

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

Minutes of the meeting held on **Friday 3<sup>rd</sup> December 2021** at **10:30** via videoconference

**Participants Present**

**Members**

Professor Sir M Pirmohamed (Chair)  
Professor J Breuer  
Professor G Dougan  
Mr VI G Fenton-May  
Ms S Hunneyball  
Professor K Hyrich  
Professor H J Lachmann  
Mr R Lowe<sup>1</sup>  
Dr S Misbah  
Professor S Price  
Professor K M G Taylor  
Dr R Thorpe  
Professor S Walsh  
Mrs M Wang

**Apologies**

Professor N French  
Professor D Goldblatt  
Sir M Jacobs  
Professor P J Lehner  
Professor Y Perrie  
Dr A Riordan  
Professor C Robertson  
Professor T Solomon  
Professor M Turner  
Professor C Weir

**Invited Experts**

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**Observers**

██████████  
Professor WS Lim  
██████████

**Secretariats**

██████████  
██████████

**Professional Staff of MHRA Present**

**Principal Assessors**

Dr J Bonnerjea – LD  
██████████ ██████████ – VRMM

**Presenters supporting specific items<sup>5</sup>**

██████████ – VRMM  
██████████ – VRMM  
██████████ - VRMM

**MHRA Observers**

██████████ - LD  
██████████ - VRMM  
██████████ - LD  
██████████ - VRMM  
Dr S Branch - VRMM  
██████████ - VRMM  
██████████ - VRMM  
██████████ - MHRA Policy  
██████████ - Comms  
██████████ - LD  
Dr N Rose - MHRA-NIBSC  
██████████ - VRMM  
██████████ - VRMM  
Mr P Tregunno – VRMM  
██████████ - LD

**Key**

LD = Licensing Division  
VRMM = Vigilance & Risk Management of Medicines  
NIBSC = National Institute for Biological Standards & Control  
Comms = MHRA Communications

<sup>1</sup> joined during item 3

<sup>2</sup> joined for item 2 only

<sup>3</sup> joined for items 2 & 4

<sup>4</sup> joined for items 4 & 5

<sup>5</sup> supported specific items

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23<sup>rd</sup> June 2022

**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 Sir Michael Jacobs, Professors French, Goldblatt, Lehner, Perrie, Robertson, Solomon, Turner, Weir, and Dr Riordan for this meeting.

**1.5** The Chair welcomed the following invited experts:

[Redacted]  
[Redacted]  
[Redacted] UCL

[Redacted]  
[Redacted]  
[Redacted] University of Liverpool

[Redacted]  
[Redacted] Bristol Heart Institute

[Redacted]  
University Medical Centre Utrecht

**1.6** The Chair welcomed the following observers:

[Redacted]  
[Redacted] Public Health Wales

**Professor Wei Shen Lim**  
Chair of JCVI

[Redacted]  
UKHSA

## **2. General safety review of COVID-19 vaccine paediatric reports**

- 2.1** The EWG was presented with a review of the available safety data on the use of the AstraZeneca, Pfizer and Moderna COVID-19 vaccines in children and young people under the age of 18 years. The EWG considered clinical trial data, UK Yellow Card reports (with a data lock point of 17 November 2021), data from the companies, published literature and international data. The EWG also considered observed versus expected analyses of Yellow Cards for selected events in association with the Pfizer vaccine, namely myocarditis/pericarditis, cerebral venous sinus thrombosis (CVST) and multi-systemic inflammatory syndrome in children (MIS-C).
- 2.2** The EWG discussed the three Yellow Card reports of MIS-C received in association with Pfizer COVID-19 vaccine and noted that one of these cases had been medically confirmed as not related to the vaccine. The EWG considered that confounding factors also appeared to be present in the two other Yellow Card reports, and that no new concerns about this issue were raised from these reports. The EWG advised that close monitoring of MIS-C should be continued, particularly if COVID-19 vaccines were to be recommended for use in younger children in the UK.
- 2.3** The EWG considered that the four Yellow Card reports of CVST received in association with Pfizer COVID-19 vaccine may be a potential signal given the rarity of this event in children although it was acknowledged that the exact incidence of CVST in the paediatric population is not known. The EWG advised that it would also be helpful to seek an opinion on this issue from a paediatric neurologist. The EWG noted that the MHRA was in regular contact with other Regulatory Authorities regarding the paediatric safety of COVID-19 vaccines and, to date, a signal of CVST in children had not been raised in other countries with experience of vaccinating children against COVID-19.
- 2.4** The EWG also emphasised the need to keep the benefits of the use of COVID-19 vaccines in children under review as well as the risks, particularly in view of the new COVID-19 variant, Omicron.
- 2.5** The EWG agreed that, overall, the safety data in children following vaccination against COVID-19 were reassuring. The EWG advised that the use of COVID-19 vaccines in children should continue to be closely monitored and that any paediatric issues that may arise in the future should be brought back to the EWG for advice.

## **3. Anaphylaxis with booster doses - Pfizer/BioNTech and Moderna**

- 3.1** The EWG were reminded that they had previously discussed the 15-minute observation time for the administration of mRNA booster doses. The EWG previously concluded that for those receiving a homologous booster dose of the same mRNA vaccine and who have not experienced an allergic reaction or anaphylaxis with the primary doses, the requirements of the 15-minute observation period can be waived, including for third doses for immunocompromised patients. The EWG also concluded, for those receiving a heterologous booster or third dose, the requirements for a 15-minute observation period should be retained.
- 3.2** The EWG recommendation was for this advice to be included in the Regulation 174 product information, however there was no Regulation 174 stock remaining at the time of the decision and the company did not support changes to the Conditional Marketing Authorisation (CMA) so the updates were not implemented.

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- 3.3 The EWG were informed that the Department of Health and Social Care (DHSC) had enquired whether the waiving of the 15-minute observation period for homologous booster schedules could be enacted through off-label recommendations, whether the advice could be expanded to a broader definition of homologous to apply to any mRNA vaccine being administered as a booster/3<sup>rd</sup> dose following any primary course of mRNA vaccine, and whether the observation times could be shortened.
- 3.4 The EWG were presented with a summary of the Yellow Card reports of anaphylactic events following the administration of booster doses of the Pfizer/BioNTech and Moderna COVID-19 vaccines. The EWG were informed that all the reports for Moderna booster vaccines were for heterologous schedules, while there was a mix of homologous and heterologous schedules for Pfizer/BioNTech. The EWG were informed that while only a quarter of reports met the Brighton Collaboration case definition for anaphylaxis, many other reports required treatment with adrenaline. The time to onset of events occurred on the day of vaccination and ranged from immediately to hours after vaccination.
- 3.5 The EWG commented that there was a limited amount of data available on anaphylaxis following booster doses. The EWG noted that there was likely to be very limited experience with the Moderna primary/Pfizer booster heterologous schedule due to when the Moderna vaccine was deployed in the UK.
- 3.6 The EWG maintained its support for waiving the observation time for homologous booster/3<sup>rd</sup> doses for individuals who have not experienced an allergic reaction or anaphylaxis with the primary doses. The EWG noted that implementation would be through an update to the Green Book.
- 3.7 The EWG considered that there was currently insufficient data to extend the definition of homologous dosing to cover an mRNA booster/3<sup>rd</sup> dose following any mRNA primary course, due to the lack of an established mechanism of anaphylaxis with the mRNA vaccines and the differences in the components of the lipid nanoparticles and spike proteins for the mRNA vaccines. The EWG re-confirmed that the 15-minute observation time should be maintained for heterologous booster doses.
- 3.8 The EWG considered that any decrease in the observation time would result in events of anaphylaxis occurring away from the vaccination centre where treatment may not be available. It was noted that of the 17 reports which occurred within 15 minutes of vaccination, only 6 occurred within the first 5 minutes. The EWG concluded that the observation time should be maintained at 15 minutes.
4. **Myo/pericarditis update - COVID-19 vaccines**
- 4.1 The MHRA provided an update on the Yellow Card reporting of myocarditis and pericarditis for the Pfizer/BioNTech and Moderna COVID-19 vaccines. The reporting rates remained largely consistent with previous updates and broadly similar between the first and second dose, although these rates were attenuated when restricted to those meeting the case definition only. Reporting for the AstraZeneca COVID-19 vaccine has remained at a low level and no safety signal has been raised.
- 4.2 The EWG were presented with a summary of booster reports for the mRNA vaccines and those under 18 years with the Pfizer/BioNTech vaccine; no new safety concerns were raised and the MHRA will continue to monitor this data. It was requested that the MHRA continue to monitor long term follow up data as this was an area of limited information.

## NOT FOR PUBLICATION

- 4.3 The overall nature of the reports with the mRNA vaccines remained predominantly in males and younger ages and the majority showing outcome recovered with standard treatment. The updated company analysis and international data also showed the same trends in the global reporting for the Pfizer/BioNTech and Moderna vaccines.
- 4.4 The EWG saw an updated Medicines and Healthcare products Regulatory Agency (MHRA) observed expected analysis which showed signals raised for both first and second dose with Moderna and Pfizer/BioNTech vaccines in the under 50 years age group and for those under 18 years with Pfizer/BioNTech. There was a trend for reporting within the first 7 days post-vaccination. No signal was raised for AstraZeneca.
- 4.5 The EWG was presented with the response from Pfizer/BioNTech on the requested mechanistic studies for post-vaccination myo/pericarditis. The EWG were informed that the company considered there was limited evidence to support most potential mechanisms but that an innate immune response could be plausible; however, animal models of myo/pericarditis were not considered well established enough to investigate this. EWG members and invited cardiology experts highlighted potential mechanisms which could be further explored such as TGF-beta inflammation pathway and potential genetic predisposition.
- 4.6 The EWG were also informed of planned updates by the European Medicines Agency in the Pfizer/BioNTech and Moderna product information to include data from recent observational studies on the rate of myocarditis seen with the vaccines. The meeting agreed that these updates would be acceptable to include in the GB product information too.
- 4.7 The EWG concluded that the benefit risk balance remained positive for all three of the COVID-19 vaccines based on the data presented, and myo/pericarditis remained a very rare risk with the mRNA vaccines. No further regulatory action was recommended.
5. **ROC20 observational study: myocarditis and COVID-19 vaccination**
- 5.1 The EWG were presented data from the ROC20 observational study reviewing reports of myocarditis and pericarditis associated with the four COVID-19 vaccines in use in the EU (Pfizer/BioNTech, Moderna, AstraZeneca and Janssen) using large electronic health case databases in Italy, Spain, Netherlands and UK, covering 25 million people of which 12.1 had received a COVID-19 vaccine. A self-controlled risk interval study design was used with the aim of estimating incidence rate ratios.
- 5.2 The EWG were informed that the self-controlled risk interval analysis found that for the overall vaccinated population, there was no increased risk of myocarditis or pericarditis for any of the COVID-19 vaccines following the first or second dose. When stratified by age, an increased risk was seen for individuals under the age of 30 years for the second dose of the Pfizer/BioNTech vaccine. When stratified by sex, an increased risk was seen in both males and females for individuals under 30 years for the Pfizer/BioNTech vaccine, however only the male stratification was statistically significant. For the Moderna vaccine the analysis did not show an increased risk of myocarditis and pericarditis, however it was noted that limited exposure to the Moderna vaccine meant the study couldn't draw any firm conclusions for this vaccine.
- 5.3 The EWG concluded that the study results were similar to other epidemiological studies which showed an increased risk of myocarditis and pericarditis for the Pfizer/BioNTech vaccine in young males following the second dose. While the study did not show an increased risk for the Moderna vaccine, as seen in other studies, the EWG considered this was likely due to the limited Moderna vaccine exposure in this study.

6. **Any Other Business**

None.

7. **Date and time of next meeting**

The next scheduled meeting is to take place on **Friday 10<sup>th</sup> December at 12:30.**

The Meeting today started at 10:30 and ended at 12:04.

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**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 3<sup>rd</sup> 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).

**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.

**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 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).



## NOT FOR PUBLICATION

**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**

**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.

■ ■■■■■ – 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.