insufficient information to conclude on the magnitude of any risk associated with the second dose. The MHRA should continue to monitor second dose cases closely.

2.6.3 Question 3: Does the EWG consider there is any need for action with regards to the Pfizer, Moderna or Janssen vaccines in relation to this potential risk?

Based on available data, the EWG concluded that the risk associated with the Pfizer and Moderna COVID-19 vaccines appears lower than that associated with the AstraZeneca COVID-19 Vaccine. The identification of a confirmed Janssen case raises concerns that the potential risk associated with this vaccine, also based on a viral vector, is similar, although only a small number of cases have been reported. The EWG will further consider the ongoing marketing authorisation procedure for the Janssen COVID-19 Vaccine at its next meeting on 23 April 2021.

2.7 In conclusion, the EWG did not currently identify any potential trigger for urgent regulatory action.

3. Any Other Business

None.

4. Date and time of next meeting

The next meeting is scheduled to take place on Friday 23rd April at 14:00.

The Meeting today started at 17:17 and ended at 18:32.

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Sir Munir is a member of the UK COVID Therapeutics Advisory Panel (UK-CTAP), which is advising the CMO on which compounds need to be prioritised for the RECOVERY+ trial (RECOVERY is funded via NIHR/DHSC).

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

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

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Mrs Wang – Other relevant interests arising from being highly sensitive to insect stings, and plant products such as Hyacinth bulbs, as recorded on Mrs Wang's medical records. The family of Mrs Wang lives with several rare diseases and conditions, some of which result in epileptic fits.

Observers

Professor [redacted]

Professor Wei Shen Lim - NPNS arises from the institution (Nottingham University Hospitals NHS Trust) where Professor Lim works has received unrestricted investigator-initiated research funding from Pfizer for an unrelated prospective population-based cohort study of pneumococcal pneumonia in which Professor Lim is the Chief Investigator.

Dr [redacted] **-** [redacted]

COMMISSION ON HUMAN MEDICINES (CHM)
COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Friday 23rd April 2021** at **14:00** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan
Mr VI G Fenton-May
Professor N French
Professor D Goldblatt
Ms S Hunneyball
Professor K Hyrich[1]
Sir M Jacobs
Professor H J Lachmann[2]
Professor P J Lehner
Mr R Lowe
Dr S Misbah
Professor Y Perrie
Professor S Price
Professor C Robertson[3]
Professor T Solomon[4]
Professor K M G Taylor
Dr R Thorpe
Professor M Turner[3]
Dr S Walsh
Mrs M Wang
Professor C Weir

Apologies

Dr A Riordan

Invited Experts[5]

[redacted]

Observers

[redacted]
Professor W S Lim
[redacted]

Secretariat

[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted] - VRMM

Presenter supporting specific item[6]

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

MHRA Observers

[redacted] - VRMM
[redacted] - LD
[redacted] - LD
Dr S Branch - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - VRMM
[redacted] - MHRA-Policy
[redacted] - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - MHRA-Comms
[redacted] - LD
[redacted] - VRMM
[redacted] - LD
Dr J Raine - MHRA CEO
Ms N Rose - MHRA-NIBSC
[redacted] - LD
[redacted] - VRMM
Mr P Tregunno - VRMM
Dr K Wydenbach - LD

1 Joined at item 5
2 Joined during item 3
3 Left during item 7
4 Joined during item 2
5 Left after item 3
6 Supported Specific items

Key
LD = Licensing Division
VRMM = Vigilance & Risk Management of Medicines
Comms = MHRA Communications
NIBSC = National Institute for Biological Standards & Control
MHRA CEO = Chief Executive

1. Introduction and Announcement

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1.3 Participants declared interests and other relevant interests for this meeting listed at **Annex II** to the minutes.

1.4 Apologies were received from Professor Hyrich and Dr Riordan for this meeting.

1.5 The Chair welcomed the following Invited Experts, who participated for Item 3 only:

Ms [redacted]
Breastfeeding Network

Dr [redacted] Taunton and Somerset NHS Foundation Trust

Dr [redacted] BM BCh PhD
[redacted] Imperial College London
[redacted]

1.6 The Chair welcomed the following observers, who left after Item 5:

Mr [redacted]

Dr [redacted] Public Health England

Professor Wei Shen Lim
Chair of JCVI

Dr [redacted]
Public Health Scotland

Dr [redacted] Public Health Wales

Dr [redacted] National COVID-19 Vaccination Programme

2. COVID-19 Vaccines and Pregnancy/Breastfeeding

2.1 The EWG was informed of the latest Yellow Card reports received in connection with COVID-19 vaccines in pregnancy. A further 48 reports for the Pfizer-BioNTech vaccine and a further 96 reports for the Oxford-AZ vaccine have been received between 26th March and 15th April, resulting in 137 and 210 total reports respectively for these 2 vaccines. The types of exposure and suspected ADRs were similar to those reviewed previously and did not change the previous conclusions.

2.2 The EWG was informed that the advice to preferentially offer the Pfizer-BioNTech vaccine to women known to be pregnant was based on the larger amount of safety data available from use in the USA rather than any specific safety concerns with the Oxford-AZ vaccine.

2.3 The EWG noted that there are currently no restrictions on the use of COVID-19 vaccines specifically in relation to breastfeeding, since no harm is expected for breastfed infants from non-live vaccines. However sparse information is available for use of COVID-19 vaccines during breastfeeding, so the Yellow Card reports in association with breastfeeding have been monitored closely since the rollout began.

2.4 Yellow Card reports related to exposures in association with breastfeeding have been received for the Pfizer-BioNTech (n= 162), Oxford-AZ (n=778) and Moderna (n=1) vaccines from product launch up to 15/4/21. The number of women who have received the vaccine whilst breastfeeding is not currently known.

2.5 The majority of reports reported reactogenic ADRs that are seen in the general population and did not report any adverse effects either on breastfeeding or in their breastfed child (70% of Pfizer-BioNTech and 77% of Oxford-AZ vaccine).

2.6 There were a small number of reports of mastitis or mastitis-like symptoms, breast pain or breast tenderness for both Pfizer (n=6) and OxfordAZ (n=16); although some reports highlighted that these could make breastfeeding more uncomfortable, they did not appear to affect recipients' ability to breastfeed. The EWG considered these might be related to vaccine use, based on temporal association, but did not raise any particular concerns regarding breastfeeding.

2.7 There were a small number of reports of decreased lactation for both Pfizer (n=2) and OxfordAZ vaccines (n=14). The reported reductions varied from temporary complete inability to breastfeed (for 1 -2 days) to 10-20% that was sustained up to the time of report or follow up (max 5 weeks) was received.

2.8 About 20% of reports for Pfizer-BioNTech and 10% of the Oxford-AZ vaccine reported suspected ADRs in their breastfed children. The EWG considered that the reported symptoms are common conditions which occur in children of this age and may be coincidental rather than causally related to maternal vaccination.

2.9 The EWG noted that a number of factors can affect milk supply and infant behaviour, including general maternal health, amount of sleep, and anxiety. Whilst the EWG considered that some of the individual reports might be related to vaccine use, based on the information provided and temporal association, the low number of reports suggest that at most, a small number of women may experience a reduction in breast milk production.

2.10 Overall, the EWG were reassured by the reports related to breastfeeding, particularly the low number of reports and types of symptoms reported for breastfed children. The EWG recommended that no regulatory action was warranted by these data.

2.11 The EWG noted that there is a lot of uncertainty and anxiety amongst potential vaccine recipients over whether to have the vaccine or not due to lack of safety data during breastfeeding. The EWG therefore recommended communicating on the findings from these Yellow Card reports. The EWG considered that the data would not be sufficiently robust for inclusion in product information but noted that the communication via other routes, such as information on the MHRA website and/or through PHE leaflets, would be appropriate.

2.12 The breastfeeding experts highlighted that, although still limited, there is some emerging evidence on protective effects of vaccines by transfer of immunoglobulins via breastmilk, and that conveying this information from Yellow Card reports might also present an opportunity to convey this positive health benefit message.

2.13 The EWG also supported that communicating on the reports would allow messages to support contingency planning regarding having help on hand to assist with childcare if needed.

3. COVID-19 vaccine AstraZeneca post authorisation safety study protocol- C-VIPER pregnancy registry

3.1 The EWG heard an overview of the protocol for AstraZeneca's planned post authorisation safety study to look at use in pregnancy. The study is an international, prospective, observational cohort study of pregnant women which includes follow-up of liveborn infants up to one year of age.

3.2 The EWG discussed the length of follow up of babies born to mothers who received the AstraZeneca vaccine during pregnancy and whether it would be advisable to extend the follow up period beyond a year in order to detect neurodevelopmental problems. The EWG considered the difficult balance with extending follow up for gaining information on neurodevelopmental problems and reduce maintenance of participants to lengthy follow up. The EWG proposed requesting that the study organisers consider an additional questionnaire at 24 months to assess cognitive abilities. The EWG did however, comment that this could produce bias as parents of babies with a neurodevelopmental issue may be more motivated to continue to engage with the study up to 24 months.

3.3 The EWG commented that analysis on a country-by-country basis would be valuable as there may be very different prevalence rates of certain conditions in pregnancy and in babies born between countries participating in the study. The EWG acknowledged that this could raise issues with sample size, and also that some balance would be provided in the matching of cases and controls by country. The EWG also suggested that matching by region within country could also be valuable.

3.4 The EWG commented that while the study will take 5 years, major congenital malformations and other deficits will become evident early on, and so early data could provide reassurance and less significant changes can be picked up as the study continues.

3.5 Overall, the EWG was content with the proposed study.

4. Update on potential risk of GBS with COVID-19 vaccine AstraZeneca

4.1 The EWG was provided with an update on Yellow Card reports and epidemiological analyses of Guillain-Barré syndrome (GBS) up to and including 11 April 21 with the AstraZeneca vaccine. Clinical trial data and company data from the Summary Monthly Safety Review were also provided. Yellow Card reports were assessed against Brighton Collaboration Criteria for diagnosis of GBS.

4.2 The EWG commented that case numbers were increasing but there was difficulty in assessing cases using the Brighton Collaboration criteria due to a lack of information remained. Nevertheless, the EWG considered that the evidence did not require any product information updates currently and a more dedicated epidemiological study was required.

5. Updated review of COVID-19 Vaccines and the potential risk of immune thrombocytopenia

5.1 The EWG was presented with a summary of the Yellow Card reporting, company data and epidemiological evidence for Immune Thrombocytopenia (ITP) and other thrombocytopenia disorders reported following COVID-19 vaccination. This was an update to a previous assessment which had been reviewed by the EWG in February 2021.

5.2 The EWG were informed that there was very limited data on this topic for the Moderna COVID-19 vaccine due to low levels of usage in the UK. There were several UK Yellow Card reports of ITP and other thrombocytopenia events with the Pfizer COVID-19 vaccine, and it was noted that the number of fatal events was low. The company had also reported relatively low reporting of ITP events considering the global usage of the vaccine. There had been more frequent Yellow Card reporting of ITP and thrombocytopenia events with the AstraZeneca COVID-19 vaccine; however, it was noted that the data overlapped with reporting of Thrombosis with Thrombocytopenia Syndrome (TTS).

5.3 The EWG were presented with the MHRA's epidemiological analysis which did not show a signal in the observed vs expected analysis with the Pfizer COVID-19 vaccine and ITP. Similarly, in analysis by the company, the Pfizer COVID-19 vaccine did not demonstrate a signal for ITP in the global observed vs expected analysis. However, there was stronger evidence of a signal with the AstraZeneca vaccine in the MHRA's observed vs expected analysis. There was also a signal observed in the Rapid Cycle Analysis with ITP and the AstraZeneca vaccine which it was reported has been strengthening over time. A pre-print publication of an epidemiological study seen by the MHRA did not show strong evidence of an association of thrombocytopenia and bleeding events with the AstraZeneca vaccine, although some limitations to the study was noted to the EWG.

5.4 The EWG was also presented with data supporting the proposal by AstraZeneca to include thrombocytopenia as a common adverse event in the product information for the Conditional Marketing Authorisation application that is currently being reviewed by the MHRA. The limitations of the laboratory data used to support the frequency of common was described.

5.5 The EWG members highlighted the complexities of diagnosis of ITP and the range of different thrombocytopenic disorders there were with varying mechanisms. The EWG recommended that an expert haematology panel be formed to support the MHRA in reviewing reports of thrombocytopenia events following COVID-19 vaccination to underpin further review of this signal.

5.6 The EWG also noted that there appeared to be a strengthening signal of ITP with the AstraZeneca vaccine, but the experts cautioned that stimulated reporting may be impacting this signal.

5.7 The EWG supported the inclusion of thrombocytopenia in the Regulation 174 authorisation of the AstraZeneca COVID-19 vaccine with the frequency unknown and stated that the product information for the Conditional Marketing Authorisation will be discussed at the Commission on Human Medicines in due course.

6. Janssen Vaccine EU reliance Conditional Marketing Authorisation Application

6.1 The EWG noted that this is the first COVID-19 vaccine application with a single dose regimen; that this vaccine has already been approved for use by the US FDA and the EMA; and that no Regulation 174 request has been received from the DHSC.

6.2 The EWG were informed that this application was via the EU decision reliance procedure and that, in-line with the licensing division SOP, the assessment therefore focuses on 'GB specific considerations' with points raised only if considered 'decision critical'.

6.3 The EWG heard that at the time of submission, no GB specific concerns were identified that would impact the positive benefit/risk balance. However, two points were highlighted in the product information in relation to 1) inclusion of a recommendation regarding anaphylaxis for close observation for 15 minutes post vaccination and 2) that no advice is included in the product information regarding use of paracetamol for symptomatic relief of adverse events. It was noted that advice on paracetamol use is included in the PHE leaflet 'Covid-19 vaccination A guide for adults' given to all vaccine recipients.

6.4 The EWG were informed of the temporary pause in use of the Janssen vaccine in the US, EU and clinical trials whilst the FDA/CDC and EMA completed a review of US post-marketing reports of CVST with thrombocytopenia. The EWG noted the outcome of the PRAC review on 20 April 2021 that the overall benefit/risk remained positive; however, updates to the product information were required; and that these cases were considered to be very similar to those reported with COVID-19 vaccine AstraZeneca.

6.5 The EWG noted that the updates to the Janssen vaccine EU product information requested by the PRAC were very similar to those already included in the EU product information for the AstraZeneca vaccine. However, that there were some differences compared to the wording included in the UK product information for AstraZeneca. In particular, in the EU PI there is no contraindication in patients with previous HITT or HIT type 2, and no warning about administration in patients with a previous history of CVST or antiphospholipid syndrome.

6.6 The EWG agreed that the benefit risk for the Janssen vaccine was positive.

6.7 The EWG commented that if the UK are considering diverging from the EU PIL and SmPC, the 15minute observation window should be considered for removal given that a clear signal of anaphylaxis, beyond that expected for any vaccine, has not been detected. It was noted that a requirement for a 15-minute observation window might cause operational difficulties for the mass vaccination campaign.

6.8 The EWG heard that there is limited scope to change the product information in the reliance procedure, except where there are clear reasons to do so that can be justified, generally this is interpreted to be a serious issue that alters the overall benefit-risk or poses a potential risk to patient safety. With regards to removal of the 15-minute observation window it was

considered that these criteria are not met but that legal advice could be sought as to whether this could still be possible.

6.9 The EWG noted that, to lower the risk of patient harm through administration errors, the negative statement in the product information *not* to give intravascularly, intravenously, subcutaneously or intradermally should be removed. This was considered to be a clear patient safety concern.

6.10 The EWG noted that the data on the events of thrombosis with concurrent thrombocytopenia with the Janssen vaccine are based on more limited usage in the US compared with much higher usage of the AZ vaccine in the UK and EU. It was also noted that, whilst both vaccines are adenovirus vaccines, there are clear differences between the two including the type of adenovirus and DNA construct. Therefore, justifying full alignment of the product information may be difficult. It was noted that the clinical syndrome being reported for the 2 vaccines was similar and that the presence of anti-PF4 antibodies was common to cases with either vaccine. Therefore, it was considered reasonable to assume that a common form of pathophysiology is underlying the thromboembolic clinical syndromes in both the Janssen vaccine and AZ vaccine. Taking this all into consideration and that this procedure was via the EU reliance route, the EWG agreed that the updates to the proposed GB product information for Covid-19 Vaccine Janssen should be in-line with those recommended by the PRAC.

7. NVX-CoV2373 – Cycle 1 Clinical AR (immunogenicity & safety)

7.1 The EWG was presented with an assessment of the Phase I/II study of NVX-CoV2373, which enrolled about 1,500 adults up to 84 years in total. The trial evaluated adjuvanted and unadjuvanted vaccine, 2 antigen dose levels with the same dose of adjuvant, and a 1 vs 2-dose regimen.

7.2 The EWG heard the conclusions of the immunogenicity assessment, as follows. There is a need for the adjuvant and a booster dose to get a humoral response of similar magnitude to that of human convalescent sera. The adjuvant shows a significant [redacted] The antibody response in the ≥60-year olds is about half that in younger adults, but the SCR after 2 doses is >96% regardless of age. After the peak, IgG levels tend to decrease slowly up to 6 months, but more rapidly so for neutralising antibodies; nevertheless, the GMTs of neutralising antibodies at 6 months are still above 100 with SCRs around 70%. Consistent with the antibody response, adjuvant is crucial for induction of an antigen specific T cell response and a second dose of vaccine is needed to achieve a robust response. Overall, a mixed [redacted] response.

7.3 As far as reactogenicity is concerned, [redacted] especially after the second dose, when reactions increase in frequency and severity compared to the first dose. In addition, [redacted] for further development.

7.4 It is noteworthy that after a first adjuvanted dose, mild local reactions of pain and tenderness are more frequent than with placebo, but the frequencies of systemic reactions do not differ from placebo, except for myalgia. After the second dose, the most frequent reactions, which are fatigue, myalgia and headache, are each reported in about one third of the participants receiving the lower dose. These are generally short-lived (median 1 day, none after 7 days). The frequency of fever is low (4%) with only one case of Grade 3 fever (< 1%; between 39 and 40°). As expected, reactions are more frequent/severe in younger adults compared to

older subjects ≥ 60 years, but the frequency of systemic reactions after the second [redacted] dose is still lower than 50% in younger adults.

7.5 Regarding unsolicited events, their frequency appeared to be marginally increased in the adjuvanted vaccine arms compared to placebo; the difference appeared to be mostly driven by local and systemic reactions. There is no SAE of concern except for one case of acute colitis of unclear aetiology (considered as possibly vaccine related). Laboratory tests have only been provided for Part 1 of the trial and show occasional individual decreases in haemoglobin, increases in transaminases or urea across all arms without a clear pattern.

7.6 Finally, the level of vaccination discontinuation is very low, 1% overall and even lower in the vaccinated arms than in the placebo arm.

7.7 In conclusion, the [redacted] dose [redacted] selected for the Phase III trial is considered to have a very favourable reactogenicity profile, even in the younger adult population. Based on this limited safety database, unsolicited and laboratory tests do not raise any major concern. The only questions raised relate to the bioanalytical assays.

7.8 The EWG supported the findings and conclusions of the analytical procedure assessments undertaken by NIBSC assessors.

7.9 The EWG noted that the cellular response data included a prominent [redacted] which appears novel in the context of the vaccines evaluated thus far. The data broadly indicate a [redacted] profile the implications of which are not known, although hypothetically it could lead to a greater likelihood of vaccine exacerbated disease. The EWG noted the [redacted] vaccines have not been associated with a [redacted] response. Therefore, the EWG thought it to be plausible that the [redacted] response may be caused by the adjuvant included in NVX-CoV2373. The EWG noted this adjuvant is not entirely novel to vaccines, in particular recent studies of the malaria vaccine did not raise any concerns specific to this adjuvant.

7.10 The EWG was reassured by the immunogenicity data, however, should adverse events (AE) become apparent once the vaccine is marketed, the potential role of the [redacted] response in the development of AEs will need to be evaluated.

7.11 The EWG heard that the production of validation batches has been delayed. Also, the company have opted to include a different potency assay which includes [redacted] resulting in an assay that should quantify the amount of antigen. However, still outstanding is an explanation of the clinical implications of the [redacted] which will still be present in the product. The company intend to replicate the quality development of the DS process of the product used in the Phase III trial in US, in order that the quality profile at the new site is clinically qualified.

7.12 The EWG heard of inaccurate reports in the media stating that NVX-CoV2373 is expected to be authorised in the UK in the next few weeks.

8. Any Other Business

None.

9. Date and time of next meeting

The next Ad Hoc meeting on Thromboembolic events with COVID-19 Vaccines is scheduled to take place on **Monday 26th April** at **5.15pm**.

The next scheduled meeting is to take place **on Friday 30th April** at **10.00am**

The Meeting today started at 14:13 and ended at 16:50.

[redacted]

16th February 2023

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

Annex I

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

Chair and Members

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

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

Invited experts

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

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

Observers

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

Annex II

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

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

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

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

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

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

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

Professor Lehner - Other relevant interest – Professor Lehner previously held a DPAC (Discovery Partnership with Academia) agreement with GSK, but this has been completed. Professor Lehner's participation in his local hospital D and T governance committee

deliberations would form the normal activity and professional responsibility in his post and does not interfere with the EWG considerations (Sept 2020).

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

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

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

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

Mrs Wang – Other relevant interests arising from being highly sensitive to insect stings, and plant products such as Hyacinth bulbs, as recorded on Mrs Wang's medical records. The family of Mrs Wang lives with several rare diseases and conditions, some of which result in epileptic fits.

Professor Weir - NPNS - Imperial College and Other relevant interest arising from his department collaborates with Imperial College on a number of clinical trials.

Invited Experts & Observers

Dr [redacted]

Dr [redacted]

Professor Wei Shen Lim - NPNS arises from the institution (Nottingham University Hospitals NHS Trust) where Professor Lim works has received unrestricted investigator-initiated research funding from Pfizer for an unrelated prospective population-based cohort study of pneumococcal pneumonia in which Professor Lim is the Chief Investigator.

Dr [redacted]

COMMISSION ON HUMAN MEDICINES (CHM)
COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Monday 26th April 2021** at **17:15** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Mr VI G Fenton-May
Professor D Goldblatt
Ms S Hunneyball
Professor K Hyrich
Sir M Jacobs
Professor H J Lachmann
Professor P J Lehner
Mr R Lowe
Dr S Misbah
Professor Y Perrie
Professor S Price
Professor C Robertson
Professor T Solomon
Professor K M G Taylor
Dr R Thorpe
Professor M Turner
Dr S Walsh
Mrs M Wang
Professor C Weir

Apologies

Professor G Dougan
Professor N French
Dr A Riordan

Invited Expert

[redacted]*

Observers

[redacted]
Professor W S Lim
[redacted]
msav
[redacted]

Secretariat

[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD

Presenters supporting specific items*

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

MHRA Observers

[redacted] - LD
[redacted] - VRMM
[redacted] - LD
Dr S Branch - VRMM
[redacted] - MHRA-NIBSC
[redacted] - VRMM
[redacted] - MHRA-Policy
[redacted] - VRMM
[redacted] - VRMM
[redacted] - VRMM
[redacted] - Comms
[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
Ms N Rose - MHRA-NIBSC
[redacted] - MHRA-NIBSC
[redacted] - LD
[redacted] - VRMM
Mr P Tregunno - VRMM
[redacted] - LD
[redacted]

4th February 2022

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

1. Introduction and Announcement

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

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

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

1.3 Participants declared interests and other relevant interests for this meeting listed at **Annex II** to the minutes.

1.4 Apologies were received from Professors Dougan, French and Dr Riordan for this meeting.

1.5 The Chair welcomed Invited Expert, Dr [redacted] from UK Health Security Agency (HAS) who presented item 2 - Update from UK HSA on Safety for AZ Vaccine.

1.6 The Chair welcomed the following observers:

Mr [redacted]

Dr [redacted] Joint Committee on Vaccination and Immunisation, UK HSA

Professor [redacted] JCVI

Dr [redacted] Public Health Agency

Professor Wei Shen Lim
Chair of JCVI

Dr [redacted]
Public Health Scotland

Dr [redacted]
UK Health Security Agency

Dr [redacted] Public Health Wales

[redacted]d
National COVID-19 Vaccination Programme

2. Update from UK HSA on Safety for AZ Vaccine

2.1 UK HSA England, AZ safety item 26/04/2021

The EWG heard a presentation from Professor [redacted] of UK Health Security Agency (UK HSA) on estimations of rates of vaccine-prevented COVID-19 cases, hospitalisations, ICU/HDU admissions and deaths. The rates of benefit were based on a wave equivalent to that of the second wave and the analysis was stratified by age and risk group status. The benefit data was based on a complete vaccination course (two doses) of the AstraZeneca Vaccine. The EWG heard that the data and calculations presented on vaccine effectiveness assumptions were largely based on data from the second wave scenario.

2.2 The EWG asked for further detail on the QCOVID score, and how this was used to benchmark rates of risk. The QCOVID data was used as one form of cross checking / data validation, and for comparison of risks between wave one and wave two. The EWG heard the QCOVID calculator computes a combination of risk of infection and the subsequent risk of acquiring a complication (if infected), in other words an absolute population risk during the 12 weeks during the first wave. The EWG also heard the rates used in the data analysis to calculate risk are available to the group for reference.

2.3 The EWG heard that projection modelling of a potential third wave is on-going. Currently, the model estimates third wave hospitalisation rates will be approximately 50% of second wave rates. The data period inputs for the model cover the first and second waves, and presently, but lack data on emerging variant strains. The current model is therefore limited in terms of its predictive accuracy in a situation where new strains may result in substantial differences in protection from the vaccine. The EWG also heard that the uncertainty level in the modelling was already very high but may improve when further data are inputted.

2.4 The Chair thanked [redacted] and the other contributors for the clear presentation on what is a complex subject.

3. Update on COVID-19 Vaccines and risk of thromboembolic events with concurrent thrombocytopenia

3.1 The VBR EWG was presented with the latest data on thromboembolic events with thrombocytopenia associated with the authorised COVID-19 Vaccines up to a data lock point of 21 April 2021. The data lock point for the Janssen vaccine was 12 April 2021. A summary of regulatory actions taken by the EMA and FDA since the last EWG meeting on 19 April 2021 was also presented.

3.2 Concerning the AstraZeneca COVID-19 vaccine, 2 recent draft publications on causal mechanisms and 4 published case reports were presented. The papers by [redacted] team on potential mechanisms suggested that the underlying causes of thromboembolic events with thrombocytopenia in Covid-19 infection were different to those following vaccination and the proposed sequence of pathophysiological events involving neutrophils was interesting and could support causality. However, some of the data on excipients was speculative and the published versions of the draft articles may contain additional information. The data presented would also require independent verification

3.3 An overview of the case reports associated with the AstraZeneca COVID-19 Vaccine was presented including a summary table of the 4 reported cases after a second dose. Four of these cases were probable or possible, two of them tested negative for PF4 antibodies and the results are awaited or unknown in the 2 other cases. Additional follow-up clarified that a case was wrongly reported as occurring during pregnancy as we have not received any thromboembolic events with thrombocytopenia in pregnancy associated with the vaccine. The overall case fatality rate for all doses is stable at 20%.

3.4 The EWG was also given an overview of available outcome data for all confirmed cases. It was noted that the majority of cases were not associated with significant comorbidities that might be expected to limit function or quality of life before vaccination. However, the data on residual disability is limited as pre- and post-vaccination status has not been assessed using validated outcome measures and neurological deficits can recover after a year or more. UK haematologists are collecting long-term outcome data alongside HaemStar and the MHRA may receive this data.

3.5 The UK and foreign cases associated with the Pfizer, Moderna and Janssen COVID-19 vaccines were summarised using the same case definition. The FDA has lifted the recommended pause on Janssen COVID-19 vaccine use after its safety review identified 15 cases of thrombosis-thrombocytopenia syndrome following the administration of more than 6.8 million doses.

3.6 The estimated number of second AstraZeneca COVID-19 vaccine doses administered has significantly increased to 4.4 million whilst the number of first doses has increased slightly, in line with the current deployment programme to 22 million. Estimated case incidence rates for CVST and CVST plus non-CVST events were presented by age-stratified 5-year intervals and by gender. The overall incidence rate is 9.3 (8.1, 10.7) per million for first/unknown doses and the overall fatal incidence rate is 1.8 (1.3, 2.5) per million doses. The risk estimates were then compared with the expected benefits of vaccine in age subgroups.

3.7 The EWG considered the following 3 questions:

3.7.1 Question 1: based on the evidence presented does the EWG consider the benefit-risk balance remains favourable for all patients and for all age groups?

The EWG advised that the overall benefit-risk profile of the AstraZeneca COVID-19 Vaccine remains positive. However, depending on the status of the COVID-19 pandemic, its severity and impact on hospitalisation, the benefits of immunisation in individuals aged under 30 years may be outweighed by the potential risks.

3.7.2 Question 2: Does the EWG consider there might be an increased risk for the second dose of the vaccine?

The EWG advised that the emerging data on the risk of thromboembolic events occurring with thrombocytopenia following second doses is reassuring but limited so the MHRA should continue to monitor second dose cases closely.

3.7.3 Question 3: Does the EWG consider there is any need for action with regards to the Pfizer, Moderna or Janssen vaccines in relation to this potential risk?

Based on available data, the risk associated with the Pfizer and Moderna COVID-19 vaccines appears lower than that associated with the AstraZeneca COVID-19 Vaccine. This risk should be monitored and there is no need for regulatory action.

3.8 In conclusion, the EWG did not identify any potential trigger for urgent regulatory action.

4. Any Other Business

None.

5. Date and time of next meeting

The next meeting is scheduled to take place on Friday 30th April at 13:00.

The Meeting today started at 17:18 and ended at 18:33.

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

Annex I

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

Chair and Members

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

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

Invited experts

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

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

Observers

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

Annex II

The following participants declared interests and other relevant interests at the meeting today:

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

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

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

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

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

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

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

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

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

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

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

Mrs Wang – Other relevant interests arising from being highly sensitive to insect stings, and plant products such as Hyacinth bulbs, as recorded on Mrs Wang's medical records. The family of Mrs Wang lives with several rare diseases and conditions, some of which result in epileptic fits.

Professor Weir - NPNS - Imperial College and Other relevant interest arising from his department collaborates with Imperial College on a number of clinical trials.

Observers

Professor [redacted]

Professor Wei Shen Lim - NPNS arises from the institution (Nottingham University Hospitals NHS Trust) where Professor Lim works has received unrestricted investigator-initiated research funding from Pfizer for an unrelated prospective population-based cohort study of pneumococcal pneumonia in which Professor Lim is the Chief Investigator.

Dr [redacted]

Dr [redacted]

COMMISSION ON HUMAN MEDICINES (CHM)
COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Tuesday 4th May 2021** at **14:00** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor G Dougan
Mr VI G Fenton-May
Professor N French
Professor D Goldblatt
Ms S Hunneyball
Sir M Jacobs
Professor P J Lehner
Mr R Lowe
Dr S Misbah
Professor Y Perrie
Professor S Price
Dr A Riordan
Professor C Robertson
Professor T Solomon
Professor K M G Taylor
Dr R Thorpe
Professor M Turner
Dr S Walsh
Mrs M Wang

Apologies

Professor J Breuer
Professor K Hyrich
Professor H J Lachmann
Professor C Weir

Observers

[redacted]
Professor W S Lim
[redacted]

Secretariat

[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted] - VRMM

Presenters supporting specific items

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

MHRA Observers

[redacted] - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - LD
Dr S Branch - VRMM
[redacted] - MHRA-NIBSC
[redacted] - MHRA-Policy
[redacted] - VRMM
[redacted] - Comms
[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - LD

[redacted]

4th February 2022

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

1. Introduction and Announcement

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

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

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

1.3 Participants declared interests and other relevant interests for this meeting listed at **Annex II** to the minutes.

1.4 Apologies were received from Professors Breuer, Hyrich, Lachmann and Weir for this meeting.

1.5 The Chair welcomed the following observers:

Mr [redacted]

Dr [redacted] ublic Health England

Professor [redacted] JCVI

Dr [redacted] Public Health Agency

Dr [redacted]

Professor Wei Shen Lim
Chair of JCVI

Dr [redacted]
Public Health Scotland

Dr [redacted]
Public Health England

Dr [redacted] Public Health Wales

Dr [redacted]

2. Update on COVID-19 Vaccines and risk of thromboembolic events with concurrent thrombocytopenia

2.1 The EWG was presented with the latest data on thromboembolic events with thrombocytopenia associated with the authorised COVID-19 Vaccines up to a data lock point of 28 April 2021. Summaries of the CDC/FDA and Health Canada reviews of thrombosis with thrombocytopenia syndrome associated with the Janssen COVID-19 vaccine were also presented. The data lock point for the Janssen vaccine was 12 April 2021.

2.2 A review of recent publications concerning the AstraZeneca COVID-19 vaccine identified a paper on a proposed mechanism, a study reporting the prevalence of anti-PF4 antibodies in Norwegian health care workers, 2 small case series and 3 case reports. The EWG noted that two patients in a [redacted] cases series experienced thrombotic events after receiving a 2-day course of intravenous immunoglobulin but 1 of these patients responded well to eculizumab.

2.3 The EWG was also presented with analyses of Yellow Cards reported up to the 21st April data lock point including analyses of numbers of reports by report date, by reaction date and by vaccination date. Charts were also presented showing the time between vaccination date and reporting date and days between fatal event dates and reporting dates.

2.4 An overview of the case reports associated with the AstraZeneca COVID-19 Vaccine was presented including a summary table of the 6 reported cases after a second dose. It was noted that none of the reported cases had cerebral venous sinus thromboses or platelet factor 4 antibodies.

2.5 The EWG was also given an overview of the platelet count distributions for venous and arterial thromboembolic events with thrombocytopenia. Half of those with reported platelet values and venous or arterial events had significant thrombocytopenia with platelet counts under 50 x 10^9/L, all of those with myocardial infarctions had counts under 50 whilst approximately 20% with deep vein thrombosis and/or pulmonary embolus had mild thrombocytopenia with counts of 100 or more.

2.6 The UK and foreign cases associated with the Pfizer, Moderna and Janssen COVID-19 vaccines were summarised using the same case definition.

2.7 The estimated number of second AstraZeneca COVID-19 vaccine doses administered has significantly increased to 5.9 million whilst the number of first doses has increased slightly, in line with the current deployment programme to 22.6 million. Estimated case incidence rates for CVST and CVST plus non-CVST events were presented by age-stratified 10-year intervals and by gender. The overall incidence rate is 10.5 (9.2, 11.9) per million for first/unknown doses and the overall fatal incidence rate is 2.1 (1.6, 1.8) per million doses. The estimated case incidence rate following a second dose is 1 per million doses. The risk estimates were then compared with the expected benefits of vaccine in age subgroups. The reported incidence rates are now plateauing, consistent with complete reporting of retrospective cases, so the estimated case incidence rates can be considered reliable.

2.8 The EWG considered the following 3 questions:

2.8.1 Question 1: based on the evidence presented does the EWG consider the benefit-risk balance remains favourable for all patients and for all age groups?

The EWG advised that the overall benefit-risk profile of the AstraZeneca COVID-19 Vaccine remains positive. However, the benefits of immunisation in individuals aged under 30 years may be outweighed by the potential risks, depending on the status of the COVID-19 pandemic, its severity and impact on hospitalisation.

2.8.2 Question 2: Does the EWG consider there might be an increased risk for the second dose of the vaccine?

The EWG advised that the emerging data on the risk of thromboembolic events occurring with thrombocytopenia following second doses is reassuring but limited, and so the MHRA should continue to monitor second dose cases closely.

2.8.3 Question 3: Does the EWG consider there is any need for action with regards to the Pfizer, Moderna or Janssen vaccines in relation to this potential risk?

Based on available data, the risk associated with the Pfizer and Moderna COVID-19 vaccines appears lower than that associated with the AstraZeneca COVID-19 Vaccine. This risk should be continuously monitored and there is currently no need for further regulatory action.

2.9 In conclusion, the EWG did not identify any potential trigger for regulatory action.

3. Any Other Business

None.

4. Date and time of next meeting

The next meeting is scheduled to take place on Friday 7h May. Time to be confirmed.

The Meeting today started at 14:02 and ended at 15:01.

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

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

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

Observers

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

Annex II

The following participants declared interests and other relevant interests at the meeting today:

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

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

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

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

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

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

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

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

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

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

Mrs Wang – Other relevant interests arising from being highly sensitive to insect stings, and plant products such as Hyacinth bulbs, as recorded on Mrs Wang's medical records. The family of Mrs Wang lives with several rare diseases and conditions, some of which result in epileptic fits.

Observers

Professor [redacted]

Professor Wei Shen Lim - NPNS arises from the institution (Nottingham University Hospitals NHS Trust) where Professor Lim works has received unrestricted investigator-initiated research funding from Pfizer for an unrelated prospective population-based cohort study of pneumococcal pneumonia in which Professor Lim is the Chief Investigator.

Dr [redacted]

Dr [redacted]

COMMISSION ON HUMAN MEDICINES (CHM)
COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the Ad Hoc meeting held on **Monday 10th May 2021** at **17:15** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan
Mr VI G Fenton-May
Professor N French
Professor D Goldblatt
Ms S Hunneyball
Professor K Hyrich
Sir M Jacobs
Professor H J Lachmann
Professor P J Lehner
Mr R Lowe
Dr S Misbah
Professor Y Perrie
Professor S Price
Dr A Riordan
Professor C Robertson
Professor T Solomon
Professor K M G Taylor
Dr R Thorpe
Professor M Turner
Dr S Walsh
Mrs M Wang
Professor C Weir

Observers

[redacted]

Secretariat

[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted] - VRMM

Presenters supporting specific items

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

MHRA Observers

[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
Dr S Branch - VRMM
[redacted] - MHRA-NIBSC
[redacted] - MHRA-Policy
[redacted] - VRMM
[redacted] - VRMM
[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
[redacted] - Comms
[redacted] - VRMM
Mr P Tregunno - VRMM
[redacted] - LD
[redacted] - VRMM
Dr K Wydenbach - LD

[redacted]

4th February 2022

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

1. Introduction and Announcement

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

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

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

1.3 Participants declared interests and other relevant interests for this meeting listed at **Annex II** to the minutes.

1.5 The Chair welcomed the following observers:

Dr [redacted]
[redacted] Public Health England

Professor [redacted]
[redacted] JCVI

Dr [redacted]
[redacted] Public Health Agency

Dr [redacted]
[redacted]

Professor [redacted]
[redacted] JCVI

Dr [redacted]
[redacted] Public Health Wales

2. Update on COVID-19 Vaccines and risk of thromboembolic events with concurrent thrombocytopenia

2.1 The EWG was presented with the latest data on thromboembolic events with thrombocytopenia associated with the authorised COVID-19 Vaccines up to a data lock point of 5 May 2021. The data lock point for the Janssen vaccine was 28 April 2021.

2.2 The EWG was informed of the updated statement on the AstraZeneca COVID-19 vaccine published by the Joint Committee on Vaccination and Immunisation (JCVI) on 7 May 2021. It was also made aware of new guidance aligned with this statement issued by Public Health England on 9 May 2021.

2.3 The EWG was then presented with a review of recent publications concerning the COVID-19 vaccines including: recommendations on clinical and laboratory diagnosis of vaccine-induced immune thrombotic thrombocytopenia (VITT) made by the Platelet Immunology Subcommittee of the International Society on Thrombosis and Haemostasis (ISTH); an expert opinion article intended to provide practical guidance to healthcare professionals; and a description of a flow cytometric assay to detect platelet activating antibodies in VITT that could be adopted by more laboratories as it does not require washed platelets. The EWG noted that the ISTH recommendations included primary and secondary immune thrombocytopenia and considered isolated thrombocytopenia with abnormal coagulation parameters as a possible early sign of VITT. The MHRA has also identified possible cases of thrombosis with thrombocytopenia and isolated thrombocytopenia associated with PF4 antibodies so the current case definition should be reconsidered. The EWG was also aware of the proposed Brighton Collaboration criteria for thrombosis-thrombocytopenia syndrome although these criteria do not necessitate prior COVID-19 vaccine exposure and are intended for epidemiological studies rather than regulatory or clinical use.

2.4 An overview of the case reports associated with the AstraZeneca COVID-19 Vaccine was presented including a summary table of the 8 reported cases after a second dose. It was noted that none of the reported second dose cases were associated with cerebral venous sinus thromboses or had platelet factor 4 antibodies. The EWG was reassured by the emerging data but advised that second dose cases should remain under close monitoring as the vaccine programme moves into younger patients. An extra case was identified after the presentation was circulated and although there were not significant overall changes to the assessment, a revised version of the slides will be circulated for audit purposes.

2.5 The UK and foreign cases associated with the Pfizer, Moderna and Janssen COVID-19 vaccines were summarised using the same case definition. The EWG was also informed of the regulatory actions taken by the EMA following a signal assessment of thromboembolic events with thrombocytopenia conducted by the PRAC for the Janssen COVID-19 vaccine.

2.6 The estimated number of second AstraZeneca COVID-19 vaccine doses administered has increased to 7.5 million whilst the number of first doses has increased slightly, in line with the current deployment programme to 23.3 million. Estimated case incidence rates for CVST and CVST plus non-CVST events were presented by age-stratified 10-year intervals and by gender. The overall incidence rate is stable at 10.9 (9.6, 12.3) per million for first/unknown doses and the overall fatal incidence rate is 2.1 (1.6, 2.8) per million doses. The risk estimates were then compared with the expected benefits of the vaccine in age subgroups. The reported incidence rates are now plateauing, consistent with complete reporting of retrospective cases, so the estimated case incidence rates can be considered reliable.

2.7 The EWG then considered the following 3 questions:

2.7.1 Question 1: based on the evidence presented does the EWG consider the benefit-risk balance remains favourable for all patients and for all age groups?

The EWG advised that the overall benefit-risk profile of the AstraZeneca COVID-19 Vaccine remains positive although the benefits of immunisation in individuals aged under 40 years are probably outweighed by the potential risks, depending on the status of the COVID-19 pandemic, its severity and impact on hospitalisation. The benefit-risk assessment has not changed since it was reviewed on 4 May 2021.

2.7.2 Question 2: Does the EWG consider there might be an increased risk for the second dose of the vaccine?

The EWG advised that the emerging data on the risk of thromboembolic events occurring with thrombocytopenia following second doses is reassuring but limited so the MHRA should continue to monitor second dose cases closely, particularly as younger patients will now be receiving their booster immunisations.

2.7.3 Question 3: Does the EWG consider there is any need for action with regards to the Pfizer, Moderna or Janssen vaccines in relation to this potential risk?

Based on available data, the risk associated with the Pfizer and Moderna COVID-19 vaccines appears lower than that associated with the AstraZeneca COVID-19 Vaccine. This risk should be monitored and there is no need for regulatory action.

2.8 In conclusion, the EWG did not identify any potential trigger for regulatory action.

3. Any Other Business

None.

4. Date and time of next meeting

The next scheduled meeting is to take place **on Friday 14th May** at **10.30am**.

The Meeting today started at 17:15 and ended at 17:52.

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

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Observers

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

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The following participants declared interests and other relevant interests at the meeting today:

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

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

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

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

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

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

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

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

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

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

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

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

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

Mrs Wang – Other relevant interests arising from being highly sensitive to insect stings, and plant products such as Hyacinth bulbs, as recorded on Mrs Wang's medical records. The family of Mrs Wang lives with several rare diseases and conditions, some of which result in epileptic fits.

Professor Weir - NPNS - Imperial College and Other relevant interest arising from his department collaborates with Imperial College on a number of clinical trials.

Observers

Professor [redacted] - NPNS - University of Oxford employee (with no involvement in research or clinical trials related to Oxford AZ vaccine)
[redacted] JCVI

Professor [redacted] **-** NPNS arises from the institution ([redacted] University Hospitals NHS Trust) where Professor [redacted] works has received unrestricted investigator-initiated research funding from Pfizer for an unrelated prospective population-based cohort study of pneumococcal pneumonia in which Professor [redacted] s the Chief Investigator.

COMMISSION ON HUMAN MEDICINES (CHM)
COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Friday 14th May 2021** at **14:00** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan
Mr VI G Fenton-May
Professor N French
Professor D Goldblatt
Ms S Hunneyball
Professor K Hyrich
Sir M Jacobs
Professor P J Lehner
Mr R Lowe
Dr S Misbah
Professor Y Perrie
Professor S Price[1]
Dr A Riordan[2]
Professor T Solomon
Professor K M G Taylor
Dr R Thorpe
Professor M Turner[3]
Dr S Walsh
Mrs M Wang

Apologies

Professor H J Lachmann
Professor C Robertson
Professor C Weir

Secretariat

[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea – LD
[redacted]

Presenters supporting specific items

[redacted] – VRMM
[redacted] – LD
[redacted] – VRMM
[redacted] – LD

MHRA Observers

[redacted] – LD
Dr S Branch – VRMM
[redacted] – VRMM
[redacted] – Comms
[redacted] – LD
[redacted] – LD
[redacted] – VRMM
[redacted] – VRMM
Dr K Wydenbach – LD

[redacted]

16th February 2023

[1] joined during item 2
[2] joined during item 4
[3] left during item 5

Key
LD = Licensing Division
VRMM = Vigilance & Risk Management of Medicines
Comms = MHRA Communications

1. Introduction and Announcements

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

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

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

1.3 Participants declared interests and other relevant interests for this meeting listed at **Annex II** to the minutes.

1.4 Apologies were received from Professors Lachmann, Robertson and Weir for this meeting.

2. Review of the possible risk of neurological autoimmune conditions with COVID-19 vaccines

2.1 The EWG was presented with an assessment of data for the adverse events of multiple sclerosis, optic neuritis, transverse myelitis and Neuromyelitis Optica Spectrum Disorder (NMOSD) reported following vaccination with the AstraZeneca, Pfizer-BioNTech and Moderna COVID-19 Vaccines. The assessment included a review of the UK Yellow Card data, data from the most recent safety summary surveillance report for each of the vaccines, and epidemiological analyses (observed vs expected analyses of Yellow Card reports and rapid cycle analyses using the CPRD).

2.2 For the AstraZeneca vaccine, the EWG were informed that the number of reports of neurological autoimmune conditions was low in the context of the usage of the AstraZeneca vaccine. For transverse myelitis, the majority of reports met the case definition, but had very rapid onset times not associated with transverse myelitis. For multiple sclerosis and optic neuritis, the majority of reports were consistent with reactogenicity reactions and were transient, short-duration reactions. Company observed vs expected analysis did not identify an increase in these events.

2.3 For the Pfizer/BioNTech vaccine, the EWG were informed that there had been limited reports of multiple sclerosis, optic neuritis or transverse myelitis and no reports of NMOSD. The EWG noted that there was no clear patterns of onset times or occurrence after a specific dose, and company data did not show an increased risk of these events. For all events the number of reports was small in the context of the use of the vaccine.

2.4 For the Moderna vaccine, the EWG noted there had been no Yellow Card reports of multiple sclerosis, optic neuritis, transverse myelitis or NMOSD and that there were very few reports from international data.

2.5 The EWG were presented the MHRA epidemiological data, with observed vs expected analysis identifying a signal of transverse myelitis for the AstraZeneca vaccine assuming 100% reporting for all age groups, and for the Pfizer/BioNTech vaccine assuming 50% reporting in the under 50 years age group, and 25% reporting in the 50-64 years age group. Rapid cycle analysis did not identify any signals for any of the neurological autoimmune conditions or vaccines.

2.6 The EWG considered that the majority of reports of multiple sclerosis, optic neuritis and NMOSD were not related to new onset of these events, with the reports describing either flare-up of these events or reactogenicity events. For transverse myelitis, the EWG considered that for the AstraZeneca vaccine, while reports did meet the case definition, the reports did not relate to new-onset of transverse myelitis. The EWG considered that transverse myelitis should continue to be closely monitored and was aware of potential epidemiological studies that would be investigating this. The EWG concluded that the available evidence did not support any updates to the product information for any of the COVID-19 vaccines.

3. Risk of Capillary Leak Syndrome with COVID-19 Vaccine AstraZeneca

3.1 The VBR EWG was reminded that it had previously considered an assessment of UK cases of capillary leak syndrome (CLS) reported following vaccination with COVID-19 Vaccine AstraZeneca at its meeting on 12 April 2021. At that time the EWG advised that a causal association could not be determined based on the data available, and that the signal should be closely monitored.

3.2 The EWG was presented with an updated review of this signal which included an assessment of UK cases of CLS reported for COVID-19 Vaccine AstraZeneca via the Yellow Card Scheme, together with an assessment of a cumulative review of worldwide clinical study and post-authorisation cases and a literature review submitted by the company.

3.3 The EWG agreed that the currently available data did not suggest an association between COVID-19 Vaccine AstraZeneca and CLS. Causality assessment was difficult in some cases because the patients had a prior history of CLS or other significant illness. Causality was also considered unlikely in some cases due to the time to onset being inconsistent with a vaccine-related effect. The EWG also noted that most cases did not have the IgG paraprotein typical of classical CLS.

3.4 The EWG agreed that no updates to the SmPC or Risk Management Plan for COVID-19 Vaccine AstraZeneca were warranted based on the data presented and supported the proposal to keep the issue under review.

4. COVID-19 Vaccine AstraZeneca: Assessment of the draft protocol for a Post Authorisation Safety Study (PASS) to ascertain the incidence rate of adverse events of special interest

4.1 The VBR EWG was presented with an assessment of the draft protocol for a secondary database study in the VAC4EU (Vaccine Monitoring Collaboration for Europe) research environment to ascertain the incidence rates of adverse events of special interest in individuals vaccinated with COVID-19 Vaccine AstraZeneca.

4.2 The EWG agreed with the assessment of the study protocol and with the comments and lists of questions for the company proposed by the MHRA and the European Medicines Agency (EMA).

4.3 In particular, the EWG agreed with concerns raised about the proposed timelines for the study given the pace of roll out of the vaccine in the UK, and fully supported the proposal to ask the company to submit the first interim report and the statistical analysis plan (SAP) much sooner than had been proposed in the protocol. The EWG also recommended that the company should be asked to provide further information about when the study will start; information that had not been included in the draft protocol.

4.4 The EWG discussed the limitations of the cohort study design which the company proposed to use as the primary study approach. The EWG supported the concerns raised regarding the likely issues with finding concurrent controls for the cohort study as more unvaccinated individuals become vaccinated with time. The EWG discussed the company's rationale for proposing the cohort design as the primary approach (that the self-controlled risk interval (SCRI) design is less able to study outcomes with a gradual onset, such as multiple sclerosis and peripheral neuropathies) but agreed with the assessment that these difficulties could be overcome by using the date of onset of first symptoms as the index date rather than date of diagnosis, and by studying a range of different risk intervals. The EWG supported proposals to make the SCRI design rather than the cohort design as the primary study approach.

The EWG further suggested that the company be asked to consider a more sophisticated statistical approach to the SCRI design, for example by modelling exponential decline in risk rather than specifying 'at risk' and 'not at risk' periods.

4.5 In addition, the EWG expressed concerns as to whether data on individuals taking immunosuppressants and individuals living with HIV would be adequately collected in the study. The EWG questioned whether this information was captured in the two non-UK databases proposed by the company to be used in the study, noting that information about use of immunomodulators other than methotrexate would not be captured in CPRD (the 3rd database to be proposed for the study) and was not readily available from other sources in the UK. Similarly, information about individuals living with HIV would not be adequately captured in CPRD. The EWG suggested that these data may be more readily available in other European countries. The EWG recommended that the company further explore the availability of data on immunosuppressed individuals and those living with HIV in the databases currently proposed for the study and if necessary, to include additional European databases in the study to ensure that the safety of the vaccine in this important group of individuals can be evaluated in the study. If adequate data are not available, this should be included as an important limitation of the study in the protocol.

4.6 The EWG noted that only 3 databases had been selected by the company for the study. To increase the power of the study and yield more meaningful data, the EWG suggested that the company be requested to select a number of additional European databases for the study.

5. Brief Update on COVID-19 Vaccines

5.1 The VBR EWG was updated on the progress status of each of the vaccines under review or to be evaluated in the future. Regarding the SPC for the Janssen vaccine, the EWG agreed with the company proposal to include 'Patients with a history of heparin-induced thrombocytopenia and thrombosis (HITT or HIT type 2)' as a warning in section 4.4 rather than a contraindication in section 4.3.'

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

6.1 None.

7. Date and time of next meeting

The next Ad Hoc meeting on Thromboembolic events with COVID-19 Vaccines is scheduled to take place on **Monday 17th May** at **5.15pm**.

The next scheduled meeting is to take place **on Friday 21st May** at **2.30pm**.

The Meeting today started at 10:34 and ended at 12:32.

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Annex I

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

Chair and Members

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

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

Invited experts

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

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

Observers

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

Annex II

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

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

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

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

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

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

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

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COMMISSION ON HUMAN MEDICINES (CHM)
COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the Ad Hoc meeting held on **Monday 17th May 2021** at **17:15** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan
Mr VI G Fenton-May
Professor N French
Professor D Goldblatt
Ms S Hunneyball
Professor K Hyrich
Sir M Jacobs
Professor H J Lachmann
Professor P J Lehner
Mr R Lowe
Dr S Misbah
Professor Y Perrie
Professor S Price
Dr A Riordan
Professor C Robertson
Professor K M G Taylor
Dr R Thorpe
Professor M Turner
Dr S Walsh
Mrs M Wang
Professor C Weir

Apologies

Professor T Solomon

Observers

[redacted]
Professor W S Lim
[redacted]

Secretariat

[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted] - VRMM

Presenters supporting specific items

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

MHRA Observers

[redacted] - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - LD
Dr S Branch - VRMM
[redacted] - MHRA-NIBSC
[redacted] - MHRA-Policy
[redacted] - VRMM
[redacted] - VRMM
[redacted] - VRMM
[redacted] - Comm
[redacted] - VRMM
[redacted] - VRMM
Mr P Tregunno - VRMM
[redacted] - LD
[redacted] - VRMM

[redacted]

4th February 2022

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

1. Introduction and Announcement

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

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1.3 Participants declared interests and other relevant interests for this meeting listed at **Annex II** to the minutes.

1.4 Apologies were received from Professor Tom Solomon for this meeting.

1.5 The Chair welcomed the following observers:

Dr [redacted]
[redacted], Public Health England

Professor [redacted]
[redacted] JCVI

Dr [redacted]
Locum Consultant in Health Protection, Public Health Agency

Dr [redacted]

Professor [redacted]
[redacted] JCVI

Dr [redacted]
Public Health Scotland

2. Update on the review for major thrombotic events associated with thrombocytopenia

2.1 The EWG was presented with the latest data on thromboembolic events with thrombocytopenia associated with the authorised COVID-19 Vaccines up to a data lock point of 12 May 2021.

2.2 The EWG was informed of the updated recommendations issued by the [redacted] on 3rd May 2021.

2.3 The EWG was then presented with a summary of recent publications concerning the AstraZeneca COVID-19 vaccine including: interim reactogenicity and safety data results from the COM-CoV study of heterologous prime-boost COVID-19 vaccines; a review of 20 published cases of vaccine-associated immune thrombosis and thrombocytopenia; a review of COVID-19 vaccine platforms that included a proposed causal mechanism to explain observed events of thrombosis with thrombocytopenia; and a small study reporting the frequency and platelet-activation properties of PF4 antibodies detected in healthy volunteers after immunisation with the AstraZeneca and Pfizer COVID-19 vaccines.

2.4 An overview of the case reports associated with the AstraZeneca COVID-19 Vaccine was presented including summary tables of the 15 reported cases occurring after a second dose.

2.4.1 It was noted that a female of unknown age had experienced cerebral venous sinus thrombosis and deep vein thrombosis with severe thrombocytopenia at 8 days after her second dose although her PF4 antibody status was not known.

2.4.2 Another case was reviewed in detail: an elderly female with localised lymphoma in remission developed an incidental hepatic vein thrombosis with mild thrombocytopenia about 28 days after her first dose of the vaccine. She experienced an acute occipital arterial infarct associated with moderate thrombocytopenia and PF4 antibodies (optical density 2.46). The events following the second dose were confounded by recent COVID-19 infection. The EWG advised that this was probably a positive rechallenge case confounded by COVID-19 infection. It also noted that second doses are contraindicated in patients who have experienced major venous and/or arterial thrombosis occurring with thrombocytopenia following vaccination with any COVID-19 vaccine which seems to be supported by this particular case.

2.4.3 The EWG advised that the emerging data on second dose cases might have identified a different clinical phenotype to early first dose cases but is based on an older group. More data on the risks associated with second doses in younger people is required and so this issue should remain under close monitoring as the vaccine programme moves into younger patients. It also requested that age-stratified second dose incidence rate data should be presented at future weekly meetings.

2.5 The UK and foreign cases associated with the Pfizer, Moderna and Janssen COVID-19 vaccines were summarised using the same case definition. The EWG noted that the case incidence rates for the Janssen COVID-19 vaccine reported by the [redacted] are gradually increasing and are now comparable to those for the AstraZeneca COVID-19 vaccine.

2.6 The estimated number of second AstraZeneca COVID-19 vaccine doses administered has increased to 9.0 million whilst the number of first doses has increased slightly, in line with the current deployment programme to 23.9 million. Estimated case incidence rates for CVST and CVST plus non-CVST events were presented by age-stratified 10-year intervals and by gender. The overall incidence rate is stable at 12.3 (10.9, 13.7) per million for first/unknown doses and the overall fatal incidence rate is also stable at 2.3 (1.7, 3.0) per million first/unknown doses. The incidence rate associated with second doses has increased slightly from 1.1 to 1.7 (0.9, 2.7) per million doses but the 95% confidence intervals are overlapping. The risk estimates were then compared with the expected benefits of vaccine in age subgroups. The EWG noted that all new fatal cases have cerebral venous sinus thromboses. The reported incidence rates showed a small increase since last data lock point, while risk-benefit ratio remained relatively unchanged.

2.7 The EWG then considered the following 3 questions:

2.7.1 Question 1: based on the evidence presented does the EWG consider the benefit-risk balance remains favourable for all patients and for all age groups?

The EWG advised that the overall benefit-risk profile of the AstraZeneca COVID-19 Vaccine remains positive although the benefits of immunisation in individuals aged under 40 years are probably outweighed by the potential risks, depending on the status of the COVID-19 pandemic, its severity and impact on hospitalisation. The benefit-risk assessment has not changed since it was reviewed on 10 May 2021.

2.7.2 Question 2: Does the EWG consider there might be an increased risk for the second dose of the vaccine?

The EWG advised that the emerging data on the risk of thromboembolic events occurring with thrombocytopenia following second doses is reasonably reassuring but limited, and so the MHRA should continue to monitor second dose cases closely, particularly as younger patients will now be receiving their second doses. The case of positive rechallenge reported after the second dose of the AstraZeneca COVID-19 vaccine, although confounded, validates the contraindication in those with thrombotic events associated with thrombocytopenia after a first dose of any COVID-19 vaccine.

2.7.3 Question 3: Does the EWG consider there is any need for action with regards to the Pfizer, Moderna or Janssen vaccines in relation to this potential risk?

Based on available data, the risk associated with the Pfizer and Moderna COVID-19 vaccines appears lower than that associated with the AstraZeneca COVID-19 Vaccine. This risk should be monitored and there is no need for regulatory action.

2.8 In conclusion, the EWG did not identify any potential trigger for regulatory action.

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

None.

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

The next scheduled meeting is to take place on **Friday 21st May 2021** at **2.30pm**.

The Meeting today started at 17:17 and ended at 18:03.

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Observers

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

Annex II

The following participants declared interests and other relevant interests at the meeting today:

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

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

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

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

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

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

Mrs Wang – Other relevant interests arising from being highly sensitive to insect stings, and plant products such as Hyacinth bulbs, as recorded on Mrs Wang's medical records. The family of Mrs Wang lives with several rare diseases and conditions, some of which result in epileptic fits.

Professor Weir - NPNS - Imperial College and Other relevant interest arising from his department collaborates with Imperial College on a number of clinical trials.

Observers

Professor [redacted] - NPNS - University of Oxford employee (with no involvement in research or clinical trials related to Oxford AZ vaccine)
[redacted] JCVI

Professor [redacted] **-** NPNS arises from the institution ([redacted] University Hospitals NHS Trust) where Professor [redacted] works has received unrestricted investigator-initiated research funding from Pfizer for an unrelated prospective population-based cohort study of pneumococcal pneumonia in which Professor [redacted] is the Chief Investigator.

Dr [redacted] – Lapsed and NPNS - Regarding companies to declare interests for, prior to joining Public Health Scotland, Dr [redacted] worked for a company that provided epidemiological services to the pharmaceutical industry. Whilst working there, she supported respiratory vaccine development activities at Janssen (Johnson & Johnson). Dr [redacted] has now left that role.

COMMISSION ON HUMAN MEDICINES (CHM)
COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Friday 21st May 2021** at **14:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan[1]
Mr VI G Fenton-May
Professor N French
Professor D Goldblatt
Ms S Hunneyball
Professor K Hyrich[1]
Sir M Jacobs[2]
Professor H J Lachmann
Mr R Lowe
Dr S Misbah
Professor Y Perrie
Professor S Price
Dr A Riordan
Professor K M G Taylor
Dr R Thorpe
Professor M Turner
Dr S Walsh
Professor C Weir

Apologies

Professor P J Lehner
Professor C Robertson
Professor T Solomon
Mrs M Wang

Observers (left after item 3)

[redacted]

Secretariat

[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted] - VRMM

Presenters supporting specific items

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

MHRA Observers

[redacted] - VRMM
[redacted] - LD
[redacted] - LD
Dr S Branch - VRMM
[redacted] - LD
[redacted] - NIBSC
[redacted] - MHRA-Policy
[redacted] - VRMM
[redacted] - Comms
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
Mr P Tregunno - VRMM
[redacted] - VRMM

[redacted]

3rd August 2021

[1] Left during item 5
[2] Joined during item 3

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

1. Introduction and Announcement

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

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

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

1.3 Participants declared interests and other relevant interests for this meeting listed at **Annex II** to the minutes.

1.4 Apologies were received from Professors Lehner, Robertson, Solomon and Mrs Wang for this meeting.

1.5 The Chair welcomed the following observers:

Professor [redacted]
[redacted] JCVI

Dr [redacted]
Public Health Scotland

2. Communications on COVID-19 vaccine safety

2.1 The EWG discussed a paper which presented options for analyses of safety data related to the occurrence of thrombotic events with concurrent thrombocytopenia that could be considered for routine publication within the `Coronavirus vaccine – weekly summary of Yellow Card reporting'.

2.2 The EWG supported transparency with regards to the publication of data on this risk but advised that the data needs to be carefully presented to ensure its limitations are clear and that estimates based on small numbers which may be unstable and/or inadvertently disclose confidential patient information should be avoided.

2.3 The EWG supported the publication of age-stratified incidence reporting rates for thrombosis with concurrent thrombocytopenia following both doses of the COVID-19 AstraZeneca vaccine alongside an accessible and clear description of the benefits and risks of vaccination.

3. Update on the Safety Data for the Moderna COVID-19 vaccine

3.1 The EWG was presented with the first safety update for the Moderna COVID-19 vaccine, which covered the first month following deployment in the UK, with a data lock point of 12th

May 2021. The EWG was informed that the ADRs reported were broadly in line with the known safety profile for the vaccine and that had been seen in clinical trials. The EWG heard a signal of dizziness has been identified for the Moderna COVID-19 vaccine, which included reports of dizziness alongside psychogenic, reactogenic and vestibular events. The EWG were informed that the Marketing Authorisation Holder (MAH) had been requested to review the signal of dizziness with a particular interest in cases reporting vestibular events such as tinnitus. The meeting supported the continuous review of dizziness reports. An update to the EWG will be provided following the MAH review.

3.2 The EWG were informed that a large proportion of the Yellow Cards reported for the Moderna vaccine were related to delayed injection site reactions. These reactions include a large, raised, itchy red rash around the injection site around 7 to 8 days after vaccination. The meeting was informed that the MAH had updated their Company Core Data Sheet (CCDS) to include these delayed injection site reactions and were planning to update the product information in due course. The meeting supported the proposed update to the product information to highlight these delayed reactions to patients.

3.3 The EWG concluded that based on the data presented, the safety profile for COVID-19 vaccine Moderna was broadly in line with the expected safety profile from clinical trials. The EWG supported the proposed actions on the delayed injection site reactions and dizziness signals.

4. Covid-19 mRNA vaccine BNT162b2

4.1 The EWG heard that immunobridging of neutralising antibody levels between adolescents aged 12-15 years and young adults aged 16-25 years has been established and that the neutralising antibody levels seen in adolescents actually exceeded those in young adults.

4.2 The EWG noted that these immunobridging results are supported by a very high level of short-term efficacy data in adolescents against symptomatic disease after 2 doses of the vaccine.

4.3 The EWG heard that the safety data in adolescents was generally comparable with that seen in young adults, with the majority of adverse events being mild to moderate and relating to reactogenicity. Additionally, no new adverse events are identified in the trial. The EWG noted that 3 serious adverse events of depression were reported in the adolescent group compared with 2 non-serious reports in the placebo group. All 3 subjects had a significant past medical history that included depression, but none were considered related to the vaccine and 2 of the 3 cases resolved after 5 days. The EWG agreed that currently there was no basis to list depression as a safety concern in the RMP. However, this will be kept under review in the post authorisation period, through the monthly summary safety reports submitted by the company.

4.4 The EWG noted that overall, when compared to adults 16-55 years of age, there is an increase in reactogenicity seen in adolescents. However, it was agreed that this is not unexpected as the same trend was seen previously in subjects 16-55 years compared with those aged > 55 years of age. This trend is already reflected in the GB SmPC for the conditional marketing authorisation and this wording will be aligned in the Regulation 174 product information.

4.5 The EWG were made aware of an open letter that has been received by the MHRA, signed by over 40 UK doctors, raising their concerns about covid-19 vaccination in children. Other media coverage was highlighted on the ethics of vaccinating children and adolescents that have a low risk of severe COVID-19 whilst the majority of the adult population worldwide is

not yet vaccinated. The EWG concluded that while the latter is an important moral and ethical question it is not one for the EWG to address as the licensing remit of the MHRA focuses on the assessment of the quality, safety, and efficacy of medicinal products.

4.6 The EWG discussed the adequacy of the efficacy and safety follow-up duration available in subjects aged 12-15 years (median > 2months). It was noted that this duration is the same as what was previously agreed for subjects aged 16 years and over. The EWG agreed with the Paediatric Medicines EAG that it seems reasonable to be on the same line for adolescents, particularly given the significant post-marketing safety data now available for this vaccine. The EWG noted that it is anticipated for younger children under 12 years of age, longer term safety data would be requested before any approval.

4.7 The EWG were made aware that no notable changes were proposed by the company to the risk management plan in terms of the safety concerns, pharmacovigilance plan or risk minimisation measures. The EWG agreed that based on the available safety data, no additional safety concerns specific to the adolescents aged 12-15 years are required at this time.

4.8 The EWG noted that the list of adverse events of special interest (AESIs) for COVID-19 vaccine BNT162b2 already includes events of relevance to the adolescent age group, including narcolepsy, chronic/post viral fatigue syndrome, myalgic encephalomyelitis, post orthostatic tachycardia syndrome and paediatric inflammatory multisystem syndrome. The EWG noted that these events will be subject to observed-expected analyses and that age-appropriate background rates should be considered by the company. The EWG agreed with the proposed questions to the company, including requesting a discussion on how safety data in the adolescent population could be collected in existing PASS studies, and the inclusion of a separate analysis of safety data in the adolescent population in the monthly summary safety reports.

4.9 The EWG noted the clinical trial data continues to be blinded to participants and clinical trial investigators except if participants are offered vaccination under emergency use authorisation, but the data have been unblinded to the independent scientists that undertook the statistical analysis.

4.10 The EWG noted immunogenicity and safety data in the 12-15 year olds provides a good level of reassurance. The efficacy data is also supportive of a positive recommendation albeit that the data is limited in this age group.

4.11 The EWG noted vaccination of 12-15-year olds could be an important means by which to limit the evolution of SARS-CoV-2 through controlling circulation of the virus.

4.12 The EWG noted that careful consideration may need to be paid to the natural background mental and behavioural health of 12-15-year-olds when assessing vaccine surveillance safety data, as this age group are likely to have been particularly affected by the pandemic.

4.13 The EWG agreed that six months follow-up data in 12-15 years should be added as a condition.

4.14 The EWG agreed with the conclusions of the Paediatric Medicines EAG. The EWG endorsed the clinical assessor's recommendation, that the Regulation 174 approval can be amended to lower the indication age to 12 years and above.

5. A single-blind, randomised, phase II study to determine safety and immunogenicity of the Coronavirus Disease (COVID-19) vaccine ChAdOx1 in UK healthy children and adolescents (aged 6-17) COV006

5.1 The EWG heard the proposal to continue dosing in the Oxford paediatric trial and to administer booster/second doses is supported by the CTU. Use of the AstraZeneca COVID-19 (AZD1222) vaccine in UK national deployment has been restricted by the Joint Committee on Vaccination and Immunisation (JCVI) following reports of extremely rare adverse events of concurrent thrombosis and thrombocytopenia following vaccination with the first dose of AZD1222. However, such a risk has not yet been convincingly demonstrated for second doses.

5.2 The risk of thrombosis with concurrent thrombocytopaenia has not been demonstrated for any doses in children and is therefore not known. A total of 261 children aged 6-17 years have received the prime dose with no complications and 74 children aged 12-17 years have been given their booster doses on Day (D) 28 also with no complications. The EWG heard, the MHRA-CTU has reviewed the safety profile of the 74 children in the older age group (12-17 years), where the prime and booster doses were administered on D28 with no safety concerns identified; and together with consideration of the updated benefit risk assessment provided by the Sponsor, the proposal to administer a booster dose to the remaining 76 older children and the remaining 111 younger children (aged 6-11years) in this trial is supported.

5.3 The EWG also heard that appropriate additional safety blood tests have been introduced, at D2 and D7 for a subset of 6-11 year olds (20 participants at each timepoint post boost). These include full blood count (FBC), urea and electrolytes (U&E), liver function tests (LFT) and C-Reactive protein (CRP), with clotting studies. Trial participants will also be fully informed of the potential risks (with the ability to withdraw should they choose). Administering booster doses to the children in this trial will provide data to demonstrate efficacy which could be crucial for having a COVID-19 vaccine for specific groups within the paediatric population in the future and for any future variant vaccine. Immunogenicity data from prime (single-dose) dosing in the COV006 cohort is pending. However adult studies show that a single dose provides 76% protection against symptomatic infection, which persists over at least a 12-week period rising to >82% after a second and providing prolonged protection. If similar results can be extrapolated to the paediatric population, a second dose is required for prolonged efficacy and if the booster doses are not given trial participants will complete the trial having not been fully vaccinated, i.e. not fully covered against COVID-19, which has ethical considerations.

5.4 The EWG heard on 19th May the Paediatric Medicines EAG broadly agreed that the trial could proceed with administering booster doses. And, that overall, the risk mitigation in place was considered appropriate. However, there was discussion around the updated patient information and the advice that those with headaches persisting more than 4 days after vaccination should seek medical assessment. Experts noted that 4 day headaches are rarer in children compared to adults and felt this should be reconsidered and trial participants asked to seek advice earlier.

5.5 The EWG was asked to provide advice to the Clinical Trails Unit (CTU) regarding dosing of second doses to paediatric subjects within an ongoing clinical trial using the AZD1222, and to discuss the 4 day duration of headache in the patient advice.

5.6 The EWG noted the additional safety blood tests, and proposed D-Dimer to also be included. A member noted that the trial should be allowed to proceed on the basis of a) the

additional blood tests to be included b) that no convincing cases of thrombosis with concurrent thrombocytopenia have occurred at second dose, and c) that participants and parents / guardians of participants will be reapproached for consent with much clearer information. The member also noted that it is also important to complete the study in order to gain as much data / information as possible.

5.7 The EWG noted an argument in favour of providing a booster dose, and the possibility of enhanced protection which could be afforded to the participants. This argument was noted to carry two substantial caveats: the majority of the paediatric population has not been vaccinated because the risk of moderate / severe disease is extremely low in these young age groups, and secondly the purpose of a clinical trial is not to provide clinical care to the participants. In an interconnected point the EWG also referred to good clinical practice (GCP) and the stipulation to protect trial participants from risk supersedes the need for science to understand the article being tested. In this trial there is a very small but potentially very serious risk of thrombosis with concurrent thrombocytopenia associated with the vaccine at first dose, which could theoretically occur with the second dose in children.

5.8 The EWG noted if the trial was to proceed, the interval between doses will be approximately 3.5 months for those children awaiting their second dose and this would make data comparison e.g. immune bridging of data difficult to interpret because the data collected from adults is of a shorter interval.

5.9 The EWG noted that recent surveillance data in adults has identified cases of thrombosis with concurrent thrombocytopenia after the second dose. However, the rate is far less than that reported following first dose and it is not clear whether the rate is any higher than the expected background rate.

5.10 Thrombotic events in adults appear to be immune mediated, as such, it is plausible that the incidence could also be similar in children, who are capable of powerful immune responses. However, the data to help understand the aetiology or mechanism of this SAE is limited in adults and non-existent in children. Therefore, predictions of incidence of the risk of thrombosis with concurrent thrombocytopenia upon vaccination in children will be unreliable at this stage. The member disclosed a conflict of interest, i.e. being the father of two children in the age ranges that are subject of the trial.

5.11 The EWG noted that second doses of AZD1222 are being given to people in the general UK population (including those under 40 years) who have had their first dose of the same vaccine.

5.12 The EWG noted that should the trial continue, the data gathered could be relevant / valuable to future vaccine campaigns in other nations. Notable limitations were also discussed: children in developing countries often respond differently to vaccination, surveillance systems to identify rare adverse events are often not available in many developing countries, and campaigns in these countries in many cases are only just beginning to vaccinate older at-risk populations.

5.13 The EWG further discussed the pros and cons of continuing the trial through to completion. The group arrived at the below list of questions to be sent to the trial Sponsor in expectation that the answers may help to better inform the Commission on Human Medicines (CHM).

1. The original purpose of the trial has been questioned. The original study was presumably set up to study immunogenicity of ChadOx1 in younger age groups to aid the extension of any approval to younger age groups. How will D112 booster data be used to aid in the evaluation of ChadOx1 in young children in

the UK, for example to support national rollout or to support vaccination of specific vulnerable groups?

2. If not relevant to UK children (given the fact it is unlikely the AZ vaccine will be rolled out to children in the UK) how could data from the trial be used to support / inform dosing in children in other countries e.g. under developed countries.

3. How will the fact that the data generated from continuation of the trial which may be of little value to children in the UK be shared with trial participants / parents in patient facing documents?

4. D-dimers should be added to the safety bloods.

5. Blood testing measures are possibly falsely reassuring given that once abnormalities are detected there is often no successful intervention (seen in the VITT first dose patients). Would this be explained to families?

6. The direct benefit of the trial to the individual or generally is quite remote. Individual benefit of vaccination with this vaccine for younger individuals when balanced against risk is low and it is unlikely to be used in the UK in this population. If used in the rest of the world, the patient population will be different from the population in this trial.

7. Does the immunogenicity data suggest that a second dose is actually needed for children?

8. How will the data generated by boosting the remaining children be of use (since the AZ vaccine is unlikely to be given to children in resource rich settings and not a priority in resource poor settings)?

5.14 In post meeting email correspondence, a small number of additional questions were also suggested by members of the EWG, these are listed below for ease of reference:

1. Will parents be asked to re-consent for the booster dose as the balance of risk/ benefit has changed since their original consent was taken?

2. Even if the issues can be addressed by a very detailed consent process, should this population be asked to give consent? It is already a difficult population for consent purposes, i.e. parents of nearly Gillick competent children and/or immature but Gillick competent children. They will be subject to the pressure of being asked to continue in a trial for a life-saving vaccination by a world leading institution in face of a global pandemic. Trial participants will be under pressure to consent and such pressure is increased given that if they say no, other subjects cannot be obtained, and the trial cannot proceed. Individual choice is usually favoured however in such circumstances it is questionable whether consent can be ethically attempted.

3. The paper states that there “There have been no clearly identified safety concerns identified for thrombosis/thrombocytopenia associated with the second dose of the AstraZeneca (AZD1222) vaccine.” This statement does not refer to the very rapid increase in understanding, and possible future position; in that information is building slowly but as it is a rare disease and more first doses given than second the picture may not be complete. The risk, albeit slight, is confirmed by introduction

of blood testing measures in the study itself. Would this slight risk be communicated to participants?

4. 'Thrombosis' should be added as a stopping criterion.

6. Any Other Business

None.

7. Date and time of next meeting

The next Ad Hoc meeting on Thromboembolic events with COVID-19 Vaccines is scheduled to take place on **Monday 24th May** at **5.15pm**.

The next scheduled meeting is to take place **on Tuesday 25th May** at **12.00pm**.

The Meeting today started at 14:31 and ended at 16:05.

Annex I

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

Chair and Members

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

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

Invited experts

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

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

Observers

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

Annex II

The following participants declared interests and other relevant interests at the meeting today:

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

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

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

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

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

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

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

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

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

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

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Professor Weir - NPNS - Imperial College and Other relevant interest arising from his department collaborates with Imperial College on a number of clinical trials.

Observers

Professor [redacted] - NPNS - University of Oxford employee (with no involvement in research or clinical trials related to Oxford AZ vaccine)
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COMMISSION ON HUMAN MEDICINES (CHM)
COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the Ad Hoc meeting held on **Monday 24th May 2021** at **17:15** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan
Mr VI G Fenton-May
Professor D Goldblatt
Ms S Hunneyball
Professor K Hyrich
Sir M Jacobs
Professor H J Lachmann
Professor P J Lehner
Mr R Lowe
Dr S Misbah
Professor Y Perrie
Professor S Price
Dr A Riordan
Professor C Robertson
Professor T Solomon
Professor K M G Taylor
Dr R Thorpe
Dr S Walsh
Mrs M Wang
Professor C Weir

Apologies

Professor N French
Professor M Turner

Observers

[redacted]

Secretariat

[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted] - VRMM

Presenters supporting specific items

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

MHRA Observers

[redacted] - VRMM
[redacted] - LD
[redacted] VRMM
[redacted] - LD
Dr S Branch - VRMM
[redacted] - MHRA-NIBSC
[redacted] – VRMM
[redacted] – MHRA Policy
[redacted] - Comms
[redacted] - VRMM
[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
Mr P Tregunno - VRMM
[redacted] - LD
[redacted] - VRMM

[redacted]

4th February 2022

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

1. Introduction and Announcement

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1.3 Participants declared interests and other relevant interests for this meeting listed at **Annex II** to the minutes.

1.5 The Chair welcomed the following observers:

Dr [redacted], Public Health Agency

Dr [redacted]

Professor [redacted] JCVI

Dr [redacted] Public Health Scotland

Dr [redacted]

2. Update on COVID-19 Vaccines and risk of thromboembolic events with concurrent thrombocytopenia

2.1 The EWG was presented with the latest data on thromboembolic events with thrombocytopenia associated with the authorised COVID-19 Vaccines up to a data lock point of 19 May 2021.

2.2 The EWG heard that the MHRA met with representatives of the Expert Haematology Panel (EHP) to discuss case definition for events associated with the AstraZeneca COVID-19 vaccine on 21 May 2021. The EHP are revising their case definitions for vaccine-induced thrombocytopenia (VIT) and vaccine-induced thrombosis and thrombocytopenia (VITT) and

are considering introducing threshold values for optical densities for PF4 antibodies in confirmed cases and are also reconsidering D-dimer threshold values. Platelet activation tests may be required in all cases or in those with negative PF4 antibodies if the clinical suspicion of VITT is high. The EHP also mentioned that some patients are experiencing recurrent thrombocytopenia on follow-up and thromboembolic events have occurred despite anticoagulation. Some patients are requiring rituximab treatment and PF4 antibodies have persisted in all cases on follow-up of up to 8 weeks. Additionally, the EHP commented that some confirmed cases associated with the Pfizer COVID-19 vaccine have also been reported with a longer time-to-onset than those following immunisation with the AstraZeneca (AZ) COVID-19 vaccine. The EWG agreed to keep the topic of case definition open for consideration as new evidence emerges.

2.3 The EWG was informed of the updated product information recommendations issued by the Committee for Medicinal Products for Human Use on 21 May 2021. The new contraindication and advice for expert haematology input are similar to UK guidance provided in the Reg 174 information for Healthcare Professionals.

2.4 The EWG was then presented with a summary of a recent publication describing a French case series of 9 patients with suspected VITT and the results of different tests for PF4 antibodies. A PF4-enhanced serotonin release assay was positive in 7 patients, but all of these patients tested negative in rapid immunoassays and the sensitivity of different ELISA tests varied with only the Lifecodes PF4 IgG Immunocor ELISA test identifying all patients with platelet activation. The EWG noted the therapeutic potential of imlifidase in patients with refractory VITT that has not responded to intravenous immunoglobulin therapy.

2.5 An overview of the case reports associated with the AstraZeneca COVID-19 Vaccine was presented including summary tables of the 17 reported probable and possible UK cases occurring after a second dose and a fatal cerebral venous sinus thrombosis case associated with thrombocytopenia in pregnancy from Brazil. The EWG was reassured by the clinical phenotypes of the second dose cases but advised that AstraZeneca should be requested to provide data on all foreign cases.

2.6 The UK and foreign cases associated with the Pfizer, Moderna and Janssen COVID-19 vaccines were summarised using the same case definition. The clinical details of 2 confirmed Pfizer cases reported from the UK were reviewed. The EWG commented that similar cases have not been reported from countries with much greater Pfizer vaccine usage but this could reflect differences in the effectiveness of post-marketing monitoring, adherence to national expert guidance on investigating VITT cases, different case definitions or different background event rates. The EWG advised that the MHRA should continue to closely monitor Pfizer cases.

2.7 The estimated number of second AstraZeneca COVID-19 vaccine doses administered has increased to 10.7 million whilst the number of first doses has increased slightly, in line with the current deployment programme to 24.2 million. Estimated case incidence rates for CVST and CVST plus non-CVST events were presented by age-stratified 10-year intervals and by gender. The overall incidence rate is stable at 13.0 (11.6, 14.5) per million for first/unknown doses and the overall fatal incidence rate is also stable at 2.4 (1.8, 3.0) per million first/unknown doses. The age-stratified incidence rates associated with second doses were presented and the overall rate was stable at 1.6 (0.9, 2.6) per million doses. The risk estimates were then compared with the expected benefits of vaccine in age subgroups. The reported incidence rates showed a small increase since the last data lock point, while the risk-benefit balance remained relatively unchanged.

2.8 The EWG was updated on ongoing work to ascertain background incidence rates of thrombosis with thrombocytopenia. It was noted that two presentations from different

research groups looking at the rate of thrombosis with thrombocytopenia with and without vaccination will be given at the next EWG meeting on 25 May.

2.9 The EWG then considered the following 3 questions:

2.9.1 Question 1: based on the evidence presented does the EWG consider the benefit-risk balance remains favourable for all patients and for all age groups?

The EWG advised that the overall benefit-risk profile of the AstraZeneca COVID-19 Vaccine remains positive although the benefits of immunisation in individuals aged under 40 years are probably outweighed by the potential risks. The benefit-risk assessment has not changed since it was reviewed on 17 May 2021.

2.9.2 Question 2: Does the EWG consider there might be an increased risk for the second dose of the vaccine?

The EWG advised that the emerging data on the risk of thromboembolic events occurring with thrombocytopenia following second doses is reasonably reassuring but limited, and so the MHRA should continue to monitor second dose cases closely, particularly as younger patients will now be receiving their second doses.

2.9.3 Question 3: Does the EWG consider there is any need for action with regards to the Pfizer, Moderna or Janssen vaccines in relation to this potential risk?

Based on available data, the risk associated with the Pfizer and Moderna COVID-19 vaccines appears lower than that associated with the AstraZeneca COVID-19 Vaccine. This risk should be monitored and there is no need for regulatory action. Events associated with the Pfizer COVID-19 vaccine should continue to be closely monitored.

2.10 In conclusion, the EWG did not identify any potential trigger for regulatory action.

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

None.

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

The next scheduled meeting is to take place on **Tuesday 25th May 2021** at **12.00pm**.

The Meeting today started at 17:18 and ended at 17:57.

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

Annex I

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

Chair and Members

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

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

Invited experts

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

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

Observers

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

Annex II

The following participants declared interests and other relevant interests at the meeting today.

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

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

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

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

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

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

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

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

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

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

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

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

Mrs Wang – Other relevant interests arising from being highly sensitive to insect stings, and plant products such as Hyacinth bulbs, as recorded on Mrs Wang's medical records. The family of Mrs Wang lives with several rare diseases and conditions, some of which result in epileptic fits.

Professor Weir - NPNS - Imperial College and Other relevant interest arising from his department collaborates with Imperial College on a number of clinical trials.

Observers

Professor [redacted] - NPNS arises from the institution [redacted] University Hospitals NHS Trust) where Professor [redacted] works has received unrestricted investigator-initiated research funding from Pfizer for an unrelated prospective population-based cohort study of pneumococcal pneumonia in which Professor [redacted] is the Chief Investigator.

Dr [redacted] – Lapsed and NPNS - Regarding companies to declare interests for, prior to joining Public Health Scotland, Dr [redacted] worked for a company that provided epidemiological services to the pharmaceutical industry. Whilst working there, she supported respiratory vaccine development activities at Janssen (Johnson & Johnson). Dr [redacted] has now left that role.

COMMISSION ON HUMAN MEDICINES (CHM)
COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Tuesday 25th May 2021** at **12:00** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Mr VI G Fenton-May
Professor D Goldblatt
Ms S Hunneyball
Professor K Hyrich
Professor H J Lachmann
Professor P J Lehner
Mr R Lowe
Dr S Misbah
Professor Y Perrie
Professor S Price
Dr A Riordan
Professor C Robertson[1]
Professor T Solomon
Professor K M G Taylor
Dr R Thorpe
Dr S Walsh
Mrs M Wang
Professor C Weir

Apologies

Professor G Dougan
Professor N French
Sir M Jacobs
Professor M Turner

Visiting Experts

[redacted]

Observers (left after item 4)

[redacted]

Secretariat

[redacted]

[1] Left during item 5

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted] - VRMM

Presenters supporting specific items

[redacted] - LD

MHRA Observers

[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
Dr S Branch - VRMM
[redacted] - VRMM
[redacted] - VRMM
[redacted] - Comms
[redacted] - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
Dr J Raine - MHRA CEO
[redacted] - VRMM
Mr P Tregunno - VRMM
[redacted] - LD
Dr K Wydenbach - LD

[redacted]

4th February 2022

Key
LD = Licensing Division
VRMM = Vigilance & Risk Management of Medicines
MHRA CEO = Chief Executive
Comms = MHRA Communications

1. Introduction and Announcement

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

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

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

1.3 Participants declared interests and other relevant interests for this meeting listed at **Annex II** to the minutes.

1.4 Apologies were received from Professors Dougan, French, Turner and Sir Michael Jacobs for this meeting.

1.5 The Chair welcomed the following Visiting Experts:

Dr [redacted]
[redacted] Public Health England

Professor [redacted]
[redacted] University of Oxford

Professor [redacted] MA MPH BMBCh PhD FRCP FRCPath FMedSci
Professor of Clinical Microbiology, Wellcome Senior Fellow in Clinical Science
[redacted]

Professor [redacted] ChB MD FRCP DRCOG FRCGP
Professor of Clinical Epidemiology and General Practice
Professorial Fellow, [redacted]

1.6 The Chair welcomed the following observers:

Dr [redacted]
[redacted], Public Health Agency

Dr [redacted]
[redacted]

2. Update from COG-UK on Spread of the Variant first identified in India

2.1 The EWG was presented with information on the emergence and biological properties of SARS-CoV-2 B.1.617. The EWG heard that lineage B.1.617 is now of global significance. There are two main lineages of B.1.617 (B.1.617.1 and B.1.617.2). A furin cleavage mutation (P681R) that increases host cell-cell fusion is common to both. The B.1.617.1 lineage has two mutations (L452R and E484Q) in the receptor binding domain (RBD) that partially evade mRNA elicited neutralising antibody. Evidence of additive / synergistic effects of the two mutations in the RBP has not been found.

2.2 The EWG heard Cambridge Institute for Therapeutic Immunology and Infectious Disease are investigating the effect of patient age on T-cell immunity but only with Wild Type (WT) virus. Other groups are exploring T-cell immunity and vaccine escape, where the data show that the variant B.1.351 includes escape mutations in T-cell epitopes, but the relevance of this finding is less clear. The findings in the literature indicate that to prevent infection with SARS-CoV-2, antibodies are required because the virus is highly infectious. The role of T-cells in COVID-19 most likely occupies the later phases of infection and may contribute to hindering the progression of disease and severity of disease.

2.3 The EWG heard the samples were taken from healthcare professionals (HCPs) who were recently vaccinated (earliest January 2021) and the vaccine interval was understood to be 4 weeks, but the specific interval data is due. The Chair noted the interval used in the UK is 12 weeks for ChadOx1. The invited expert was uncertain if the higher peak antibody levels observed with an interval of 12 weeks would be sustained.

2.4 The EWG commented that serum samples of breakthrough cases have shown very high antibody levels (Hacisuleyman et al, 2021; NJEM 2021). The invited expert segued into a question, do the variant studies provide greater understanding of vaccine breakthrough considering that there are a number of other factors aside from phenotypic changes involved in the process of breakthrough (such as viral load). The EWG heard that by way of example the mutation at the furin cleavage site mutation (P681) potentially promotes the ability of the virus to tolerate neutralising antibodies through modulation of S1/S2 cleavage. The EWG heard there also appears to be good consistency between in vitro data and trial data, whilst the invited expert acknowledged multiple mechanisms would be involved in vaccine breakthrough. Reassuringly the fold changes in a reduction of neutralisation seen with the B.1.617 lineages do not yet confer a loss of vaccine efficacy in terms of severe disease.

2.5 The EWG noted interpretation of the molecular epidemiology data from India requires careful consideration of the limitations, since approximations of transmissibility are known to be affected by the number of samples versus the extent and evenness of geographical coverage. In India, sequencing is currently very concentrated in a few areas. The data from India may indicate that B.1.617.2 is outcompeting B.1.617.1, but it is not known if it is also outcompeting B.1.1.7. The most robust data on transmission is UK based, covering almost all positives to a high level of viral genome coverage and the data show a fairly steady rise of B.1.617.2 that has spread outside areas of travel, and is therefore, less likely to be an artefact of people movement and more likely due to increased transmissibility as a trait of B.1.617.2.

2.6 The EWG noted that vaccine breakthrough data are not reliable due to the absence of unvaccinated sera controls. Without this, the level of breakthrough cannot be assessed compared to the other variants or WT virus, but hitherto can only show that the variant circulating in and around the period of sample collection is able to breakthrough. The EWG also noted that B1.617.2 is representative of a selective sweep and thus would not reveal adequate information about transmissibility. The EWG noted that interpretations from the

data should be conservative, with careful consideration of denominator data. The UK HAS England data do not appear to show that B.1.617 lineages are producing more events of vaccine breakthrough. However, if this understanding changes, it also needs to be understood if lineages of B.1.617 are associated with more severe cases of COVID, i.e. result in more hospitalisations and deaths.

2.7 The EWG noted that mutations altering the phenotype are common in respiratory viruses and tend to become part of the background variation not often associated with more severe disease. Norovirus maybe one of a number of exceptions where disease can become more severe seasonally as the viral genome acquires mutations.

2.8 The Invited expert agreed that due to sweep of B1.617.2, from these data it is not possible to determine if B1.617.2 is more able than other variants or WT to breakthrough. The expert however, maintained that the consistency of findings in the in vitro and in vivo data supports a hypothesis that phenotypic variation enables a biological mechanism for B1.617 to breakthrough, but caveated this by noting that further data would be required to substantiate this claim.

2.9 The EWG heard that B1.617.2 is concentrated in discrete locations in the UK, and therefore, until there is a more generalised B1.617.2 epidemic, analysis of UK epidemiological data will carry limitations. As the time expires awaiting this scenario, as well as that required to confirm that the infectivity and virulence of B1.617.2 is greater—the human cost will likely have already been accrued. The EWG noted that an exception may be if there is a clear signal.

2.10 The EWG heard, in terms in importations from other locations in the subcontinent, that in a current outbreak in Nepal, 33 out of 35 randomly sampled sequences were B1.617.2, but data from other countries was not readily available.

2.11 The EWG heard that bamlanivimab loses binding affinity for B1.617.2 completely, but, the other Regeneron antibody cocktail (dual therapy) still has neutralising activity. In terms of the real world situation, this is currently not a pressing issue as access to monoclonals is very limited.

3. Presentation form Prof [redacted] on thrombocytopenia/thrombosis

3.1 The EWG was presented with data on the short-term risks of thrombocytopenia and thromboembolism associated with vaccination or natural infection during the vaccine roll out in the 2nd and 3rd pandemic waves in England. The study was in a population that was the largest, most representative, and diverse to date. The main limitations of the study included the short exposure window (28 days), a reliance on clinical coding and therefore, an absence of formal adjudication of outcomes, study of 1st vaccine dose only, and those still in hospital not included with the potential for misclassification or under-ascertainment of outcomes—likely to be non-differential with regard to each vaccine.

3.2 The key findings consisted of:

- increased risk of thrombocytopenia, venous thromboembolism VTE, and other rare arterial thrombotic events following first dose of the AstraZeneca vaccine
- increased risk of arterial thromboembolism (ATE) and ischemic stroke following a first dose of Pfizer/BioNTech. Increased risk of cerebral venous sinus thrombosis (CVST) was found following a first dose of both AstraZeneca vaccine or Pfizer/BioNTech in the 8-14 day and 15-21 risk windows respectively.

- importantly the risk of these outcomes following vaccination were much lower than those associated with SARS-CoV-2 infection in the same population.

3.3 To contextualise their findings the group estimated the number of exposures needed for one excess event and the excess number of events per 10 million exposed for each outcome.

3.4 For the AstraZeneca vaccine the excess events were 107 for thrombocytopenia, 66 for VTE and 7 for CVST. For the Pfizer/BioNTech vaccine there were 143 extra cases of ischemic stroke and 5 of CVST. For SARS-CoV-2 infection, there were an estimated 934 additional cases of thrombocytopenia, 12,614 of VTE, 1,699 of ischemic stroke and 20 of CVST.

3.5 The EWG was presented with a draft visualisation of a lay summary of findings from the study.

3.6 Question and Answer

3.6.1 The EWG heard that the analysis of thrombocytopenia was conducted separately to that of thrombosis. The diagnosis of thrombocytopenia but without platelet counts work is being undertaken to obtain this information from hospital systems for future analysis in real-time. The study data on thrombocytopenia with thrombosis can be analysed together but will not be linked to platelet counts.

3.6.2 The EWG heard a sub-group analysis grouped by age (below 50 year and 50 and over) produced results that were fairly consistent but with wide confidence intervals.

3.6.3 The EWG noted the association of Pfizer with ischemic stroke appears to be a novel finding and highlighted a distinction in the US where despite wider use of this vaccine in the US, a signal of stroke has not been identified by the FDA. The EWG heard there was a possibility that the finding of stroke could possibly be due to chance, another possibility is that CVST was mis-coded as ischemic stroke. The Chair noted this may apply particularly to the elderly where a CT venogram may not have been completed. The EWG heard the group did not identify any particular bias that applied to stroke but not the other outcomes. The EWG heard there were some cases of stroke in younger people <50 years, but to give a specific number the data would be required to be checked.

3.6.4 The EWG heard in the self-controlled case series the 28 days before vaccination was removed from the baseline comparator risk period to limit risk of bias due to prior VTE. When studying the 28-day period data, there was a reduced risk of VTE, indicating that the patients were postponing vaccination until recovery or discharge from hospital following a VTE event. The expert noted that the same period in the Scottish study was 14 days, in the age stratified analysis an association with VTE was not identified for either of the two vaccines.

3.6.5 The EWG heard a call is planned with haematologists with an aim of improving validation of clinical outcomes against hospital coded data, which if successful will help to substantiate the study outcomes.

3.6.6 The EWG noted with a self-controlled case series one limitation is the end of follow-up in conjunction with the person time beyond 28 days. If there is lack of completion in the cases, cases may be missed from the analysis that otherwise would have been included in the study period - if it were not for the delay to obtain the information. This could result in a case deficit / underreporting of adverse outcomes. Similarly, for the pre-period if there was a permanent deferral or contraindication, the pre-data is prone to a lower incidence in that period. The invited expert acknowledged when compared to other options there are strengths and weaknesses of using a self-controlled case series and mentioned that the

scope for biases needs to be controlled as well as possible. In terms of the beyond 28 days, the vaccination outcomes drop to ~1 (22-28 days post-vaccination) but there could still be some increased risk, more particularly with SARS-CoV-2 infection the increased risk had not reduced by 28 days.

3.6.7 The EWG heard the study included individuals with SARS-CoV-2 infection pre-vaccination and after vaccination numbers were considered insufficient to explore the interactions between the two. The EWG noted that the invited experts may revisit this and remarked that this would be of benefit because the effect of infection lasts for longer in terms of the risk of thrombosis.

3.6.8 The invited experts confirmed they have not yet evaluated the potential causes or mechanisms that may account for the differing dates of onset of CVST in the period following vaccination, for each of the two vaccines.

3.6.9 The invited experts confirmed that an analysis of thrombocytopenia with thrombosis as combined outcome could be undertaken, and these results could be included in the same publication. The invited experts also confirmed that once completed the analysis and results would be made available to the EWG.

3.6.10 The EWG noted that the term 'slight risk' in the lay messaging may exaggerate the risk given the rate is per 10 million exposed, for example for CVST with is 5 additional cases for Pfizer. The EWG suggested terminology that maintains a context of an exceedingly rare event. The invited experts volunteered to refer the comments / subject to the patient group.

4. Update on PHE analysis of thrombosis with thrombocytopenia

4.1 The EWG was presented with upon on cohort analysis of Secondary Uses Service SUS data after COVID-19 vaccines from PHE.

4.2 The EWG heard the PHE data shows that following vaccination with the AZ vaccine, there is an increased risk of: dose specific thrombotic events, thrombocytopenia, and concurrent thrombocytopenia with thrombotic events. The EWG heard that the longer follow-up time increases the confidence in these associations. However, coding changes could occur due to prior awareness of these potential associations amongst medical professionals. This denotes a caveat to the results, though it is likely to be minor.

4.3 The EWG heard it was not possible to adjust for known SARS-CoV-2 infection when using the cohort analysis approach, and therefore, changing infection risk can only be evaluated in relation to the time period by number of weeks in the study.

4.4 The EWG heard from the MHRA, that there has been indication of signal of myocarditis in the Israeli data particularly after the second dose and in males (age ~30 and below).

4.5 In the US, the CDC have not detected an imbalance in their observed-expected figures of myocarditis, but they have identified a clustering of reports post second dose in a very similar demographic to that of Israel for both mRNA vaccines (Moderna and Pfizer). The CDC do not stratify their observed expected by age. The MHRA observed expected data have also not shown any imbalance with respect to myocarditis age-related or generally.

4.6 The invited expert mentioned acute myocarditis was included in the PHE analysis in direct response to the indication of a signal from Israel. The EWG heard events of arterial thromboembolism were also included in the UK PHE analysis.

5. COVID-19 Vaccine AstraZeneca (ChAdOx1-S [recombinant]), 1 x 1011vp-mL, solution for injection

5.1 The EWG heard a presentation on the submission of a conditional marketing authorisation (CMA) for Covid-19 vaccine AstraZeneca (AZD1222) in Great Britain (GB). Covid-19 Vaccine AstraZeneca has been granted a temporary authorisation under Regulation 174 of the Human Medicines Regulations 2012 (Regulation 174 authorisation) on 29 December 2020.

5.2 Similarly, to the Regulation 174 authorisation, no quality major objections have been raised with this conditional marketing authorisation (CMA) application as all other concerns have been appropriately addressed. The EWG heard, that initially there will be concurrent supply of the regulation 174 authorisation packs alongside the CMA packs in order to ensure uninterrupted supply to Northern Ireland.

5.3 The EWG heard there were no new clinical trial data received since the last update of the Reg. 174 public assessment report. The United Stated (US) trial data, very recently submitted by the Company, will be assessed in the near future. Of interest are two pre-prints provided by the Company, which describe similar immune response in people living with human immunodeficiency virus (HIV) (under treatment and immunocompetent) compared to healthy subjects.

5.4 The EWG heard about the non-clinical assessment of the product. An updated biodistribution study showed no unexpected results, i.e. the replication incompetent virus does not travel far from the injection site. Separately, the report from GLP inspection for the reproductive toxicity study was satisfactory.

5.5 The EWG heard the content of the product information and conditions require consideration. The assessment team have aimed to abide by two principles: to align as far as possible with the EU/NI product information, and where the UK has additional data /experience in the Regulation 174 authorisation to carry this over to the CMA as 'additional text'.

5.6 The EWG agreed that the SmPC sections 1 & 2 should updated to be brought closer in line with the EU/NI SmPC. It was also agreed to remove the negative statement regarding routes of administration present in section 4.2 of the EU/NI SmPC

5.7 Of note, the EWG heard that, in-line with the R174 product information, it is not proposed to include a recommendation for a15-minute observation period post vaccination in Section 4.4 of the GB SmPC. The EU/NI SmPC includes this recommendation, in keeping with all Covid-19 vaccines approved in the EU to date. The EWG noted that, in view of the significant clinical experience accrued in the UK with over 30 million COVID-19 Vaccine AstraZeneca ChAdOx1 (AZD1222) vaccinees, in terms of a broad recommendation for protocols in mass vaccination centres it was considered appropriate not to include this recommendation.

5.8 The EWG noted that, in-line with the R174 product information, a cautionary statement about use in individuals with a history of heparin-induced thrombocytopenia and thrombosis (HITT or HIT type 2) was to be retained in the GB SmPC due to the possibility of an interconnected pathophysiology with Thrombosis with Thrombocytopenia Syndrome (TTS). However, the EWG heard this information is now to be located under section 4.4, special warnings and precautions, rather than in section 4.3, contraindications.

5.9 Given the quantity of accruing data that does not show any evidence for an association between APS and TTS, it was considered to be an overly cautious approach to include APS in section 4.4, noting it places an unnecessary burden on haematologists, i.e. a resource

cost to other patients. Therefore, the EWG agreed that the cautionary statement about use in individuals with anti-phospholipid syndrome (APS) that was previously included in the R174 PI, can be removed from section 4.4. because there are no confirmed cases of patients with a history of anti-phospholipid syndrome developing TTS following vaccination.

5.10 The EWG noted cerebral venous sinus thrombosis (CVST) is a far rarer condition and it would be practical to recommend a patient with a history of CVST seeks an alternative vaccine. The EWG noted that they would welcome confirmation from neurology experts on the CHM as to whether they agree with the EWG view that, on a precautionary basis, the text on administration of the vaccine in individuals with a past history of CVST included in the R174 PI, should be retained in section 4.4 of the GB SmPC.

5.11 The EWG agreed with the Agency's proposals to largely harmonise text in section 4.4.with the EU/NI SPC, but with a slight divergences in some areas: a) to include angioedema under the umbrella of hypersensitivity reactions, b) to reflect clinical parameters from cases of TTS rather than the average age at onset of TTS which was not reflective of UK experience of b) to give national advice on the healthcare pathway for patients with TTS and c) to include a statement about real-world efficacy data in elderly subjects.

5.12 The EWG heard that fertility and pregnancy information in the EU/NI SmPC is not yet furnished with information on animal studies; the proposal for the UK SPC is to include the outcomes of relevant animal studies in the fertility, pregnancy, and lactation (section 4.6).

5.13 The EWG heard all figures in the tabulated summary of ADRs in section 4.8 have been updated in accordance with the December safety analysis—EU/NI text has not yet been updated.

5.14 The EWG supported the proposal to include the recommendation on use of analgesic and/or anti-pyretic medicinal products if required to manage symptomatic relief from post vaccination ADRs that is already in the R174 product information, in the GB SmPC.

5.15 On rare and very rare ADRs, the EWG heard that defined frequency designations must be followed, which can lead to difficulties when trying to contextualise the likelihood of a particular ADR/s and to avoid what could be interpreted as contradictions between the ADR frequency range and the paragraphs of text in the SmPC and PIL. The EWG noted the need to reassure patients that these events are extremely rare by adding context to the frequency of events of thrombosis with thrombocytopenia syndrome in the PIL. The EWG acknowledged the potential limitations but asked the agency to aim to minimise any disconnect between the ADR table designated frequency and the contextualised information / retain as much clarity as possible.

5.16 The EWG heard the approximate frequency in figures of TTS proposed by the company has not been included in the EU/NI SmPC. The EWG noted it would be favourable to adopt the same position because the frequency is evolving, and the distribution of cases by age is also uneven.

5.17 The EWG noted there was a risk that 'influenza like illness' could be misconstrued by readers to be related to an active infection acquired through vaccination, which is obviously not the case. However, EWG concluded that the text should remain because this terminology has been present in the regulation 174 authorisation for many months without causing any notable issue. The EWG also considered there to be some added descriptive value in using the term to healthcare professionals.

5.18 The EWG noted text in section 4.8 on neuroinflammatory disorders should be retained because there is data emerging on GBS.

5.19 The EWG agreed that section 5.3 of the SmPC contained an appropriate level of detail was commensurate with the scope of studies submitted.

5.20 The EWG heard that both the former and proposed versions of the GB SmPC still refer to advice on 6 hour in use times (section 6.6), text in the proposed SmPC also includes a statement to align with the EU/NI SmPC that the product may be kept in-use at temperatures up to 30°C for a single period of up to 6 hours, but due to the inclusion of the word may, this does not contradict the UK recommendation for use up to 25°C.

5.21 The EWG supported the specific obligations for the CMA and the obligations to conduct post-authorisation measures.

6. Any Other Business

None.

7. Date and time of next meeting

The next Ad Hoc meeting on Thromboembolic events with COVID-19 Vaccines is scheduled to take place on **Tuesday 1st June at 3.15pm**.

The next scheduled meeting is to take place **on Friday 4th June** at **10.30am**.

The Meeting today started at 12:01 and ended at 14:14.

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

Annex I

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

Chair and Members

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

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

Invited experts

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

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

Observers

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

Annex II

The following participants declared interests and other relevant interests at the meeting today:

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

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

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

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

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

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

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

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

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

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

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

Mrs Wang – Other relevant interests arising from being highly sensitive to insect stings, and plant products such as Hyacinth bulbs, as recorded on Mrs Wang's medical records. The family of Mrs Wang lives with several rare diseases and conditions, some of which result in epileptic fits.

Professor Weir - NPNS - Imperial College and Other relevant interest arising from his department collaborates with Imperial College on a number of clinical trials