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

Minutes of the meeting held on **Friday 4th June 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
Ms S Hunneyball
Professor K Hyrich[1]
Mr R Lowe[2]
Dr S Misbah
Professor Y Perrie
Professor S Price
Dr A Riordan[3]
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 D Goldblatt
Sir M Jacobs
Professor H J Lachmann
Professor P J Lehner
Professor T Solomon

Observers (left after item 4)

[redacted]

Secretariat

[redacted]

[1] joined during item 2
[2] joined during item 3
[3] left during item 4

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted] - VRMM

Presenters supporting specific items

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

MHRA Observers

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

[redacted]

18th November 2022

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, 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 Goldblatt, Lachmann, Lehner, Solomon and Sir Michael Jacobs for this meeting.

1.5 The Chair welcomed the following observers:

[redacted] JCVI

[redacted] NHS England [redacted]

[redacted] Public Health Scotland

[redacted] Public Health England

2. Menstrual Disorders and COVID-19 Vaccines

2.1 The EWG was informed of MHRA's previous detailed review of reports of menstrual disorders with the Pfizer vaccine in January 2021 including reports of menstrual bleeding outside of the usual cycle, heavy and/or painful periods, bleeding associated with long term contraception or post-menopausal bleeding. The EWG noted that at that time it was concluded that the number of reports was small in the context of vaccine usage, and it was agreed to continue to monitor these reports. The EWG was informed that since then, the number of Yellow Card reports of menstrual disorders had increased alongside the usage of the vaccines and recent media coverage relating to menstrual disorders and COVID-19 vaccination.

2.2 The EWG considered an assessment of clinical trial data and spontaneous reports of menstrual disorders reported via the UK Yellow Card Scheme for the AstraZeneca, Pfizer-BioNTech and Moderna COVID-19 vaccines with a data lock point of 17 May 2021. The EWG also considered written comments received from members of the Medicines for Women's Health Expert Advisory Group.

2.3 The EWG agreed that the evidence from the clinical trials did not suggest an increased incidence of menstrual disorder events with the COVID-19 vaccines compared with the comparator groups. The EWG noted that a diverse range of menstrual disorders had been reported via the Yellow Card Scheme for all three vaccines currently deployed in the UK and agreed that the number of these reports was low in relation to the exposure to COVID-19 vaccines in females, particularly given the high prevalence of menstrual disorders in women generally.

2.4 The EWG advised that the currently available evidence does not appear to support an association between menstrual disorders, postmenopausal haemorrhage and/or vaginal/uterine haemorrhage with the vaccines reviewed (COVID-19 vaccine AstraZeneca, Pfizer-BioNTech COVID-19 vaccine or the Moderna COVID-19 vaccine). The EWG advised that no regulatory action was required; however, reports of menstrual disorders with COVID-19 vaccines should continue to be kept under close review.

2.5 The EWG supported communicating the findings of this review in the MHRA coronavirus weekly summary of Yellow Card reporting and recommended working with NHS England, and the other devolved NHS bodies, to provide information on menstrual disorders and COVID-19 vaccines to General Practitioners and other healthcare professionals who were receiving queries about this issue. The EWG advised that any communications should make it clear that the current evidence does not suggest that menstrual disorders are caused by COVID-19 vaccines and that women should not delay seeking medical attention for menstrual disorders, when appropriate.

3. Update on Capillary Leak Syndrome with COVID-19 vaccine AstraZeneca

3.1 The EWG heard an update on reports of capillary leak syndrome (CLS) which included UK cases received up to and including 2nd June 2021, as well as data from Europe up to and including 25th May 2021. The EWG also heard that the European Medicines Agency (EMA) had made a preliminary recommendation to incorporate warnings in section 4.3 and 4.4 of the AstraZeneca product information to contraindicate use in people who had previously experienced capillary leak syndrome and warn of a risk of recurrence of CLS in patients with a history of the syndrome. The EWG considered that in the totality of the evidence, the case numbers are low, though some individual cases were persuasive.

3.2 The EWG commented that it was difficult to contextualise the reports received in patients with a history of CLS in the absence of any information on patients who might have received the vaccine without an issue. The EWG proposed exploring rates of use of IV immunoglobulin for CLS before and after introduction of the vaccine to try to establish whether rates of CLS have increased.

3.3 The EWG considered that there remained some uncertainty within the evidence and that it was difficult to confirm a signal; however, the EWG would lean towards precautionary statement, given the deadly nature of the disease, but felt that there was insufficient evidence for a contraindication.

4. Verbal update on the international and UK evidence on the risk of myo/pericarditis with the Pfizer COVID-19 vaccine

4.1 The EWG were presented with the available UK and international data on the risk of myocarditis and pericarditis with the Pfizer/BioNTech vaccine, and international data on the Moderna vaccine, as the number of doses administered in the UK for this vaccine remained low.

4.2 The EWG were presented with UK Yellow Card data for the Pfizer/BioNTech vaccine, which showed an increase in the number of reports of myocarditis and pericarditis. There remained an even split of reports between males and females and the average age of patients was decreasing. The reporting rates for the second dose of Pfizer/BioNTech were higher than those for the first dose. The EWG noted that some Yellow Card submissions were reporting symptoms of myocarditis; however, it was not clear if patients had sought medical attention or if they had been medically diagnosed with myocarditis.

4.3 The EWG were presented with UK observed vs expected analysis which did not show an increased risk for myocarditis or pericarditis following the first or second dose of the Pfizer/BioNTech vaccine and has only crossed the signal threshold at the 10% reporting level in the under 50-years age group following first dose. Public Health England SUS data showed an increased risk after the second dose of Pfizer/BioNTech vaccine in the 15-39-years age group. The SUS analysis also identified an increased risk for the AstraZeneca vaccine following the first dose.

4.4 The EWG were presented with company data for Pfizer/BioNTech which noted a single report of pericarditis in the active arm of the clinical trial. Company observed vs expected analysis has not shown an increased risk of myocarditis or pericarditis and therefore, the company concluded that there was no signal for myocarditis or pericarditis.

4.5 The EWG were presented with international data from the US and Israel, which shows much higher reporting rates following the second mRNA vaccine dose compared to the first dose, with reporting rates higher in males under the age of 30 years following the second dose. Observed vs expected analysis varied between datasets, with analysis from Israel and the World Health Organisation (WHO) showing an increased risk following the second dose of mRNA vaccines, while analysis from the European Medicines Agency (EMA) and Health Canada not seeing an increased risk. The EWG noted the difference in dose intervals, with 21-days used for Pfizer/BioNTech US and Israel while longer dose intervals were used elsewhere.

4.6 The EWG discussed the various proposed mechanisms for the myocarditis and pericarditis events. The EWG considered that there was currently no clear evidence on a potential mechanism and further research would be required.

4.7 The EWG considered that the Israeli second dose data suggested a possible signal but noted that there might be genetic factors in the Israeli population that could lead to higher rates of myocarditis and pericarditis. The EWG noted that the same increased risk of myocarditis and pericarditis following the second dose was not yet being seen in the UK and European data. The EWG concluded that no regulatory action was required at this time but reports of myocarditis and pericarditis should be closely monitored particularly, with second dose deployment starting in younger age groups.

5. Clinical Trials Authorisation - COV008 (Phase I of intranasal ChAdOx1 nCoV-19)

5.1 The EWG heard, that a Phase I study is on-going to determine safety, tolerability and immunogenicity of intranasal (IN) administration of the COVID vaccine ChAdOx1 nCOV-19 in healthy UK adults (COV008). COV008 is the first study of a new route of administration for COVID-19 vaccines. One of the main objectives of the trial is to investigate whether the vaccine initiates robust mucosal immunity, and the study is motivated by pre-clinical data demonstrating efficacy of ChAdOx1 nCoV-19 against SARS-CoV-2 challenge in non-human primates and hamsters, in particular substantial reduction in viral titres in the upper and lower respiratory tracts. In the case of the hamster study, efficacy of IN administration was significantly better than that seen in a contemporaneous intramuscular (IM) control group.

5.2 The EWG heard, that on the 7th of April, at the request of the MHRA the eligibility criteria for the trial were modified to exclude those under 30 years due to the safety concern of thrombosis with concurrent thrombocytopenia. The original criteria for the trial had been wider including 18-40 year old participants, some of which have received the vaccine within the trial. The Sponsor is now proposing to broaden the eligible age range for the study to enrol COVID-19 vaccine-naïve 18-55 year olds, owing to an expected difficulty recruiting COVID-19 vaccine-naïve 30-40 year olds. The proposal also includes 41-55 year olds who have declined IM vaccination but are willing to receive IN, but the Sponsor anticipates that few such individuals would be able/willing to accept the study procedures.

5.3 The EWG noted it should be taken into account that the JCVI advice was later revisited and the exclusion from receiving the COVID-19 Vaccine AZD1222 amended from those aged under 30 years to those under 40 years of age. It was also noted that a number of trial participants in the 30-40 year age range have already been vaccinated by the IN route.

5.4 The EWG noted the IN route was likely to be advantageous, primarily because SARS-CoV-2 is a respiratory virus. The other advantages listed by the assessor were also considered by the EWG to be valid: ease of administration; the ability to use a lower dose, which may accelerate global supply; and that the IN route may also offer better protection against asymptomatic infection. However, it should be noted that many previous trials of IN vaccinations have failed due to a safety signal of Bell's Palsy associated with reactogenicity—others have succeeded. COV008 is an important trial and should continue to recruit, but adverse effects and immune responses need to be carefully monitored.

5.5 The EWG noted that under the expanded eligibility criteria, all participants would be aged over 18 years, therefore, to obtain full informed consent would not be contentious.

5.6 The EWG noted that it would not be inconsistent to regulate a clinical trial of an IMP differently to an equivalent or same authorised product. Research is a separate domain, and data gathered on the IN route will be valuable. The EWG also noted there is a risk that by limiting recruitment, the contribution of existing participants could go to waste.

5.7 The EWG noted it is not advisable to reach a figure in terms of risk of thrombosis with concurrent thrombocytopenia with the vaccine given IN, as there is not enough evidence to produce a reliable estimate. The EWG elaborated that it would not be unreasonable to expect the risk to be equivalent to that seen with IM, or perhaps lower, but this is not presently known.

5.8 In terms of aetiology, there is a reasonable degree of confidence that anti-platelet factor 4 (PF4) /polyanion complexes are responsible for these severe adverse events with IM, but alternative hypothesises have also been proposed. Additionally, the mechanism connecting the vaccine to these antibodies is not well understood.

5.9 The EWG noted the IN or oral route of vaccine administration does invoke a systemic immune response. If this is also the case with COVID-19 vaccine AZD1222, then the Sponsors hypothesis that the IN vaccine will have less exposure to platelets or will not come into contact with platelets at all, is incorrect. Therefore, a likely, very low, but serious potential risk of thrombosis with concurrent thrombocytopenia needs to be clearly conveyed to participants within the informed consent process. The Sponsor should avoid use of the mechanistic rationale as a basis to support a lower risk of vaccine induced thrombosis with thrombocytopenia (VITT) with IN compared to IM because there is little evidence to support this standpoint.

5.10 The EWG noted that the validity of full informed consent rests, not only in the literature provided, but also upon conversation that takes place with participants, and the Sponsor should be notified of the need for detailed conversations during the consent process.

5.11 The EWG supported continued recruitment with full informed consent in the younger age group of 18--29 year olds. The patient information leaflet needs to be explicit in stating that there is a risk of thrombosis with thrombocytopenia, whilst also stating that the incidence is not known. The EWG also noted in support of expanding eligibility criteria by age, that the risks associated with this Phase I trial are comparable to those of any Phase I trial; in this trial, like the others, the response to the IMP in healthy human participants will not be known until post-administration.

6. Novavax NC AR Sequence 2

6.1 The EWG heard the assessment of sequence 2 for Novavax SARS-CoV-2 rS, NVX-CoV2373, an adjuvanted recombinant protein vaccine.

6.2 The company have provided evidence that the mode of action of the [redacted] is via [redacted] and processing in injected muscle and in the draining lymph node, which leads to the release of [redacted] and [redacted] including [redacted] The role of the adjuvant includes the recruitment of innate immune cells and cell activation comprising upregulation of MHC class II, which implies enhanced antigen presentation. Importantly, the data showed a need for co-localised antigen and adjuvant. When given apart (anatomically or temporally), the adjuvant effect was lost. The EWG heard the current understanding of the fate and clearance of the [redacted]

6.3 The EWG heard that with ongoing changes to manufacturing during development, a concern was put to the company that the material used in the toxicity studies might be different from that to be placed on the market. The EWG were informed that herein lies a question, if comparability is established not to be robust, would repeating toxicity studies hold enough value to justify the use of further animals, especially, when the substantial clinical experience, which is due to be provided in >26,000 human subjects, is considered. The EWG heard the company's view represented that the changes do not obviate the relevance of the toxicity studies: a judgement on this matter could be made when further clinical data is expected to be available, i.e., closer to the time of the licensing decision.

6.4 The EWG heard the company are not planning to undertake an in vivo genotoxicity study, and the interpretation is that this should be acceptable, given that no risk is recognised with the very short-term use (2 doses) of the vaccine. The original data included only an interim report on reproductive toxicity data; a more complete iteration was later provided and the EWG were informed that new data confirmed 100% immunogenicity in animals in this study and that there was nothing of concern.

6.5 The EWG heard there are on-going studies which the company need to report, but these likely do not preclude authorisation in the context of an ongoing pandemic (e.g., long-term

immunogenicity; biodistribution of the adjuvant). The company's proposals for aspects of the SmPC text are also awaited in future submissions.

6.6 The EWG noted the genotoxicity and reproductive toxicity data are acceptable. The EWG noted comparability of the Phase 3 clinical trial product to the product used in pre-clinical trials is imperfect. However, the clinical trial data will be generated with product that does resemble that to be put on the market. The company continue to improve the quality of their product.

6.7 The EWG noted the need to consider the company's proposals for the SmPC and including the section on pregnancy and lactation, in due course.

6.8 The EWG noted there is some experience with the adjuvant in the clinical setting, but this is fairly limited. The adjuvant is complex involving multiple components and this may mean technology transfer issues are more likely; this area will need to be monitored to ensure consistency of the adjuvant and also the final product is not affected.

6.9 The EWG noted it can be anticipated that, due to its different nature as a recombinant protein vaccine, the qualitative and quantitative nature of the immune response to Novavax may be different from the mRNA vaccines or the ChAdOX-1-nCoV-19 vaccine (AZD1222); this could lead to better protection, and also conversely the potential to elicit, more, or more pronounced immunological adverse effects. The EWG noted the immune protection afforded by Novavax may act via a different mechanism compared to the other vaccines authorised for temporary use in COVID-19; this may entail different modes of immunological stimulation as well as a different immunological repertoire. It is also a possibility that this vaccine may cause responses that vary considerably in the individual. These aspects are important because the vaccine may cause unforeseen effects.

6.10 The EWG noted that partly due to the majority of the adult population having received one of the currently available vaccines, the use of this vaccine is not yet clearly defined. Although this is not directly a scientific issue, the EWG expressed that it may be beneficial to have Novavax available to use for boosting. The EWG noted the evaluation should be viewed from a perspective of a population that through vaccination or natural infection has already been exposed to the SARS-CoV-2 antigen, but not exposed to the relatively novel adjuvant.

6.11 [redacted] The EWG noted the cellular response is predominantly a [redacted] response for the product to be put forward for authorisation. The EWG also heard from the clinical assessor, that the situation might not be so straightforward as immunogenicity trial data showed a mixed response with [redacted]

6.12 [redacted]

6.13 [redacted]

7. Any Other Business

7.1 The CHM reached a decision that the trial regarding the paediatric trial of ChAdOx1 nCoV-19 vaccine (AZD1222) can proceed with the booster dosing for the remaining children. The CHM arrived at this decision after a full consideration of the data and surrounding facts, the overall basis for allowing the trial to continue rested on three main factors, little evidence for elevated risk at second (booster) dose, the proviso of explicit informed consent, and the

potential benefits of more complete data from the clinical trial. The Sponsor is aware of the outcome and has also agreed to make the updates to the documentation in line with CHM's request. The MHRA assessor thanked the COVID-19 Vaccine BR EWG for their comments and queries at their meeting of Friday 21 May 2021 because the responses obtained from the Sponsor were critical to the decision-making process.

7.2 A member of EWG was contacted by a neurologist at UCL ([redacted]) who noticed through the national immunoglobulin database that in March and April there were reports of ~20-30 patients with a diagnosis of Guillain-Barre Syndrome (GBS) receiving immunoglobulin, and anecdotally immunologists are reporting clusters of cases. [redacted] is working with NHS England to ascertain NHS numbers to equate the proportion / details of vaccinated individuals.

8. 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 7th June at 5.15pm**.

The next scheduled meeting is to take place **on Monday 14th June** at **10.30am**.

The Meeting today started at 10:34 and ended at 12:55.

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.

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).

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

[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 [redacted]. [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.