

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

Minutes of the meeting held on **Friday 18th February 2022** at **11:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer¹
Professor G Dougan
Mr VI G Fenton-May¹
Professor N French
Professor D Goldblatt
Ms S Hunneyball¹
Professor H J Lachmann¹
Professor P J Lehner
Mr R Lowe
Dr S Misbah
Professor Y Perrie
Professor S Price
Dr A Riordan
Dr R Thorpe
Mrs M Wang¹
Professor C Weir

Apologies

Professor K Hyrich
Sir M Jacobs
Professor C Robertson
Professor T Solomon
Professor K M G Taylor
Professor M Turner
Professor S Walsh

Invited Experts

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

Observers

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

Secretariat

[REDACTED]
[REDACTED]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea – LD
[REDACTED] – VRMM²

Presenters supporting specific items²

[REDACTED] - VRMM
[REDACTED] - VRMM
[REDACTED] - VRMM
[REDACTED] - LD
[REDACTED] - VRMM

MHRA Observers

[REDACTED] - VRMM
[REDACTED] - LD
[REDACTED] - LD
Dr A Cave - Chief Safety Officer
[REDACTED] - MHRA-Policy
[REDACTED] - VRMM
[REDACTED] - VRMM
[REDACTED] - LD
[REDACTED] - VRMM
Mr P Tregunno - VRMM
[REDACTED] – Government Legal Team
[REDACTED] - LD
[REDACTED] - Comms

[REDACTED]

13th April 2022

Key

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

¹ joined during item 2

² supported specific items

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 Hyrich, Solomon, Robertson, Turner, Taylor, Walsh & Sir Michael Jacobs for this meeting.

1.5 The Chair welcomed the following invited experts for their specific items:

[REDACTED]
[REDACTED]
[REDACTED]
Cambridge University Health Partners

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED] Thrombosis UK

[REDACTED]
[REDACTED]
[REDACTED]
Oxford University Hospitals NHS FT

[REDACTED]
[REDACTED]
[REDACTED] Bristol Heart Institute

1.6 The Chair welcomed the following observers to the meeting:

[REDACTED]
[REDACTED]
Public Health Scotland

[REDACTED] Public Health Wales

NHS England [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED]
UKHSA

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

2. Valneva Vaccine

2.1 [REDACTED]
[REDACTED]
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[REDACTED]

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[REDACTED]
[REDACTED]
[REDACTED]

2.2 [REDACTED]
[REDACTED]
[REDACTED]

2.3 [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED]
[REDACTED]

2.4 Valneva vaccine – Risk Management Plan

2.4.1 [Redacted]

2.4.2 [Redacted]

2.4.3 [Redacted]

2.4.4 [Redacted]

2.4.5 [Redacted]

2.4.6 [Redacted]

2.4.7 [Redacted]

2.4.8 [Redacted]

3. **Thromboembolic events with concurrent thrombocytopenia following administration of mRNA COVID-19 vaccines**

3.1 The EWG were presented with a review of thromboembolic events with concurrent thrombocytopenia following administration of the Pfizer/BioNTech and Moderna vaccines. The EWG were reminded that previous reviews found that thromboembolic events with concurrent thrombocytopenia was associated with the AstraZeneca vaccine, but a signal had not been identified for the mRNA vaccines. The EWG noted that up to DLP 02/0202022, there had been a total of 437 UK cases classified as confirmed, probable or possible for the AstraZeneca vaccine.

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- 3.2** The EWG were presented an overview of UK cases from the Yellow Card scheme. For the Pfizer/BioNTech vaccine, with a total of 31 cases classified as confirmed, probable or possible with 4 cases having a fatal outcome. The EWG noted that the majority of thrombosis events were non-cerebral venous sinus thrombosis (CVST) events. For the Moderna vaccine, there were a total of 4 cases classified as probable or possible and no cases having a fatal outcome. The EWG noted that none of the cases were CVST events.
- 3.3** The EWG were presented with company data from both Pfizer/BioNTech and Moderna. Reports of thromboembolic events with concurrent thrombocytopenia were assessed against the Brighton Collaboration criteria (BCC), with 161 Pfizer/BioNTech and 10 Moderna cases meeting the “Definite” criteria, however the BCC criteria do not require positive anti-PF4 antibodies (which are required for “confirmed” cases in MHRA case definition). Only 9 Pfizer/BioNTech cases and 1 Moderna case identified positive anti-PF4 antibodies. Observed vs Expected analysis from both companies did not raise a signal for thromboembolic events with concurrent thrombocytopenia.
- 3.4** The EWG considered that there was a difference between background events of thrombosis with concurrent thrombocytopenia and events of vaccine-induced immune thrombotic thrombocytopenia (VITT), which is characterised by the presence of anti-PF4 antibodies. The EWG considered that the cases identified in the UK Yellow Card scheme and company data did not suggest a causal association between the Pfizer/BioNTech and Moderna vaccines and thromboembolic events with concurrent thrombocytopenia, as the majority of cases were negative for anti-PF4 antibodies.
- 3.5** The EWG were presented with an observational study following Vaccine Induced Immune Thrombocytopenia and Thrombosis (VITT) for changes in reactivity of platelet-activating anti-platelet factor 4 IgG antibodies, which found that patients that went on to have mRNA COVID-19 vaccine as a second dose did not experience new thromboses.
- 3.6** The EWG concluded that the available data do not suggest an association between thromboembolic events with concurrent thrombocytopenia and either the Pfizer/BioNTech or Moderna COVID-19 vaccines. The EWG agreed that routine monitoring of thromboembolic events with concurrent thrombocytopenia can be undertaken for the mRNA COVID-19 vaccines.
- 4. CVST with Pfizer and Moderna COVID-19 vaccines**
- 4.1** The EWG was updated with new information received since the previous update presented on 19 November 2021. The new information concerns cerebral venous sinus thrombosis (CVST) events (without thrombocytopenia) following mRNA COVID-19 vaccine exposure.
- 4.2** The trigger for this update was a recent publication from the Health Sciences Authority (HSA) which is the medicines regulator for Singapore. In a safety update published on 19 January 2022, the HSA summarised the findings of its observed versus expected (O:E) analysis and self-controlled case series (SCCS) for CVST events and mRNA COVID-19 vaccines (Pfizer and Moderna). The HSA identified a small increase in incidence of CVST with mRNA COVID-19 vaccines in their O:E analysis (about 1 additional case of CVST per million doses). The SCCS analysis showed a statistically significant increased risk overall, but lower than that with COVID infection itself. However, to date, the HSA had not undertaken any regulatory action.
- 4.3** The EWG was presented with a review of relevant data sources including UK vaccine usage data, clinical trial data, post-authorisation information in the form of Yellow Cards and monthly

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safety reports from the Marketing Authorisation Holders, literature, data from other regulators and MHRA O:E analyses of Yellow Card data.

- 4.4** The EWG noted that the review of clinical trial and post-authorisation data had not raised a signal of concern. Almost half of the Yellow Card reports exhibited confounding factors.
- 4.5** The EWG acknowledged that current literature evidence is insufficient to establish a clear causal relationship. Case reports add to evidence of a potential association between mRNA Covid-19 vaccine and CVST events without concurrent thrombocytopenia, however findings are not replicated across larger studies or populations to consistently implicate specific vaccines to the event of interest (CVST) and/or to increased risk in specific age/gender/dosing groups. Limitations in identifying whether thrombocytopenia was present or not alongside the potential for residual confounding/unmeasured variables to impact the findings must be taken into account.
- 4.6** The EWG noted that MHRA epidemiological analysis does not suggest a signal for an overall risk within 7 days or 42 days following any dose of the Pfizer or Moderna vaccine. The EWG noted that O/E analyses for CVST without thrombocytopenia are very sensitive to the choice of background rate.
- 4.7** The EWG noted that the O/E and SCCS analyses from the HSA do demonstrate an imbalance in the event of interest, however they should be interpreted with caution owing to limitations in identifying whether thrombocytopenia was present or not, the inclusion of secondary CVST diagnoses and the lack of a data breakdown by specific vaccine or dosing. Other regulators (TGA and AEMPS) have not raised a signal based on their own O/E analyses.
- 4.8** The EWG was informed that further research is required to corroborate the findings to date and to demonstrate consistent associations between the event of interest and different vaccines as well as how any association behaves when comparing dose 1, dose 2 and booster doses. It was concluded there is a need to understand the biological mechanisms underpinning any association and for studies to explore and assess causality.
- 4.9** The EWG commented that the current product information for the AstraZeneca COVID-19 vaccine lists CVST as a recognised adverse drug reaction (ADR). The current product information for the Janssen COVID-19 vaccine lists venous thromboembolism as a recognised ADR. Previous data reviews have not established a clear signal of concern for the mRNA COVID-19 vaccines with any thromboembolic event without thrombocytopenia.
- 4.10** The EWG then considered the following 3 questions:
- 4.10.1 Question 1: Based on the evidence presented does the EWG agree that an association with the mRNA COVID-19 vaccines and the risk of CVST without concurrent thrombocytopenia has not been established?**
- The EWG agreed that an association with the mRNA COVID-19 vaccines and the risk of CVST without concurrent thrombocytopenia has not been established.
- 4.10.2 Question 2: Does the EWG agree that no regulatory action is currently warranted?**
- The EWG agreed that no regulatory action is currently required.
- 4.10.3 Question 3: Does the EWG agree that the benefit:risk for mRNA COVID-19 vaccines remains unchanged based on the evidence presented?**

The EWG agreed that the benefit:risk for mRNA COVID-19 vaccines remains unchanged based on the evidence presented.

5. Update of myocarditis and pericarditis following administration of Pfizer/BioNTech, Moderna and AstraZeneca COVID-19 vaccines

5.1 The EWG were presented with an update on the Yellow Card reports for myocarditis and pericarditis with the three COVID-19 vaccines in use in the UK vaccination programme as well as new international data and literature.

5.2 The EWG noted that the reporting rates seen following third/booster doses for Pfizer/BioNTech and Moderna were lower than those seen for the primary dose schedule of the vaccines and that the rates were similar for both vaccines. The EWG were reassured by the lower reporting rates and considered that it would be useful to understand what factors may have resulted in the lower rates, such as potentially the half-dose for the Moderna booster and the different intervals between booster and primary series doses. For AstraZeneca, the reporting rates for first and second doses have remained similar to previous reviews and overall were lower than both of the mRNA vaccines.

5.3 The EWG were presented with long-term follow-up myocarditis and pericarditis reports to the Yellow Card scheme. The EWG heard that the majority of patients had recovered or were recovering from myocarditis and pericarditis at 3 months post-diagnosis and that patients who had further diagnostic tests including cardiac MRI and ECG were not showing long-term complications associated with severe outcomes from myocarditis and pericarditis. Updated long-term follow-up from the US CDC also continued to show that the majority of patients recovered with no signs of serious long-term harm. The EWG were reassured by the follow-up data but agreed that this should continue to be monitored.

5.4 The EWG were presented with data from the US CDC review of the Moderna vaccine, following the FDA's approval of the full biologics licence application (BLA), covering clinical trial data, vaccine safety datalink (VSA) analysis and benefit/risk analysis. While it was noted that the VSD rapid cycle analysis and head-to-head analysis of Moderna vs Pfizer/BioNTech suggest the risk of myocarditis was higher for the Moderna vaccine, the benefit/risk analysis found that the Moderna vaccine prevented more hospitalisations from COVID-19 infection per million doses than the Pfizer/BioNTech vaccine. The EWG were reassured by the benefit/risk analysis which showed that the benefits of the Pfizer/BioNTech and Moderna vaccines far outweighed the risk of myocarditis.

5.5 The EWG were presented with late-breaking information on a pre-print publication regarding two fatal cardiomyopathy reports from the US. The EWG noted there were some limitations in the detail of the reports. The EWG considered that cardiac histopathology is a very specialised area and with the pre-print stating that the cardiac conduction system was not looked at, this suggested this might not be an expert histopathological review. It was suggested that further data on these cases were sought from FDA and the authors.

5.6 The EWG concluded that the benefits continued to exceed the risks overall for all vaccines and for all authorised subpopulations. No regulatory action was required based on the data presented.

6. Any Other Business

None.

7. Date and time of next meeting

The next meeting has been scheduled for **Friday 4th March 2022** at **14:30**.

The Meeting today started at 11:32 and ended at 13:50.

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

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 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. 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).

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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.

Observer

■ ■■■■■ – 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.