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

Minutes of the meeting held on **Tuesday 9th November 2021** at **14:30** via videoconference

Participants Present

Members

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

Apologies

Mr R Lowe
Dr S Misbah
Professor Y Perrie
Professor T Solomon
Professor M Turner

Observers

Professor WS Lim
[redacted]

[1] joined during item 6
[2] joined during item 2
[3] supported specific items

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea – LD
[redacted] – VRMM[3]

Presenters supporting specific items[3]

[redacted] – VRMM
[redacted] – VRMM
[redacted] – VRMM

MHRA Observers

[redacted] – VRMM
Dr S Branch – VRMM
[redacted] – VRMM
[redacted] – MHRA Policy
[redacted] – VRMM
[redacted] – VRMM
[redacted] – LD
[redacted] – VRMM
[redacted] – MHRA Policy
[redacted] – LD
[redacted] – VRMM
[redacted] – VRMM

Secretariat

[redacted]

[redacted]
16 February 2023

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 Perrie, Solomon, Turner, Dr Misbah and Mr Lowe for this meeting.

1.5 The Chair welcomed the following observers:

Professor Wei Shen Lim
Chair of JCVI

[redacted]
Public Health Scotland

[redacted]
UK Health Security Agency

[redacted]
NHS England and NHS Improvement (National)

2. Update on myocarditis and pericarditis with COVID-19 vaccines

2.1 The EWG was presented with an update on the Yellow Card reports of myocarditis and pericarditis with the three COVID-19 vaccines in use in the UK vaccination programme as well as new international data and literature which had become available since the last update on this topic on 19 October 2021.

2.2 The EWG was informed that reporting rates remain similar between first and second dose of the Pfizer vaccine, and the Moderna vaccine has both higher reporting after the second dose in the younger groups compared to the first dose and higher reporting rates overall compared to the Pfizer vaccine. The EWG heard that for the AstraZeneca vaccine the reporting rates

were overall lower than both of the mRNA vaccines. The rates were largely similar between first and second dose with the exception of the second dose in 18-29 years which is slightly higher than the first dose although it was noted that this is likely to be an unusual population due to AstraZeneca not being recommended in under 40's by JCVI.

2.3 The EWG heard that the nature of the Yellow Card reports was similar to that previously presented for the vaccines, with higher proportions of reports in males and in younger ages, and with the average age of the mRNA vaccine reports being younger than the AstraZeneca reports. The majority of reports had outcomes of recovering or recovered and mainly describe mild symptoms and standard treatment. It was noted that there had been improvements in the quality and detail of the reports with the introduction of specific online questions for myo/pericarditis in the Yellow Card reporting forms and with the initiation of the long term follow up questionnaire.

2.4 The EWG were also informed of new data that had been identified from international regulators, which followed a largely similar pattern of more frequent reporting in younger ages and males following the second dose. The EWG commented on the consistent pattern of higher reporting rates for Moderna compared to Pfizer in the international and UK spontaneous reporting data, and it was discussed whether the extended dose interval in the UK may explain this difference. It was also considered whether the half dose of Moderna currently in use in the UK as a booster may result in lower reporting rates for these events. It was noted that Pfizer was the preferred vaccine in the UK for under 18-year olds.

2.5 The EWG also discussed the role of strenuous exercise in the events reported. The EWG was informed that only a small proportion of UK reports indicated strenuous activity preceding the onset of symptoms, and expert advice provided at the EWG meeting of 19 October 2021 had stated this is likely to be in line with typical presentation of myocarditis and pericarditis where symptoms are often aggravated or present themselves on exercise. The MHRA reassured the EWG that they will continue to monitor reports where strenuous exercise is described. It was also noted by members that the reporting rate for pericarditis is likely to be lower than the background rates for these events.

2.6 The EWG requested that further information be provided on long term outcomes when it becomes available, and members commented that it was reassuring that the long-term outcomes available so far do not indicate long term harm. The EWG also highlighted the desire to have mechanistic work undertaken by the companies and the EWG were informed this can be pursued through the RMP update which had recently been submitted.

2.7 It was noted by members that a higher reporting rate with Moderna was seen consistently in a number of external and international data sources. The EWG were informed that reports do not appear more severe following Moderna booster and noted that half dose Moderna boosters may have lower incidence. The meeting also commented it would be helpful to further understand the impact of longer dose interval on myocarditis/pericarditis reporting rates.

2.8 The EWG concluded that no further regulatory action was required based on the data presented.

3. Report of TTS in an adolescent following vaccination with Pfizer/BioNTech

3.1 The EWG were presented with a fatal report of cerebral venous sinus thrombosis (CVST) with low platelet count in an adolescent following vaccination with the Pfizer/BioNTech COVID-19 vaccine. The EWG heard the timeline of events, which included a headache starting 5 days prior to receiving the vaccine which they had sought medical help for. The investigations

carried out were also described which included a negative COVID test, slightly depressed platelets on admission, raised D-dimer, negative anti-PF4 tests and an MRI which identified CVST with haemorrhage. The patient was treated with heparin however, they sadly passed away.

3.2 The EWG were informed that medical adjudication had been carried out on this report by two MHRA medical assessors and it was confirmed this was unlikely to be a report of thrombosis with thrombocytopenia syndrome (TTS) due to the pre-existing headache and negative anti-PF4 test. The EWG was informed that the same conclusion was made by the hospital physicians at the time of treating the patient and by the independent haematology panel which reviews UK cases of suspected thrombosis with thrombocytopenia following vaccination.

3.3 The EWG was reassured that the MHRA was closely monitoring reports of suspected TTS following COVID-19 vaccination as well as closely monitoring safety data in those under 18 years of age. The EWG heard that the MHRA is also continuing to follow up on the report and is seeking the results of the post-mortem once completed.

3.4 The EWG agreed with the MHRA conclusion this this is unlikely to be a report of TTS associated with the Pfizer/BioNTech COVID-19 vaccine. The EWG supported the planned review of the post-mortem once it was available and that if any significant new information be identified then the EWG should be updated.

4. Erythema Multiforme and mRNA COVID-19 vaccines Update

4.1 The EWG was presented with written comments from dermatology experts regarding the review of erythema multiforme (EM) following vaccination against COVID-19 with the Pfizer-BioNTech and Moderna COVID-19 vaccines which had been presented to the VBR EWG on 06/10/2021.

4.2 The EWG were informed that the dermatology experts considered EM to be a very uncommon, benign and self-limiting condition which could plausibly be triggered by COVID-19 vaccination; the dermatology experts had however noted that the overall number of reports of EM received with both vaccines was low especially given the likelihood of over reporting due to urticaria being misdiagnosed as EM.

4.3 The EWG was informed that following a review of this issue by the Pharmacovigilance Risk Assessment Committee (PRAC) during September 2021, it was concluded that although the number of reports received was low, there were cases reported with a reasonable time to onset and without alternative causality. The EWG heard that the PRAC had therefore recommended that EM should be included in section 4.8 of the SmPC for the Pfizer and Moderna COVID-19 vaccines.

4.4 The EWG were informed that the dermatology experts had also recommended that there was sufficient overall evidence to include EM in the product information for the Pfizer and Moderna vaccines. The EWG agreed that updates to the UK product information for both COVID-19 vaccines to include EM as an adverse event with a frequency of unknown were warranted. Their recommendations will be taken forward.

5. Pfizer-BioNTech COVID-19 Vaccine. Assessment of the draft protocol for Study C4591009 - a post-authorisation observational safety study of adverse events of special interest (AESIs) including myocarditis and pericarditis, using real world data in the United States

5.1 The EWG was presented with an assessment of a draft study protocol for the Pfizer-BioNTech COVID-19 vaccine. The EWG heard that this retrospective cohort study had been designed to assess the occurrence of safety events of interest among individuals in the general US population and in sub-cohorts of interest – pregnant women, those who are immunocompromised and those with a prior history of COVID-19 infection.

5.2 The EWG noted the strengths and limitations of the study and agreed with the assessment and the proposed list of comments and questions to the company. In particular, the EWG noted the proposed study milestones and expressed concern regarding the overall utility of the study in informing ongoing vaccination campaigns given the final report will not be available until 2025. The EWG was unclear as to why the study should take 3 years to complete and agreed that the company should be requested to revise the milestones so that the study is completed, and the results are available much sooner than currently proposed.

5.3 In addition to the list of questions included in the assessment report, the EWG recommended that the company be requested to include analyses of data according to dose interval (ie, recommended vs extended dose interval), as well as to provide further information about any censoring of follow up in the matched pair if the unvaccinated control becomes vaccinated during the course of the study.

6. Capillary Leak Syndrome and Moderna & Pfizer COVID-19 vaccines

6.1 The EWG were presented with a paper on the risk of capillary leak syndrome (CLS) with the Moderna and Pfizer/BioNTech vaccines. It was noted that regulatory action had previously been taken to include CLS as an adverse event for the AstraZeneca and Janssen vaccines as well as including a contraindication in patients with prior history of CLS.

6.2 The EWG were informed that there have been no UK reports for either Moderna or Pfizer/BioNTech. For Moderna, the company identified a total of 7 cases worldwide, with 4 cases reporting prior history of CLS. The company observed vs expected analysis did show increased reporting for the 40-49 years age group, particularly for females, however the analysis lacked precision due to the small number of cases. For Pfizer/BioNTech there was a worldwide total of 18 cases of CLS, however many were not medically confirmed or included possible alternative caused of CLS. Prior history of CLS was not reported in the Pfizer/BioNTech cases.

6.3 The EWG were informed that the European Medicine Agency's Pharmacovigilance Risk Assessment Committee (PRAC) have reviewed the signal of CLS for Moderna and Pfizer/BioNTech vaccines. For Moderna, PRAC confirmed the signal procedure and have requested further information from the Marketing Authorisation Holder to further assess the signal. For Pfizer/BioNTech, PRAC concluded that the available evidence did not support a causal association.

6.4 The EWG noted that a consistent approach should be taken for assessing this signal, as the updates for AstraZeneca and Janssen were based on limited data. The EWG considered that in many of the reports, the presenting symptoms and severity did not appear to reflect an accurate diagnosis of CLS. The EWG considered that people with a history of CLS would be

clinically vulnerable to COVID-19 infection and any recommendation to include a contraindication in such patient group would need to be carefully considered.

6.5 The EWG concluded that a further review of the signal should be undertaken following submission of the additional company data and PRAC assessment.

7. Any Other Business

None.

8. Date and time of next meeting

The next scheduled meeting is to take place on **Friday 19th November** at **09:30**.

The Meeting today started at 14:30 and ended at 15:49.

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).

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.

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 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 [redacted]. [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.