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

Minutes of the meeting held on **Wednesday 13th October 2021** at **10:30** via videoconference

Participants Present

Members

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

Apologies

Mr VI G Fenton-May
Sir M Jacobs
Mr R Lowe
Professor Y Perrie
Dr A Riordan
Professor C Robertson
Professor T Solomon

Observers

[redacted]
[redacted]
Professor WS Lim
[redacted]
[redacted]
[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted] - VRMM

Presenters supporting specific items[2]

[redacted] - VRMM

MHRA Observers

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

Secretariats

[redacted]
[redacted]

Key
LD = Licensing Division
VRMM = Vigilance & Risk Management of Medicines
Comms = MHRA Communications & Engagement

[redacted]

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

5th May 2023

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, Robertson, Solomon, Dr Riordan, Mr Lowe, Mr Fenton-May and Sir Michael Jacobs for this meeting.

1.5 The Chair welcomed the following observers:

[redacted] Joint Committee on Vaccination and Immunisation, UK Health Security Agency

[redacted] Public Health Wales

[redacted] NHS England [redacted]

Professor Wei Shen Lim
Chair of JCVI

[redacted] Public Health Scotland

[redacted] NHS England and NHS Improvement (National)

2. Case review of myocarditis/Pericarditis with the COVID-19 vaccines

2.1 The EWG heard that the MHRA had carried out independent case adjudication of Yellow Card reports of COVID-19 vaccines and suspected myo/pericarditis where the patient was under 18 years of age (up to 29 September 2021). The EWG heard that the aim of the exercise was to gain expert insight and advice on how to apply the case definition criteria, and considerations for causality assessment.

2.2 The EWG heard that the US Centres for Disease Control (CDC) case definition criteria for myocarditis, pericarditis and myo/pericarditis were used to classify the reports. The EWG had previously agreed that in particular for myocarditis, the case definition was most appropriate for spontaneous data in that it was less restrictive than some other available case definitions. The EWG were reminded that the CDC criteria is broken down into two levels of diagnostic certainty; probable and confirmed, based on symptoms and the presence of findings from investigations such as blood tests, ECG and cardiac MRI.

2.3 The EWG were presented with an overview of the methodology for the process, which included identification of Yellow Card reports, initial report review to exclude duplicates and classification errors, detailed case review for initial classification (confirmed, probable, unlikely, case definition not met), internal review by an MHRA medical assessor and finally independent adjudication by two cardiology experts.

2.4 The EWG noted that for the 12 reports included in the review, there was consensus on case classification between the internal and external review, with half of the myocarditis reports considered to meet the criteria for probable and the other half not meeting the criteria. It was noted that all reports reviewed lacked information on cardiac MRI to confirm case definition. Myo/pericarditis could not be excluded in any of the reports due to missing information on alternative causes. The EWG heard that further information was requested from the reporters, but that it is often the case that cardiac MRI is not conducted.

2.5 The EWG heard that consideration should be given on a plausible time to onset, with immediate onset considered unlikely to be related to vaccination. The EWG also heard that at present the review process would not set a maximum time cut off post vaccination, as the mechanism for the event was not established.

2.6 The EWG were informed that the MHRA planned to continue an internal case adjudication process for reports of myocarditis in older age groups, seeking expert input where needed, and that updates were being made to the coronavirus Yellow Card reporting form, to include specific questions to increase the level of detail provided by reporters.

2.7 The EWG discussed the findings of the review, in particular the level of detail likely to be available in Yellow Card reports and the challenges in excluding alternative aetiologies such as previous COVID-19 infection and Lyme carditis.

2.8 The EWG were presented with recently available information shared in confidence from a Nordic cohort study which found a higher risk of myocarditis observed following the second dose of Moderna COVID-19 vaccine compared to the Pfizer vaccine in younger adults. A higher incidence of myocarditis was observed following COVID-19 itself. The EWG also heard that the public health authorities in the Nordic countries were offering the Pfizer vaccine in younger adults. The EWG noted that the MHRA were in close contact with the European Medicines Agency and other regulators to gather further information on any regulatory implications based on of the findings from the Nordic study.

2.9 The EWG were updated with some additional recently available information on this topic provided in confidence, including initial details of a Scottish self-controlled case series which also found increased incidence of myocarditis following the mRNA COVID-19 vaccines in younger adults. Similar to other analyses, the study found an increased incidence of myocarditis and pericarditis following SARS-CoV-2 infection. In addition, the EWG noted information from the US CDC concerning a head-to-head comparison of myo/pericarditis after mRNA vaccines in 18–39-year-olds which found an increased risk following Moderna compared to Pfizer. The EWG noted that MHRA were seeking further details from the Nordic and Scottish analyses and any further detail would be provided at the next meeting.

2.10 The EWG heard an update from NHS England and Wales on use of the mRNA vaccines in the booster programme.

2.11 The EWG discussed the data presented on myo/pericarditis following COVID-19 vaccination, noting that the evidence so far concerned first and second doses, and that currently, there was little UK data concerning the risk after booster doses due to limited exposure, therefore this should be closely monitored by MHRA.

2.12 The EWG noted that data were still emerging on the differing risks of myocarditis in different age groups following the Moderna and Pfizer vaccines, but the benefits still exceeded the risks overall for each vaccine and for all authorised subpopulations and that no regulatory action was required based on the data presented.

3. Corneal transplant rejection and COVID-19 vaccines

3.1 The EWG was presented with an assessment of UK Yellow Card data and world-wide published literature reports of corneal transplant rejection following vaccination with the Pfizer-BioNTech, AstraZeneca and Moderna COVID-19 vaccines. The Group heard that the signal had been raised following correspondence from the Chair of the Ocular Tissue Advisory Group (OTAG) at NHS Blood and Transplant. The correspondence highlighted an observed increase (considered by the OTAG to be significant) in the number of reports of corneal graft rejection following COVID-19 vaccination and questioned whether patients with corneal grafts should be given prophylactic topical steroids for COVID-19 vaccination.

3.2 The EWG commented that although the overall number of reports was small there was likely to be underreporting of these events and, without information on the denominator i.e., the number of people with corneal grafts who had received a COVID-19 vaccine, it was difficult to determine the size and potential impact of the signal, if confirmed. The EWG agreed that it would be important to obtain further information regarding the number of people who had undergone corneal transplant in the UK and if possible, how many of these had been vaccinated against COVID-19. The EWG commented that people who undergo corneal transplant tended to be older and therefore it was likely that most would have been vaccinated.

3.3 The EWG discussed the reports. The EWG agreed that overall, it was difficult to assess causality given the lack of detail in the reports. However, the EAG noted that some reports appeared atypical, in particular the case of bilateral corneal graft rejection which the OTAG correspondence stated to be almost unheard of. The EWG discussed potential mechanisms underlying corneal graft rejection including that in those experiencing subclinical transplant rejection, a non-specific immune response to vaccination could exacerbate rejection.

3.4 Overall, the EWG agreed that the limited data available did not allow for a conclusion to be drawn on whether the reports of corneal transplant rejection were likely to be related to COVID-19 vaccines. However, given the concern from ophthalmologists, the atypical nature of some of the reports and that there were plausible biological mechanisms for COVID-19

vaccines and corneal transplant rejection, the EWG agreed that there was a need to further investigate the signal.

3.5 The EWG recommended that the following additional information be sought and included in the assessment: the number of people who have undergone corneal transplant in the UK; the background incidence and risk factors for corneal transplant rejection; further clinical details for the reports, including those cited in the correspondence from the OTAG; non-UK reports from the marketing authorisation holders as well as details of any reports of corneal transplant rejection received by other medicines regulatory authorities world-wide. The EWG agreed that it would be important to have expert ophthalmological advice when the additional data are discussed.

3.6 The EWG noted that a small number of reports of other transplant rejection had also been reported. Given that no signal of disproportionate reporting of rejection had been observed following COVID-19 vaccination for other types of transplant, the EWG agreed that the further review should initially focus on corneal transplants. Should the signal for corneal transplant rejection following COVID-19 vaccination be confirmed, the EWG agreed that further review of reports of other transplant rejection following vaccination may be warranted.

3.7 The EWG agreed with the proposed timeline for completion of the additional review and its presentation to the Group.

4. Any Other Business

None.

5. Date and time of next meeting

The next scheduled meeting is to take place on **Tuesday 19th October** at **14:30**.

The Meeting today started at 10:30 and ended at 11:37.

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Annex I

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

Chair and Members

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

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

Invited experts

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

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

Observers

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

Annex II

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

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

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

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

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

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

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

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

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

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

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.