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.

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 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.