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

Minutes of the meeting held on **Thursday 19th August 2021** at **10:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan[1]
Mr VI G Fenton-May
Ms S Hunneyball
Professor P J Lehner[2]
Mr R Lowe
Dr S Misbah
Professor Y Perrie
Professor S Price
Dr A Riordan
Professor C Robertson[3]
Professor K M G Taylor
Dr R Thorpe[4]
Professor M Turner[4]
Professor S Walsh
Mrs M Wang
Professor C Weir

Apologies

Professor N French
Professor D Goldblatt
Professor K Hyrich
Sir M Jacobs
Professor H J Lachmann
Professor T Solomon

Observers

[redacted][5]

Secretariat

[redacted]

[1] left during item 4
[2] joined during item 2
[3] left during item 6
[4] left during item 5
[5] Joined during item 5

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

MHRA Observers

[redacted] - VRMM
[redacted] - VRMM
[redacted] - Comms
[redacted] - VRMM
[redacted] - VRMM
[redacted] – VRMM
[redacted] - LD
[redacted] - VRMM
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[redacted] – VRMM
[redacted] - VRMM

[redacted]

25th August 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 Apologies were received from Professors French, Goldblatt, Hyrich, Lachmann, Solomon and Sir Michael Jacobs for this meeting.

1.5 The Chair welcomed the following observers:

[redacted]
Public Health Agency

[redacted]
Public Health Scotland

[redacted]
NHS England and NHS Improvement (National)

2. Review of COVID-19 Vaccines and the risk of thromboembolic events without thrombocytopenia

2.1 The EWG was presented with available data of thrombotic events without concurrent thrombocytopenia following administration of the COVID-19 vaccines.

2.2 The EWG was updated that recent publications of observational studies report increased rates of thrombosis in vaccinated cohorts. The EWG noted that thrombosis with thrombocytopenia syndrome (TTS) cases are subject to separate on-going regular reviews since March 2021 and that this review would therefore not focus on TTS data.

2.3 The publications presented to the EWG include those characterising background rates of thrombosis in populations prior to the coronavirus pandemic, those characterising rates of thrombosis in a COVID-19 cohort and those comparing thrombosis rates between the general population, Covid-19 cohort and/or vaccinated cohorts.

2.4 The EWG was also presented with a review of other data sources including UK vaccine usage data, post-authorisation information in the form of Yellow Cards and monthly safety reports from the Marketing Authorisation holders, position of other regulators and internal epidemiological analysis.

2.5 The EWG noted that the review of the post-authorisation data and MHRA epidemiological analyses (ecological and rapid cycle analyses) had not raised a signal of concern.

2.6 The EWG noted the challenges faced by researchers investigating this topic via observational studies. These include the substantial heterogeneity between databases, validation of clinical diagnoses, the need to account for confounding factors and the requirement for different methodologies to help triangulate potential signals of interest.

2.7 The EWG noted that the underlying mechanisms underpinning TTS could be of relevance because there are important gaps in knowledge concerning the presentation/spectrum of that disorder i.e. the possibility of a proportion of patients who present with thrombosis with normal platelets in comparison to those who present with low platelets but no evidence of thrombosis. The underlying mechanisms of TTS are subject to ongoing research which may inform our understanding of thrombosis cases without thrombocytopenia occurring after Covid-19 vaccination.

2.8 The EWG emphasised the available evidence suggests there is a clinically substantial risk of thrombosis following Covid-19 infection. This should be taken into consideration when assessing the relative risk of any such events in recipients of a Covid-19 vaccine and the impact on the benefit-risk of Covid-19 vaccination.

2.9 The EWG then considered the following 2 questions:

2.9.1 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 whilst the observational studies provide evidence of potential association between Covid-19 vaccination and thromboembolic events, the findings are not replicated across studies/populations to consistently implicate specific vaccines to events of interest (DVT, PE, MI, Stroke, CVST) and/or to increased risk in specific age/gender groups. The potential for residual confounding/unmeasured variables to impact the findings must also be taken into account.

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

The EWG highlighted the absence of a recording of thrombocytopenia in the health care records used for these studies cannot be used as a reliable exclusionary criterion to confirm the platelets were normal. Studies would need access to haematological results to confirm normal platelet counts in relevant thromboembolic cases before conclusions can be drawn on whether there are increased thromboembolic events with normal platelet counts after Covid-19 vaccination.

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. There is also a need to understand the biological mechanisms underpinning such potential risk and for studies to explore and assess causality.

The EWG requested that this topic be brought back for further discussion once the MHRA has completed additional epidemiological analyses currently in progress.

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

3.1 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 11 August 2021.

3.2 The last presentation of thromboembolic events with thrombocytopenia data to the EWG took place on 19 July 2021 (DLP 14/07/2021). On 23 July 2021 the EWG accepted a proposal to cease the weekly updates and requested an update in 4 weeks' time.

3.3 The EWG was presented with a list of publications of interest identified since the last presentation on 19 July 2021. Summaries were provided for two publications of particular interest. The first summary outlined a prospective cohort study involving patients with suspected Vaccine Induced Immune Thrombocytopenia and Thrombosis (VITT) who presented to hospitals in the United Kingdom between 22 March and 06 June 2021. On review the study offers insight into the patient demographic, clinical presentation and potential for coagulation markers as prognostic markers. The second summary outlined an observational study assessing the reporting rate of cerebral vein thrombosis (CVT) based on Eudravigilance data for all four Covid-19 vaccines authorised in Europe. The authors report an increased rate of CVT with all vaccines, however the study is subject to the limitations of an observational model, the potential impact of residual confounding and the inability to stratify rates by age/country.

3.4 The EWG was presented with a summary of a report submitted by AstraZeneca concerning a phase III randomised clinical trial sub-study assessing the presence of anti-PF4 antibodies before and after vaccination with AZD1222 in comparison to placebo (Study D8110C00001). Analysis of the samples showed no apparent difference in changes of anti-PF4 levels following AZ vaccine compared to placebo in the studied population.

3.5 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 (412 cases) as well as summary tables of the 43 reported confirmed, probable and possible UK cases occurring after a second dose.

3.6 The EWG noted 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).

3.7 Data from the weekly COVID-19 safety report published by the Therapeutic Goods Administration (TGA) was summarised for the EWG. Up to 08 August 2021 the TGA reported 104 thrombotic thrombocytopenia cases attributed to AstraZeneca COVID-19 vaccine exposure in Australia. This is a rise from the data previously presented to the EWG (83 cases up to 11 July 2021).

3.8 The UK and foreign cases associated with the Pfizer, Moderna and Janssen COVID-19 vaccines were summarised using the same case definition. There was no change in the Pfizer data since the last presentation (DLP 14/07/2021). For Moderna, the details of the first 2 UK reports were presented to the EWG. For Janssen, 10 new non-UK cases were summarised. Data from the US Centres for Disease Control and Prevention (CDC) on Moderna and Janssen were summarised.

3.9 As of 11th August, a total of 24.7 million first doses and 23.9 million second doses of AstraZeneca COVID-19 vaccine had been administered. The number of second doses administered increased by 1 million whilst the number of first doses increased by 88,000 since the last DLP presented to the EWG. 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 remained relatively similar at 14.9 (13.4, 16.5) per million for first/unknown doses and at 2.7 (2.1,3.4) 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 decreased to 1.8 (1.3, 2.4) per million doses. 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 rate (per 100,000 patient years) remained at 15.4 (13.7, 17.3) for the first or unknown doses while decreased to 1.4 (0.9, 2.0) for the second doses.

3.10 The EWG then considered the following 3 questions:

3.10.1 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 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 19th July 2019.

3.10.2 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 MHRA should continue to monitor second dose cases closely, particularly as younger patients continue to receive their second dose immunisations.

3.10.3 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 currently for regulatory action. Events associated with other COVID-19 vaccines should continue to be closely monitored.

3.11 The EWG agreed that the group should receive updates for TTS data on an ad-hoc basis.

4. COVID-19 vaccines and Myo/pericarditis update

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, there had been an increase in reporting rate across all age groups following the first dose, and a decrease in reporting rates for the 18-39-year age group following second dose. Reporting rates for the Pfizer/BioNTech vaccine are now similar following first and second dose. For the Moderna vaccine, there was an increase in the reporting rate following the first dose. For the second dose the reporting rates have decreased but continue to be based on limited exposure. For the AstraZeneca vaccine the reporting rates remained lower compared to 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, there is a signal at the 25% reporting threshold for under 50 years age group, which shows the signal is not as strong as seen for the mRNA vaccines. The EWG were also presented with updated rapid cycle analysis, which had previously showed a potential signal for the AstraZeneca vaccine but in the latest analysis the signal had diminished below the threshold. For the Pfizer/BioNTech vaccine, a signal was raised for the first dose of myocarditis and pericarditis combined, and individually, and for the second dose for myocarditis and pericarditis combined.

4.3 The EWG were presented with international data from the US, which continue to show the majority of reports of myocarditis and pericarditis have occurred in younger males after the second dose of mRNA vaccines, with onset time within 7 days. The vaccine safety datalink (VSD) rapid cycle analysis showed a higher than expected number of reports for both the Pfizer/BioNTech and Moderna vaccine in the 18 to 39-year age group. The VSD also showed an increased risk of myocarditis in the 12-to-17-year age group but there was no suggestion of higher severity compared to older age groups. A head-to-head analysis between Pfizer/BioNTech and Moderna also found rates of myocarditis were significantly higher for the Moderna vaccine.

4.4 The EWG considered that the signal of myocarditis and pericarditis was continuing to strengthen for the Pfizer/BioNTech and Moderna vaccines, while the available evidence did not suggest a signal for the AstraZeneca vaccine. The EWG noted that vaccination of 16- and 17-year-olds had started and reports of myocarditis and pericarditis in this age group should be closely monitored. The EWG considered that while the clinical course of myocarditis and pericarditis appears to be mild, further data should be collected on long-term outcomes. The EWG concluded that no further regulatory action was required at this time as the benefit:risk balance for the COVID-19 vaccines remained unchanged.

5. COVID-19 vaccination & breastfeeding update (slides)

5.1 The Group noted that more than 3000 Yellow Card reports have been received from breastfeeding women up to 15 h August 2021, including 1299 and 1454 reports for the Pfizer-BioNTech and Oxford-AZ vaccines respectively.

5.2 The Group noted that the pattern of reports was similar to that seen when these were last reviewed in April 2021, with more than 90% of reports relating to suspected reactions in the breastfeeding women themselves, with no effects reported on their milk supply or on their breastfed children.

5.3 A small number of reports reported decreases in milk supply (less than 2%) or possible reactions in the breastfed child (less than 10%). The symptoms reported for the children (high temperature, rash, diarrhoea, vomiting, and general irritability) are common conditions in children of this age, and so some of the effects reported may have occurred by coincidence.

5.4 The Group considered that many factors can affect milk supply and infant behaviour, including general maternal health, amount of sleep, and anxiety. The Group concluded that overall, the reports provide reassurance that receipt of COVID-19 vaccines during breastfeeding does not cause harm to breastfed children or the ability to breastfeed.

5.5 The Group endorsed informing women of the reassuring data and of reminding women to be aware of how to maintain breast milk supply and to consider having help on hand for their childcare.

6. Second update on the Safety Data for COVID-19 vaccine Moderna

6.1 The EWG was presented with the second safety update for the Moderna COVID-19 vaccine, which covered the first four months following deployment in the UK, with a data lock point of 4th August 2021.

The EWG was informed that the ADRs reported were broadly in line with the known safety profile for the vaccine and what had been seen in clinical trials. The EWG were informed that a large proportion of the Yellow Cards reported for the Moderna vaccine continued to relate to delayed injection site reactions. The EWG was informed that the variation to include these delayed injection site reactions had been submitted and the product information would be updated soon. The EWG heard that the review of the dizziness signal had been completed by the Marketing Authorisation Holder (MAH) and the product information would be updated to include this as an adverse event.

6.2 The EWG were presented with an overview of reviewed signals for Moderna including myo/pericarditis, thrombotic thrombocytopenia syndrome and menstrual disorders. The EWG was informed that these would continue to be monitored by the MHRA.

6.3 The EWG were informed that the MAH had been requested to review the signal of serious eye disorders, erythema multiforme, glomerulonephritis and nephrotic syndrome. An update on these will be presented to the EWG in a future meeting following the MAH review.

6.4 The EWG were presented with an update on the interim post-authorisation safety study (PASS) report. The EWG was informed that for the US pharmacovigilance study providing additional evaluation of adverse events of special interest (AESI), the estimation of pre-COVID background incidence rates had been completed. For the observational pregnancy outcome study, the EWG were informed that the sample size had been increased to 1000 women and that patient recruitment had begun.

6.5 The EWG concluded that based on the data presented, the safety profile for COVID-19 vaccine Moderna was broadly in line with the expected safety profile from clinical trials. The EWG supported the proposed reviews into serious eye disorders, erythema multiforme, glomerulonephritis and nephrotic syndrome.

7. COVID-19 vaccine PV strategy update & Yellow Card Vaccine Monitor Update

The EWG were presented with an overview of the demographics for people registered with the Yellow Card Vaccine Monitor. Comparisons were made with spontaneous Yellow Card data which shows similar data. The data have been helpful in supporting signal assessment for COVID-19 vaccines. The technology has been successfully used to tailor questions and schedule follow-up. Through the SafetyConnect work, this functionality will be expanded across all products and the focus of this will be discussed at the Pharmacovigilance Expert Advisory Group.

8. Any Other Business

None.

9. Date and time of next meeting

The next scheduled meeting is to take place on **Thursday 31st August** at **11:30**.

The Meeting today started at 10:35 and ended at 13:09.

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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).

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 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).

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

[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.