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

Minutes of the Ad Hoc meeting held on **Monday 28th June 2021** at **18:15** via videoconference

Participants Present

Members

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

Apologies

Professor T Solomon
Dr R Thorpe
Professor C Weir

Observers

[redacted]

Secretariat

[redacted]

[1] Joined during Item 3

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted] - VRMM

Presenters supporting specific items

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

MHRA Observers

[redacted] - VRMM
[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
Dr S Branch - VRMM
[redacted] - VRMM
[redacted] – MHRA Policy
[redacted] - Comms
[redacted] - VRMM
[redacted] - VRMM
[redacted] – VRMM
[redacted] - LD
Ds N Rose - NIBSC
[redacted] – LD
[redacted] - VRMM

[redacted]

4th February 2022

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

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 The Chair welcomed the following observers:

[redacted]
[redacted]Public Health England

[redacted]
[redacted] JCVI

[redacted]
[redacted]
Public Health Agency

Professor Wei Shen Lim
Chair of JCVI

[redacted]
NHS England [redacted]

[redacted]
Public Health England

[redacted]
[redacted] Public Health Wales

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

1.5 Apologies were received from Professors Solomon, Weir and Dr Thorpe for this meeting.

2. Update on COVID-19 Vaccines and risk of thromboembolic events with concurrent thrombocytopenia

2.1 The EWG was presented with the latest data on thromboembolic events with thrombocytopenia associated with the authorised COVID-19 Vaccines up to a data lock point of 23 June 2021.

2.2 The EWG noted there were no new significant publications of interest identified since the last update. An active link has now been identified for the proposed International Society on Thrombosis and Haemostasis (ISTH) registry seeking to gather clinically relevant information for patients with suspected COVID vaccine related thrombosis and/or thrombocytopenia. Reports arising from this registry are anticipated at regular intervals.

2.3 The EWG was presented with an overview of the UK case reports associated with the AstraZeneca (AZ) COVID-19 Vaccine. This included the total number of UK cases classified as confirmed, probable or possible (395 cases) as well as summary tables of the 34 reported confirmed, probable and possible UK cases occurring after a second dose.

2.4 The EWG was updated that there have been no new cases concerning patients aged <40 years old who received the AstraZeneca vaccine after the Joint Committee on Vaccination and Immunisation updates on 07 April 2021 (use in <30 years old) and 07 May 2021 (use in <40 years old).

2.5 Data from the weekly COVID-19 safety report published by the Therapeutic Goods Administration (TGA) was summarised for the EWG. Up to 20 June 2021 the TGA reported 64 thrombotic thrombocytopenia cases attributed to AstraZeneca COVID-19 vaccine exposure in Australia. This is a rise from the previously reported 60 cases up to 13 June 2021. The EWG was informed that the TGA report also outlines an updated recommendation from the Australian Technical Advisory Group on Immunisation (ATAGI) dated 17 June 2021. The updated recommendation advises the preferred use of Pfizer-BioNTech Comirnaty vaccine over the AstraZeneca vaccine for those aged 16–60 years old. This is a change in the previous advice which applied to those aged 16–50 years old.

2.6 The UK and foreign cases associated with the Pfizer, Moderna and Janssen COVID-19 vaccines were summarised using the same case definition. The EWG were presented with company data from Janssen which summarised 26 non-UK cases, 2 of which were confirmed cases.

2.7 The estimated number of second AstraZeneca COVID-19 vaccine doses administered has increased to 20.7 million whilst the number of first doses has not changed since the last DLP. Estimated case incidence rates for CVST and CVST plus other thromboembolic events were presented by age-stratified 10-year intervals and by gender. The overall incidence rate of CVST plus other TE has increased slightly to 14.7 (13.2, 16.3) per million for first/unknown doses and to 2.7 (2.0, 3.4) per million first/unknown doses for overall fatal incidence rate. The age-stratified incidence rates associated with second doses were presented and the overall rate remained stable at 1.6 (1.1, 2.3) per million doses. One new fatal case following a 2nd dose have been reported up to the data lock point of 23 June 2021. The case incidence rates per 100,000 patient years following 28 days post-vaccination were also compared for first and second doses. The case incidence rates (per 100,000 patient years) were 15.3 (13.6, 17.2) for the first or unknown doses and 1.5 (0.9, 2.3) for the second doses. The risk estimates were then compared with the expected benefits of vaccine in age subgroups. The

reported incidence rates showed no increase since last data lock point with overlapping 95% confidence intervals, while risk-benefit ratio remained relatively unchanged.

2.8 The EWG then considered the following 3 questions:

2.8.1 Question 1: based on the evidence presented does the EWG consider the benefit-risk balance remains favourable for all patients and for all age groups?

The EWG advised that the overall benefit-risk profile of the AstraZeneca COVID-19 Vaccine remains positive although depending on the status of the COVID-19 pandemic, its severity and impact on hospitalisation, the benefits of immunisation in individuals aged under 40 years are probably outweighed by the potential risks. The benefit-risk assessment has not changed since it was last reviewed on 21st June 2021.

2.8.2 Question 2: Does the EWG consider there might be an increased risk for the second dose of the vaccine?

The EWG advised that the emerging data on the risk of thromboembolic events occurring with thrombocytopenia following second doses remains reassuring. The EWG noted the planned circulation of updated operational guidance from NHS Improvement and NHS England which reinforces that the use of AstraZeneca COVID-19 vaccine in those aged less than 40 years old should only be where there is an appropriate and detailed clinical justification. The MHRA should continue to monitor second dose cases closely, particularly as younger patients continue to receive their second doses.

2.8.3 Question 3: Does the EWG consider there is any need for action with regards to the Pfizer, Moderna or Janssen vaccines in relation to this potential risk?

Based on available data, the risk associated with the Pfizer and Moderna COVID-19 vaccines appears lower than that associated with the AstraZeneca COVID-19 Vaccine. This risk should be monitored and there is no need for regulatory action. Events associated with other COVID-19 vaccines should continue to be closely monitored.

3. Update on Menstrual Disorders with COVID-19 Vaccines

3.1 The EWG was presented with an update on spontaneous reports of menstrual disorders, postmenopausal haemorrhage and/or vaginal/uterine haemorrhage reported via the UK Yellow Card Scheme for the AstraZeneca, Pfizer-BioNTech and Moderna COVID-19 vaccines with a data lock point of 23 June 2021.

3.2 The EWG heard that there had been a large increase in the number of spontaneous reports of menstrual disorders received for all three COVID-19 vaccines currently deployed in the UK since the EWG had previously considered this issue, with a data lock point of 17 May 2021, at its meeting on 4 June 2021. The EWG noted that the increase in the number of reports corresponded with media reports of menstrual disorders following COVID-19 vaccination which suggested possible stimulated reporting.

3.3 The EWG noted that, in line with the previous review, a range of menstrual disorders continue to be reported for all three vaccines; however the peak age of reporting of menstrual disorders had decreased for the Pfizer and Moderna COVID-19 vaccines in parallel with the rollout of these vaccines to younger women.

3.4 The EWG agreed that it was difficult to disentangle possible vaccine-related adverse reactions and background events of commonly occurring menstrual disorders using

spontaneous reporting data. The EWG acknowledged that while a causal relationship with COVID-19 vaccines had not been established, menstrual changes following vaccination may cause anxiety in some women, including concerns about possible pregnancy and/or future fertility. The EWG agreed that given the lack of any proven causal association, it was important that anyone presenting with menstrual disorders and/or unexpected vaginal bleeding following COVID-19 vaccination should continue to be investigated in line with clinical guidance as usual.

3.5 The EWG advised that no regulatory action was required based on the currently available data; however, reports of menstrual disorders, postmenopausal haemorrhage and/or vaginal/uterine haemorrhage with the AstraZeneca, Pfizer-BioNTech and Moderna COVID-19 vaccines should continue to be kept under close review. Specifically, the EWG advised that the number of reports of menstrual disorders received with COVID-19 vaccines should be monitored to see if the trend in increased reporting seen after the recent media coverage continues or whether the number of reports falls back to previously observed levels of reporting. This will enable the EWG to obtain a clearer picture of the level and age distribution of reporting of menstrual disorders in association with COVID-19 vaccines as more young adults are vaccinated with Pfizer and Moderna COVID-19 vaccines, particularly since the background rate of reporting of menstrual disorders is age dependent. The EWG requested that this issue should be brought back to an EWG meeting in two weeks' time and that experts from the Medicines for Women's Health Expert Advisory Group should be invited to the meeting to inform the discussion. Pending this further review, the EWG recommended that the information on menstrual disorders in the MHRA coronavirus weekly summary of Yellow Card reporting and COVID-19 vaccines should state that the MHRA continues to receive reports of menstrual disorders with COVID-19 vaccines and these reports are being closely monitored by the MHRA under the advice of the EWG.

3.6 The EWG supported the planned MHRA review of Clinical Practice Research Datalink (CPRD) data to try and determine background rates of reporting of menstrual disorders, particularly in younger women, while acknowledging that many women manage menstrual changes themselves rather than seeking advice from healthcare professionals and such cases would not be captured in any CPRD analysis.

4. Any Other Business

None.

5. Date and time of next meeting

The next scheduled meeting is to take place on **Monday 5th July 2021** at **10:30am**.

The Meeting today started at 18:17 and ended at 19:09.

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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.

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.

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 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.

Observers

[redacted] University of Oxford employee (with no involvement in research or clinical trials related to Oxford AZ vaccine)
[redacted]

Professor 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] - Other relevant interest in Pfizer & GSK- arising from 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.