# @ 10:30COMMISSION ON HUMAN MEDICINES (CHM)
# COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Friday 24th September 2021** at **10:30** via videoconference

**Participants Present**

**Members**

Professor Sir M Pirmohamed (Chair)
Mr VI G Fenton-May
Professor N French
Ms S Hunneyball
Professor K Hyrich
Dr S Misbah
Professor Y Perrie[1]
Professor S Price
Dr A Riordan
Professor K M G Taylor
Professor M Turner
Professor S Walsh

**Apologies**

Professor J Breuer
Professor G Dougan
Professor D Goldblatt
Sir M Jacobs
Professor H J Lachmann
Professor P J Lehner
Mr R Lowe
Professor C Robertson
Professor T Solomon
Dr R Thorpe
Mrs M Wang
Professor C Weir

**Observers**

[redacted]

**Secretariats**

[redacted]

**Professional Staff of MHRA Present**

**Principal Assessors**

Dr J Bonnerjea - LD
[redacted] - VRMM

**Presenters supporting specific items[2]**

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

**MHRA Observers**

[redacted] - LD
[redacted] - VRMM
[redacted] - LD
Dr A Cave - Directorate
[redacted]vies - VRMM
[redacted] - VRMM
[redacted] - VRMM
[redacted] - VRMM
[redacted] – MHRA Policy
[redacted] - LD
[redacted] – VRMM
Mr P Tregunno – VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - Comms

[redacted]

18th November 2022

[1] joined during item 2
[2] 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, Dougan, Goldblatt, Lachmann, Lehner, Robertson, Solomon, Weir, Mr Lowe, Dr Thorpe, Mrs Wang and Sir Michael Jacobs for this meeting.

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

[redacted]
Public Health Scotland

[redacted]
NHS England and NHS Improvement (National)

## 2. Update on COVID-19 Vaccines and the risk of thromboembolic events without thrombocytopenia

**2.1** The EWG was updated with new information received since the previous update presented on 31/08/2021.

**2.2** The update presented to the EWG comprised two parts.

**2.2.1** The first part outlined new information from the MAH for COVID-19 vaccine Janssen dated 10/09/2021 in response to EMA/PRAC questions related to venous thromboembolism (VTE) as requested in the PRAC Assessment Report for the 5th monthly safety update report (data up to 31 July 2021). A summary of the preliminary PRAC Rapporteur assessment report dated 21/09/2021 assessing the new data submitted by the MAH was also presented.

**2.2.2** The second part was a recently completed MHRA VTE and arterial embolic events O/E analysis for Pfizer, Moderna and AstraZeneca COVID-19 vaccines with a data lock point of 01/08/2021.

**2.3** The EWG noted the rationale for the new data submitted by Janssen, i.e. during assessment of the 5th monthly summary of safety report the PRAC Rapporteur noted an imbalance for venous thromboembolism (VTE) in one pivotal clinical trial (COV3001), as well as higher MAH O/E ratios for VTE in particular among younger vaccines. There have been approximately 30 post-marketing case reports in young vaccinees without risk factors for VTE who had a time-to-onset (TTO) of VTE within 30 days after vaccination with Covid-19 Vaccine Janssen. Based on this assessment, the PRAC Rapporteur proposed an update of the product information; however, this action was held pending MAH submission of additional randomised clinical trial data of value to the assessment of this issue.

**2.4** The EWG was informed that the data submitted by the MAH comprises an analysis of thromboembolic events from the COV3001 and COV3009 studies which are pivotal phase 3 randomised, controlled trials that are currently on-going as open-label studies. In addition, the data submission also included an observational US claims database analysis carried out by the MAH.

**2.5** With respect to the clinical studies, the EWG noted that the study populations are broadly similar to each other, but important differences do exist between the studies. These include the fact that COV3001 is assessing single dose vaccine administration whilst study COV3009 was assessing a two-dose regimen, different geographical territories were covered by the studies and there was a difference in mean follow up time during the double-blind phase (123 days for COV3001; 70 days for COV3009).

**2.6** The EWG noted a numerical imbalance in thromboembolic events, skewed towards the treatment arm in comparison to the placebo arm during the double-blind phase (both full period and within 28 days) of COV3001. Venous events comprised the majority of the observed thromboembolic events and were imbalanced towards the treatment arm. This finding was not observed in study COV3009.

**2.7** A summary from the MAH reviewing deep vein thrombosis (DVT) cases in COV3001 noted the presence of multiple risk factors in those who experienced the event in both the treatment and placebo groups.

**2.8** The EWG noted the observation that when the double-blind phase of both studies was pooled there was no imbalance in thromboembolic events (arterial, venous, mixed/unspecified) when comparing the treatment and placebo arms. When looking at venous events specifically, there is a numerical imbalance skewed towards the treatment group compared with placebo for the entire double-blind study periods.

**2.9** The EWG was presented with a summary of the observational healthcare claims analysis conducted by the MAH. The analysis specification design includes a self-controlled case series (SCCS) to identify and quantify risk associated with the Janssen COVID-19 vaccine. In addition, a comparative cohort design is applied to compare the frequency of each outcome following exposure to COVID-19 Vaccine Janssen versus mRNA COVID-19 vaccines.

**2.10** The EWG noted the results of the analysis conducted by the MAH. The SCCS analysis indicated a slightly increased risk (relative risk of 1.4-1.5) of pulmonary embolism (PE) within the 28-, 42- and 90-day risk windows. A slightly increased risk (relative risk around 1.3) of PE was observed within the 42- and 90-day risk windows, as well as with all available

post-exposure time at risk, using the comparative cohort design. No increased risk was observed for DVT, in any risk window or with either design. A slightly increased risk (relative risk of 1.17-1.33) of VTE (composite endpoint [DVT or PE]) within the 90-day risk window was observed using both SCCS and comparative cohort designs. The findings of the study are subject to significant caveats and limitations inherent to the model and analysis of an observational healthcare claims dataset.

**2.11** The EWG noted the preliminary assessment of the PRAC Rapporteur who considers that there is sufficient data to conclude that there is a reasonable possibility that the Covid-19 vaccine Janssen is causally related to venous thromboembolism. Regulatory action has been proposed, with updates of the product information and a direct healthcare professional communication (DHPC). This conclusion, and proposed regulatory action, is awaiting PRAC plenary discussion on 30/09/2021.

**2.12** The EWG was presented with the findings of completed MHRA O/E analysis for VTE and arterial embolic events without thrombocytopenia reported within 42 days of vaccination with a COVID vaccine. Analyses were conducted for PE, DVT and VTE (composite endpoint [DVT or PE], myocardial infarction, stroke, and arterial embolic event (composite endpoint [myocardial infarction or stroke]). The EWG noted the limitations of the analysis which include the under-recording of thrombocytopenia in medical records and the point that observed cases have not been validated and medically adjudicated, and therefore observed numbers may be lower if there are misclassified cases or duplicate cases.

**2.13** The MHRA O/E analyses suggested no signal for an overall risk of VTE or arterial embolic events without thrombocytopenia within 42 days following a COVID vaccination. In the age-stratified analyses, a signal of increased risk of PE was raised with the 1st dose of AstraZeneca vaccine in the under 20 years age group and a signal of increased risk of MI with the 2nd dose of AstraZeneca vaccine in the under 20s. It was noted each signal was based on 1 reported case.

**2.14** The EWG then considered the following 3 questions:

**2.14.1 Question 1: Based on the evidence presented does the EWG consider there is an association with the AZ OR Pfizer OR Moderna OR Janssen COVID-19 vaccines and the risk of thromboembolism without concurrent thrombocytopenia?**

The EWG advised that the new data submitted by the MAH for COVID-19 vaccine Janssen is insufficient to reliably support a causal relationship to venous thromboembolism.

The EWG agreed that the MHRA VTE and arterial embolic events O/E analysis presented for the Pfizer, Moderna and AstraZeneca COVID-19 vaccines did not raise a signal of concern with respect to the risk of thromboembolism without concurrent thrombocytopenia.

**2.14.2 Question 2: If an association cannot be confirmed on the current data, what further analysis might be required to assess causality?**

The EWG acknowledged this is a challenging topic to assess and that interpretation of data is not straightforward. The EWG agreed that further research is required to corroborate the findings to date and to investigate potential associations between events of interest and different vaccines as well as how any association behaves when comparing dose 1 against booster doses. If a causal relationship is suspected there is a need to understand the biological mechanisms underpinning such potential risk and for studies to explore and assess causality.

For COVID-19 vaccine Janssen, venous thromboembolism is already an important potential risk in the RMP. Post-authorisation studies listed in the RMP which comprise observational US and EU studies as well as the COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER) could contribute relevant data from 2022 onwards. With respect to the request from EMA/PRAC for a study to characterise the prothrombotic potential of the Janssen vaccine, the MAH is in discussion with the EMA for a separate procedure to explore this point. Such a study may offer insight into any mechanism underpinning a potential association/causation.

The EWG noted that further data is expected with respect to the AstraZeneca vaccine as per the request from EMA/PRAC, i.e. a review of CVST events without thrombocytopenia. Submission within the 7th monthly summary of safety report due October 2021 is anticipated. The review of this data should be presented to the EWG at the next update of this topic. In addition, the MHRA will remain vigilant for other sources of relevant data for the next update including academic/COVID-19 consortium data.

**2.14.3 Question 3: Does the EWG consider there is a need for updates for the PI of the AZ, Pfizer, Moderna or Janssen vaccine?**

The EWG advised no update is required at this time based on the evidence to date.

The EWG noted that the preliminary PRAC Rapporteur assessment of the new data from the MAH for COVID-19 vaccine Janssen has recommended product information updates. This proposal is subject to PRAC plenary discussion on 30/09/2021.

If PRAC agree to proceed with the proposed update, the UK product information is expected to be aligned with the new wording as the COVID-19 vaccine Janssen is approved in the UK via the Reliance Route. The EWG noted that this vaccine has not yet been deployed as part of the UK vaccine program.

**3. Updates on reporting trends for menstrual disorders**

**3.1** The EWG was presented with an update on the currently available evidence regarding menstrual disorders and unexpected vaginal bleeding following vaccination against COVID-19. This included an update on spontaneous reports of menstrual disorders reported via the UK Yellow Card Scheme for the AstraZeneca, Pfizer-BioNTech and Moderna COVID-19 vaccines (with a data lock point of 20 September 2021) as well as an update on ongoing/planned epidemiological studies.

**3.2** The EWG was informed of a transient increase in Yellow Card reporting of menstrual disorders with the three COVID -19 vaccines following an editorial on this topic published in the British Medical Journal (BMJ) on the 16 September 2021, followed by widespread media coverage.

**3.3** The EWG agreed that the increase in Yellow Card reporting was likely to have been stimulated by the BMJ article/media coverage and did not raise any new concerns on this issue. The EWG was also reassured that the increase in reporting was not specific for any individual COVID-19 vaccine.

**3.4** The EWG were informed that the MHRA Clinical Trials Unit was currently considering the collection of information on menstrual changes in clinical trials, particularly in future trials of COVID-19 vaccines. The EWG agreed on the importance of collecting information on menstrual data in clinical trials in general and one approach could be the use of menstrual diaries in future trials.

**3.5** The EWG noted the ongoing work by the MHRA communications team to support positive messaging regarding menstrual disorders following COVID-19 vaccination on social media including on Facebook and Twitter. The Group suggested that hesitancy remained a concern in younger women, related for example to fears such as worsening of already painful periods. Consideration should be given to additional channels such as TikTok to help reach a younger audience.

**3.6** The EWG advised that data on pregnancy outcomes in women who were vaccinated prior to pregnancy would be helpful to reassure public concerns about potential effects on fertility and the Group was reassured that data sources that may capture this data were being explored by the MHRA.

## 4. Seventh update of myocarditis and pericarditis following administration of COVID-19 vaccines

**4.1** The EWG were presented with an update on reports of myocarditis and pericarditis following administration of COVID-19 vaccines. The EWG were informed that for the Pfizer/BioNTech vaccine, the reporting rate has remained similar between the first and second dose in adults. In the under 18-years age group, the reporting rate is higher for the second dose of the Pfizer/BioNTech vaccine compared to the first dose; however, the second dose rate has reduced as usage has increased. For the Moderna vaccine, the reporting rates remain higher after the second dose compared the first dose and are highest in the younger age groups. The reporting rates for the Moderna vaccine remain higher than those for the Pfizer/BioNTech vaccine. The reporting rates for the AstraZeneca vaccine remain lower than those of the mRNA vaccines.

**4.2** The EWG were presented with updated epidemiological analysis which continued to show a strengthening of the signal following the second dose of Pfizer/BioNTech and Moderna vaccines, with a clustering of cases occurring within the first 7 days of vaccine administration. For AstraZeneca the analysis was only signalling at the 25% reporting threshold for under 50 years age group, and at the 10% reporting level for the over 50-years age groups, which shows the signal is not as strong as seen for the mRNA vaccines.

**4.3** The EWG were presented data from Public Health Ontario on the effect of dosing schedules on the reporting rates of myocarditis and pericarditis. The data showed that for both the Pfizer/BioNTech, Moderna and heterologous dose schedules, the second dose reporting rates of myocarditis and pericarditis were lower when a longer duration between the first dose and second dose was used. The EWG considered that this could explain why the UK data has shown similar rates between the first and second dose compared to the US and Israel where shorted dose intervals are used, and the second dose reporting rates are much higher.

**4.4** The EWG were updated on the advice from international regulators on strenuous exercise following vaccination. The EWG noted that while Singapore has increased the time to avoid vaccination from 1 week to 2 weeks, other regulators including the FDA, Health Canada, Medsafe (New Zealand) and HPRA (Ireland) do not have any recommendations and do not consider exercise to be a risk factor. The EWG concluded that the data did not support advice to rest following vaccination for individuals who do not have any symptoms of myocarditis.

**4.5** The EWG discussed the data on dose interval, concluding that the benefit risk for the mRNA vaccines remains unchanged as the UK was already using a longer interval of at least 8 weeks between the first and second vaccine dose. The EWG concluded that no further

regulatory action was required at this time, however the signal of myocarditis and pericarditis should continue to be closely monitored.

## 5. Any Other Business

None.

## 6. Date and time of next meeting

The next scheduled meeting is to take place on **Wednesday 6th October** at **14:30**.

The Meeting today started at 10:30 and ended at 12:03.

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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.

**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.

**Observer**

[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.