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

Minutes of the meeting held on **Friday 19th November 2021** at **10:00** 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
Professor K Hyrich
Professor H J Lachmann
Mr R Lowe
Dr S Misbah
Professor Y Perrie
Professor S Price
Dr A Riordan[1]
Professor C Robertson[2]
Professor K M G Taylor
Professor M Turner
Professor S Walsh
Mrs M Wang[3]

Apologies

Professor J Breuer
Sir M Jacobs
Professor P J Lehner
Professor T Solomon
Dr R Thorpe
Professor C Weir

Invited Experts

[redacted][4]
[redacted][5]

Observers

[redacted]

Secretariats

[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea – LD
[redacted] – VRMM

Presenters supporting specific items[5]

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

MHRA Observers

[redacted] - VRMM
[redacted] - LD
Dr S Branch – VRMM
[redacted] - VRMM
[redacted] – VRMM
[redacted] – VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - VRMM
Mr P Tregunno – VRMM
[redacted] - LD
[redacted] - Comms

[redacted]
13th April 2022

[1] joined at the start of item 4
[2] joined during item 5
[3] joined during item 4
[4] joined for item 5 only
[5] joined for item 6 only
[6] supported specific items

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

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, Lehner, Solomon, Weir, Sir Jacobs and Dr Thorpe for this meeting.

1.5 The Chair welcomed the following invited experts:

[redacted]
University of Liverpool

[redacted]
UCL

1.6 The Chair welcomed the following observers:

[redacted]
Public Health Agency

[redacted] Public Health Wales

[redacted]
Public Health Scotland

[redacted]
UKHSA

[redacted]
NHS England and NHS Improvement (National)

2. Update on COVID-19 vaccines and risk of thromboembolic events without thrombocytopenia

2.1 The EWG was updated with new information received since the previous update presented on 24/09/2021. The new information concerned the recently completed PRAC review of data submitted by AstraZeneca in October 2021 regarding CVST without thrombocytopenia following COVID-19 vaccine AstraZeneca (Vaxzevria) administration. The request for this data was based on ongoing reviews of thrombotic events in the monthly summary of safety reports as well as an EMA observed vs expected analysis completed in August 2021 that highlighted an imbalance of CVST events for COVID-19 vaccine AstraZeneca (Vaxzevria) across all age groups.

2.2 The EWG was presented with a summary of the data submitted by the MAH. Data sources reviewed include the clinical development programme, literature, post-marketing reports and observed-expected analyses conducted by the MAH.

2.3 The EWG noted that the observed/expected analyses performed by the MAH are comparable with the EMA's own observed/expected analysis with DLP 31/07/2021, i.e. an increased risk of CVST without thrombocytopenia in younger age groups.

2.4 The EWG was presented with the conclusion of the PRAC, i.e. there is sufficient data of a reasonable possibility of a causal association between CVST without thrombocytopenia and Vaxzevria. The EWG noted the proposal agreed by PRAC for an update of the European product information for COVID-19 vaccine AstraZeneca (Vaxzevria) to list CVST without thrombocytopenia as a recognised adverse drug reaction.

2.5 The EWG then considered the following 3 questions:

2.5.1 Question 1: Based on the evidence presented does the EWG consider there is an association with the AZ COVID-19 vaccines and the risk of CVST without concurrent thrombocytopenia?

The EWG advised that this remains a challenging topic to assess. Previously identified caveats and limitations to data interpretation remain present and any mechanism underpinning these events remains unknown with a possibility of overlap with the current understanding of the pathophysiology of thrombosis with thrombocytopenia syndrome (TTS).

The EWG agreed with the conclusion reached by PRAC. The EWG noted that the new data for AstraZeneca adds to the existing evidence on this topic and can be considered a weak signal that supports an update of the product information for COVID-19 vaccine AstraZeneca (Vaxzevria).

2.5.2 Question 2: Does the EWG agree with the proposal to update the UK PI of the AZ vaccine in alignment with the planned update to the European PI of the AZ vaccine.

The EWG agreed with the proposal to update the UK product information of the AstraZeneca vaccine in alignment with the planned update to the European product information of the AstraZeneca vaccine. No additional UK specific amendments were proposed.

2.5.3 Question 3: Does the EWG have any comments on the need for communication?

The EWG advised that communication of this product information update within the coronavirus vaccine - weekly summary of Yellow Card reporting is sufficient. There is no need to generate additional communication material specifically for this topic.

3. COVID-19 vaccines and risk of autoimmune haemolytic anaemia

3.1 The EWG was presented with a review of the currently available evidence regarding autoimmune haemolytic anaemia (AIHA) and COVID-19 vaccines. The EWG noted that this review had been carried out following feedback from UK haematology experts reporting a number of patients presenting with this condition since the start of the COVID-19 vaccination program. The EWG considered clinical trial data, worldwide spontaneous reports, UK Yellow Card reports (with a data lock point of 29 October 2021), published literature reports and a UK Health Security Agency (UKHSA) ecological analysis.

3.2 The EWG agreed that the number of Yellow Card reports of AIHA and related terms following administration of COVID-19 vaccines was low in the context of both the usage of these vaccines and the background incidence of AIHA. The EWG was also reassured by the findings of the UKHSA ecological analysis which, while acknowledging limitations, did not provide any evidence of a major increase in cases of haemolytic anaemia in the general population over the COVID-19 vaccination period.

3.3 The EWG discussed that AIHA was associated with many factors including some infections. The EWG agreed that mechanisms involved in infections causing AIHA are not fully understood and furthermore, there is no known mechanism for a potential causal association between COVID-19 vaccines and AIHA.

3.4 The EWG noted that UKHSA were working with haematology experts and planning a survey of the epidemiology of AIHA presenting during the COVID-19 pandemic.

3.5 The EWG advised that there is no strong evidence of a potential signal with the COVID-19 vaccines and AIHA. The EWG advised that no specific risk minimisation measures were required for patients with pre-existing AIHA, and that no further actions were necessary regarding AIHA and COVID-19 vaccines but to continue to monitor this issue. The EWG advised that the information presented on COVID-19 vaccines and the risk of AIHA did not impact on the benefit risk of the AstraZeneca, Pfizer, Moderna or Janssen COVID-19 vaccines.

4. Multisystem Inflammatory Syndrome in Children (MIS-C) and adults (MIS- A) and COVID-19 vaccines

4.1 The EWG was presented with a review of the currently available evidence from clinical trials, literature and spontaneous sources (including Yellow Card data with a data lock point of 19th September 2021) regarding MIS-C and MIS-A following vaccination against COVID-19 infection with the AstraZeneca, Pfizer-BioNTech and Moderna COVID-19 vaccines. Company reviews of this issue were also presented. The EWG heard that the number of reports meeting the case definition was low and that there was little information in the literature relating to MIS-C and MIS-A post vaccination.

4.2 The EWG noted that both MIS-C and MIS-A were relatively new disorders reported following COVID-19 infection which were not fully characterised, however health care professionals are adept at recognising the conditions. The EWG considered that given the currently known prevalence of the conditions following COVID-19 infection, a much higher number of cases would have been expected if there was an association with COVID-19 vaccination. The EWG did not recommend any regulatory action based on the available evidence.

4.3 The EWG noted that the British Paediatric Surveillance Unit (BPSU) was studying children experiencing MIS-C related to COVID-19 infection and recommended that the MHRA contact

BPSU to see if it would also be possible to obtain information on cases of MIS-C following vaccination with the COVID-19 vaccines.

4.4 The EWG agreed that all potential cases of MIS-C/MIS-A reported through YC should be followed-up to gain as much systematic information as possible and endorsed the provision of a targeted follow-up template for MIS-C/MIS-A to be sent to reporters.

5. Latest information on the safety data for the COVID-19 vaccines in pregnancy

5.1 The EWG considered the latest safety information regarding COVID-19 vaccines in pregnancy, including data from the spontaneous Yellow Card reports and the Yellow Card Vaccine Monitor (YCVM) received up to and including 4th November 2021 and data from published studies.

5.2 The EWG noted that the same data had been reviewed by the Medicines for Women's Health EAG (MWHEAG) at their meeting on 15 November 2021.

5.3 The EWG noted that more than 96,000 women in England and Scotland, who reported they were or might be pregnant at the time of vaccination, had received at least one dose of vaccine against COVID-19 up to 31st September 2021. It was additionally noted that vaccination data are now available for Wales, which adds nearly 8000 additional women who received at least one dose of vaccine during pregnancy. It was noted however that vaccination rates amongst pregnant women remain lower than rates for non-pregnant women of the same age in the UK.

5.4 Up to 4th November 2021, 1549 spontaneous Yellow Card reports have been received relating to possible exposures during pregnancy. Of these, 1539 reported suspected ADRs associated with exposures during pregnancy via maternal vaccination. In addition, the Yellow Card Vaccine Monitor included information from 2163 participants who reported maternal exposures during pregnancy up to 3rd November 2021, of whom 915 participants had reported suspected ADRs following vaccination up to 4th November 2021.

5.5 The data reviewed comprised 414 spontaneous reports and 145 reports from YCVM participants who had received the Oxford-AZ vaccine (total n = 559 reports), 935 spontaneous reports and 670 reports from YCVM participants who had received the Pfizer-BioNTech vaccine (total n = 1605 reports), and 190 spontaneous reports and 100 reports from YCVM participants who had received the Moderna vaccine (total n = 290 reports). Data for Janssen vaccine were not included in the review.

5.6 The EWG noted that reports of miscarriage continue to constitute a large proportion of the spontaneous Yellow Card reports related to early pregnancy exposures. The new reports of miscarriage were similar to those previously reviewed, in terms of no clear pattern for time to onset, gestational age or presence or absence of non-pregnancy related ADRs, including pyrexia, fever or chills. The EWG noted that the new reports of miscarriage had not raised any new safety concerns. Moreover, a much lower rate of reports of miscarriage have been received through the YCVM and the overall number of reports do not suggest an elevated rate of miscarriage compared to pre-pandemic background rates in the UK.

5.7 The EWG noted that several epidemiology studies have recently been published which showed that the miscarriage rates do not appear to be elevated compared to non-pandemic background rates.

5.8 Additionally, two large case control studies examined miscarriage rates in vaccinated compared to unvaccinated women over the same time periods. One US study (Kharbanda et al, 2021) included information on 105,446 pregnancies with 13,160 miscarriages. Amongst

these, more than 8,000 pregnant women received the Pfizer-BioNTech vaccine and more than 6,000 pregnant women received the Moderna between December 2020 and June 2021. A Norwegian study (Magnus et al, 2021) included information on 18,477 pregnancies with 4,521 miscarriages, between February and August 2021. Most of the exposed pregnancies (n=790 /1003) received the Pfizer-BioNTech vaccine.

5.9 Both studies found odds ratios (ORs) close to 1, indicating no increased likelihood that a COVID-19 vaccination had occurred in the 3 to 5 weeks preceding miscarriage.

5.10 The EWG noted that comparison of miscarriage rates for those vaccinated with AstraZeneca-Oxford vaccine compared to unvaccinated women found similar results based on small numbers of exposures.

5.11 The EWG considered that these studies provided a large amount of data on the use of the vaccines in early pregnancy and concurred with the MWHEAG that they provided strong and reassuring evidence that the mRNA vaccines do not increase the risk of miscarriage.

5.12 The EWG noted information on stillbirths, premature births and other pregnancy outcomes is mainly limited to vaccinations received in 2nd and 3rd trimesters of pregnancy. The EWG noted that the small number of reports for common obstetric events did not raise concerns.

5.13 One retrospective cohort study from Israel (Wainstock et al, 2021) examined birth outcomes for 4399 pregnancies between January and June 2021, of whom 913 women received at least one dose of the Pfizer-BioNTech vaccine during pregnancy. The study found no differences between vaccinated and unvaccinated groups in pregnancy, delivery or new-born complications, including gestational age at delivery, incidence of small for gestational age and new-born respiratory complications.

5.14 The EWG noted that the COPS study found no difference in rates of stillbirth for vaccinated women compared to historical controls. The EWG highlighted that this contrasts with the finding of an approximately 3-fold increase in rates of stillbirth for unvaccinated women with COVID infection. The EWG suggested that placing the information on vaccines in this context could be helpful.

5.15 The EWG considered that the available data on pregnancy outcomes provide reassurance about the safety of the mRNA COVID-19 vaccines in later pregnancy.

5.16 The EWG considered that, although data from early pregnancy exposures reaching full term are still awaited, the available evidence on miscarriage, stillbirths and pregnancy complications all provide reassurance about the safety of the mRNA COVID-19 vaccines in pregnancy.

5.17 The EWG recommended that these conclusions should be reflected in MHRA communications to the public and endorsed the key messages agreed by the MWHEAG.

5.18 The EWG endorsed the proposals to encourage the inclusion of relevant information in the SmPCs of the Pfizer-BioNTech and Moderna Vaccines.

6. Corneal Transplant rejection with COVID-19 vaccines

6.1 The EWG and an external invited expert were presented with an assessment of the available evidence pertaining to corneal graft rejection following COVID-19 vaccination.

6.2 The review had been prompted by a communication to MHRA from a senior UK ophthalmologist from NHS Blood and Transplant, who described an increase in the number of cases of corneal transplant rejection, including cases of previously rare bilateral graft rejection, following COVID-19 vaccination.

6.3 The ophthalmologist had received a number of enquires as to whether patients with prior corneal transplant should be warned that there is an increased risk of rejection following COVID-19 vaccination, and whether patients should be advised to take a short course of prophylactic topical steroids prior to vaccination. The ophthalmologist therefore sought the MHRA's advice on whether patients who have had a corneal graft should be contacted and given topical steroids to prevent graft rejection due to COVID-19 vaccination.

6.4 An introductory paper on this issue was presented to the EWG on 13 October 2021; the paper presented data from Yellow Card reports of corneal graft rejection received in the UK and an overview of the published literature on this topic.

6.5 Having considered the analysis presented in October, the EWG recommended that the MHRA should subsequently: 1) seek advice from an expert ophthalmologist to devise a series of follow up questions to send to reporters of the Yellow Cards already received, and attempt to follow these reports up for detailed information; 2) request that the 4 companies with COVID-19 vaccines approved in the UK submit details of their spontaneous reports of corneal graft rejection and provide an analysis of possible mechanisms; 3) perform a systematic literature search to build on the literature overview previously presented; 4) clarify if any other international regulatory authorities have raised corneal transplant rejection as a possible signal and 5) seek feedback from the Royal College of Ophthalmologists on this topic.

6.6 The follow-up paper presented in November 2021 provided the data requested by the EWG. The EWG's advice was sought on the strength of the evidence for a potential signal of corneal graft rejection with the COVID-19 vaccines, and potential regulatory next steps.

6.7 The data presented to the EWG are summarized as follows: 1) no other regulatory authorities were found to be exploring corneal graft rejection as a potential signal, while the Royal College of Ophthalmologists in the UK had high awareness of the issue; 2) up to 5 November 2021, a total of 9 reports of corneal graft rejection had been received by MHRA: 6 reports with the Pfizer vaccine and 3 reports with the AstraZeneca vaccine, with no reports received for the Moderna vaccine; 3) the international published literature on the topic was sparse with no evidence higher than case reports available and 14 patients described in total; 4) the reviews of global spontaneous data submitted by the 4 companies involved small case numbers, with most of the cases being poorly detailed, and with the companies being unable to provide meaningful data on possible mechanisms underpinning the potential signal.

6.8 The EWG noted that, to date, there have been no signals of graft rejection arising for other solid organ tissue transplants. The EWG considered that the available case reports showed a possible temporal association with COVID-19 vaccination and noted a small number of cases of bilateral graft rejection following vaccination, considered unusual. However, the EWG advised that there was no signal for graft rejection arising in international data and, overall, a signal could not be confirmed. The EWG advised the MHRA to monitor the issue closely and recommended no regulatory action. The EWG noted that UK corneal transplant specialists had already discussed how to conduct studies to investigate graft rejection post-COVID-19 vaccination and concluded that these would be very difficult to do.

6.9 The EWG further advised that the MHRA should liaise with the Royal College of Ophthalmologists and NHS Blood and Transplant to support the submission of Yellow Card reports of corneal graft rejection by patients and healthcare professionals.

7. Any Other Business

None.

8. Date and time of next meeting

The next scheduled meeting is to take place on **Friday 3rd December 2021** at **10:30**.

The Meeting today started at 10:02 and ended at 12:39.

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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 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.

Professor Lachmann – NPNS in Janssen due to a talk Professor Lachmann will be giving at Janssen sponsored session on AL amyloidosis later this month. Janssen will make a contribution to the departmental R&D account. Other relevant interest as a volunteer participant in the Oxford vaccine study and no other involvement in the study. Professor Lachmann also declared an interest in Novartis arising from being a PI in the cytokine trials.

Dr Misbah - NPNS - Holds honorary Senior Lectureship with University of Oxford & Oxford University Hospitals NHS Foundation Trust. Other relevant interest in AstraZeneca arising from being part of a collaboration in which the epidemiology and therapeutic approaches to Vaccine associated Thrombosis-Thrombocytopenia (VITT).

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). Member of the independent Data Safety Monitoring Board for COV-BOOST trial.

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

[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] has now left that role.

[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.