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

Minutes of the meeting held on **Wednesday 17th November 2021** at **18:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan
Mr VI G Fenton-May
Professor N French
Ms S Hunneyball
Sir M Jacobs
Professor H J Lachmann[1]
Mr R Lowe
Dr S Misbah
Professor Y Perrie[2]
Professor S Price
Dr A Riordan[1]
Professor C Robertson[1]
Professor K M G Taylor
Dr R Thorpe[3]
Professor S Walsh
Mrs M Wang[1]
Professor C Weir

Apologies

Professor D Goldblatt
Professor K Hyrich
Professor P J Lehner
Professor T Solomon
Professor M Turner

Visiting / Invited Experts

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

Moderna Representatives[7]

[redacted]

Professional Staff of MHRA Present

Principal Assessors

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

Presenters supporting specific items[3]

[redacted] - VRMM
[redacted] – VRMM

MHRA Observers

[redacted] – Medical Writer
[redacted] – LD
Dr S Branch – VRMM
Dr A Cave – Chief Safety Officer
[redacted] – VRMM
[redacted] – VR|MM
[redacted] – Comms
[redacted] – VRMM
[redacted] – VRMM
[redacted] – LD
[redacted] – VRMM
[redacted] – VRMM
Mr P Tregunno – VRMM
[redacted] – LD
[redacted] - VRMM

Secretariats

[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

Key

[1] joined during item 2
[2] left during item 6
[3] left during item 5
[4] participated in items 4, 5 & 6
[5] participated in item 2
[6] participated for the whole meeting
[7] participated in item 3

Observers

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

Government Lawyer

[redacted]

1. Introduction and Announcement

1.1 The Chair reminded Members, invited Experts and observers that the content of papers and proceeding of the meeting are strictly confidential and should be treated as 'Official – sensitive commercial' and should not be disclosed. There is no consent for members / participants to record the meeting, take screenshots or photographs of presentations. The meeting was recorded by the MHRA Secretariat for minute taking purposes only. The Chair & Members including all participants gave full consent to the recording prior to the start of the meeting.

1.2 Conflict of Interest Policy (Annex I to the minutes)

The Chair reminded members and participants that, in accordance with the CHM Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members were also reminded to declare any other matter which could reasonably be perceived as affecting their impartiality.

1.3 Participants declared interests and other relevant interests for this meeting listed at **Annex II** to the minutes.

1.4 Apologies were received from Professors Goldblatt, Hyrich, Lehner, Solomon and Turner for this meeting.

1.5 The Chair welcomed the following visiting/invited experts:

[redacted] Imperial College London

[redacted]
Swedish PRAC Delegate

[redacted] Swedish Medical Products Agency

Moderna

[redacted]

[redacted] Bristol Heart Institute

[redacted] King's College Hospital

1.6 The Chair welcomed the following observers:

[redacted]
[redacted]
[redacted]UK Health Security Agency

[redacted]
[redacted]
Public Health Agency

Professor Wei Shen Lim
Chair of JCVI

[redacted]
Public Health Scotland

[redacted]
UK Health Security Agency

[redacted]
[redacted]
[redacted]
NHS England and NHS Improvement (National)

2. Update on Nordic study meta-analysis

2.1 The EWG heard an update from a member of the Swedish Medical Products Agency on behalf of the Nordic collaboration on 'SARS-CoV-2 vaccination and myocarditis in a Nordic cohort study of 23 million residents. This study, in individuals aged 12 years and over, found that the risk of myocarditis was higher within 28 days of vaccination compared to unvaccinated individuals with Pfizer and Moderna COVID-19 vaccines. The risk of myocarditis was higher after the second dose than after the first dose for both COVID-19 vaccines; however, the risk after the second dose was more pronounced for Moderna COVID-19 vaccine and was highest in males aged 16 to 24 years.

2.2 The EWG heard that dose intervals between COVID-19 vaccines were different in individual Nordic countries and that it was not possible to draw conclusions on any effect of shorter or longer dose intervals on the risk of myocarditis from this study at the present time. The EWG noted that further analysis and investigations were planned in this study including medical chart review for some individuals and long term follow up of cases of myocarditis.

3. Moderna company data analysis

3.1 The EWG heard a presentation from the company, Moderna, on myocarditis and Moderna COVID-19 vaccine. The presentation included published data on the epidemiology of myocarditis prior to COVID-19, the increased risk of myocarditis with COVID-19 itself and ejection fraction findings in COVID-19 vaccine-related myocarditis which indicated milder clinical disease than that associated with classical myocarditis. The company also presented US spontaneous reporting data in individuals aged 12 years and above which suggested that

the risk of myocarditis after Pfizer or Moderna COVID-19 vaccines was age- and sex-related, with the highest reporting rates found in young males after the second dose of vaccine.

3.2 In terms of company data, the EWG heard that a company observed versus expected analyses of myocarditis and pericarditis among Moderna COVID-19 vaccine recipients had found higher observed than expected rates in males aged 18 to 24 years and 25 to 39 years; no increases in observed versus expected rates were found for females in any age group. The EWG also heard that the first phase of the company's US post authorisation study using administrative claims data showed similar findings with the highest myocarditis incidence rate ratio following Moderna COVID-19 vaccine in males aged 18 to 29 years with no increase observed in females.

3.3 The company also presented an estimate of relative benefits and risks of Moderna COVID-19 vaccine that they had calculated using data presented at a US Centres for Disease Control and Prevention (CDC) Advisory Committee on Immunisation Practices (ACIP) meeting in October 2021. The company calculated that the risk of myocarditis in 18 to 39 year olds following Moderna COVID-19 vaccine was lower than the risk of hospitalisation following COVID-19.

3.4 The EWG noted that the company had not yet determined the underlying pathological mechanism(s) for myocarditis following Moderna COVID-19 vaccine but was planning to investigate this issue further. The EWG also noted that the company considered that more work was needed to characterise any impact of dose and/or the interval between doses of Moderna COVID-19 vaccine on the risk of developing myocarditis post vaccination. More information was also needed on the long-term outcomes of cases of myocarditis following Moderna COVID-19 vaccine and the company highlighted that data were likely to become available shortly from a CDC study of outcomes in cases of myocarditis following vaccination against COVID-19.

4. King's cardiac unit - myocarditis outcome data

4.1 The EWG heard a presentation from two cardiologists working at London hospitals on mRNA vaccine associated myocarditis and cardiovascular magnetic resonance imaging (MRI). The presentation included information on the diverse causes of myocarditis, the role of MRI in its diagnosis and available published data on the severity and outcomes of mRNA COVID-19 vaccine associated myocarditis including MRI findings. The clinical implications of myocarditis were also presented. The EWG heard that while the full long-term clinical significance of COVID-19 vaccine- associated myocarditis would take time to become clear, the currently available data suggested that most patients had recovered within 3 months post-vaccination.

4.2 The EWG heard that, in the cardiologists' experience, reports of myocarditis following mRNA COVID-19 vaccines were predominantly in young males whereas cases of myocarditis following COVID-19 itself tended to be in older patients with co-morbidities.

5. PHE emergency care data set analysis

5.1 The EWG heard a presentation describing a cohort study conducted by Public Health England using linked data from the Emergency Care Data Set (ECDS) to explore the risk of acute myocarditis and pericarditis following COVID-19 vaccination.

5.2 The EWG were informed that there had been an increase in the number of cases of myocarditis identified within the ECDS, particularly in younger patients since September 2021. Analyses showed that in patients aged 15-29 years there was a significantly increased risk of both myocarditis and pericarditis in the 6 days following vaccination with a first dose of the

AstraZeneca and following a first and second dose of the Pfizer and Moderna vaccines. This association was greatest following a second dose of the Moderna vaccine where an attributable risk of 88 cases of myocarditis per million doses was seen. Significantly increased risks were also seen for the Pfizer and Moderna vaccines in patients aged 30-39. The attributable risks seen for myocarditis were higher in males than females due to their greater baseline risk. The risk of pericarditis was also higher in males following the Pfizer vaccine but more comparable for the other vaccines. The risk of pericarditis following the Moderna vaccine also appeared to extend to time periods greater than 6 days following vaccination.

5.3 The EWG noted that adjustment for clinically extremely vulnerable status had little impact on the results for the Pfizer and Moderna vaccine, although a risk of residual confounding remained.

5.4 The EWG agreed that the analyses were helpful but that further data on long term outcomes were required.

6. Updated analysis of myocarditis/pericarditis with mRNA vaccines

6.1 The EWG was presented with an update on the Yellow Card reports of suspected myocarditis and pericarditis with Moderna and Pfizer COVID-19 vaccines up to 10 November 2021 as well as epidemiological analysis, literature and new international data which had become available since the last update on this topic on 19 October 2021.

6.2 The EWG was informed that reports of suspected myocarditis/pericarditis remain very rare with the Pfizer and Moderna vaccines, with higher frequency in younger ages and males and with a typically short time to onset of less than 7 days. The suspected myocarditis reports showed acute presentation with the outcome reported as recovered or recovering in the majority for both vaccines and symptoms mainly described as mild and only required standard treatment. The EWG noted the more recent data on positive longer-term outcomes for these patients. This was in contrast to cases of myocarditis following COVID-19 infection which were associated with a predicted lifelong risk of myocarditis and other events.

6.3 The EWG noted that the reporting rate (ADRs reported per number of doses administered) has been a consistently similar between first and second dose with the Pfizer vaccine. This includes an increasingly similar reporting rate in the under 18's, with a caveat that experience with second dose in this age group remains limited. The Moderna vaccine appears to have a higher reporting rate overall (reporting rate age range from 18-59 years), and larger differences between first and second dose with higher reporting after the second dose in the younger age groups. The EWG acknowledged that the data should be interpreted with caution due to the lower usage of Moderna in the UK vaccination campaign and smaller number of suspected events. The EWG heard that reporting rates were significantly attenuated upon restriction to medically adjudicated cases, highlighting the likely overestimation of the reporting rate.

6.4 The EWG was informed that there has been limited evidence of presentation or aggravation of symptoms on exercise and also a limited number of both positive and negative re-challenge reports, and that the evidence is insufficient to warrant further action based on these reports. The EWG were informed that reports following booster doses will continue to be closely monitored but that currently there was no indication of a great frequency or severity of suspected events with booster doses of the mRNA vaccines.

6.5 The EWG was also informed of updated rapid cycle analysis by the MHRA and investigation into the impact of dose interval on reporting. The analysis showed a raised signal in the 42-day risk window in the 18-49 year and overall age groups for the Pfizer vaccine after the first dose and for the Moderna vaccine after the second dose. The Pfizer vaccine second dose only had a signal raised in the overall age group. It was noted limited data was available for the first vaccination dose with the Moderna vaccine which may lead to risks being underpowered. The 7-day analysis shows a higher proportion of Moderna events with the second dose while the signal was reduced in the 7-day analysis of vaccination with first or second dose of Pfizer.

6.6 Analysis of Yellow Card reporting compared against dose interval estimates did not find an increased reporting rate associated with a shorter gap between first and second doses, and it was noted that limited data is available on dose intervals.

6.7 The EWG also heard a summary of a recently published case-control study from France where an increased risk in mRNA vaccinated individuals over unvaccinated individual was identified, particularly in younger ages and males. The study also identified a higher risk ratio with Moderna compared to Pfizer vaccine. It was noted that this study would be subject to bias based on when the vaccines were introduced and levels of usage. The EWG was informed this was in contrast to data from the FDA claims database analysis which found similar reporting rates of myocarditis/pericarditis between the Moderna and Pfizer vaccines, and it was noted that the US has the largest usage of Moderna globally.

6.8 The EWG was updated on previously presented scientific research, literature and informed of announcements from international public health agencies regarding preference for the Pfizer COVID-19 vaccine in the various younger age groups.

6.9 The EWG noted that Pfizer was the preferred vaccine in the UK for under 18-year olds and UK usage data showed very low numbers of second doses of Moderna given to this age group. It was noted that the studies presented featured small numbers exposed to Moderna and a small number of events, but that higher reporting rate with Moderna was seen in a number of external and international data sources. It was noted however that the US has the largest experience and is not currently seeing such a difference. The EWG was reassured that the long-term outcomes available so far do not indicate long term harm and that cases of myocarditis/pericarditis appear mild.

The EWG discussed the uncertainties and limitations of the data presented, noting the implications of any actions on vaccine public confidence and potential consequences for supply of vaccines.

6.10 The EWG concluded that the benefit/risk ratio of Pfizer and Moderna vaccines remained positive, and that the current available data did not provide sufficient evidence to restrict the Moderna vaccine in any age groups.

The EWG agreed the need for clear messaging on the risks of myocarditis and pericarditis with each vaccine and that the messaging should highlight the uncertainties of the current available data.

The EWG agreed that no regulatory action was required based on the data presented.

6.11 The EWG requested that data from international studies with higher usage of the Moderna vaccine be provided when available. The EWG also requested further information be provided

on long term outcomes when it is available and reiterated the importance of mechanistic work and further study regarding dose-dependent responses undertaken by the companies.

6.12 The EWG were informed of the proposed changes to the MHRA's weekly ADR publication, to provide more detailed information on the reporting rates for all three COVID-19 vaccines stratified by smaller age bands and by first and second dose, alongside breakdowns for the number of reports by age and sex, and to highlight the more even reporting between first and second dose of Pfizer in the UK. The EWG endorsed the updates to the MHRA's weekly ADR publication.

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 18:31 and ended at 21:44

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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.

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.

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). 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] 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.