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

Minutes of the meeting held on **Monday 5th July 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
Professor D Goldblatt[2]
Ms S Hunneyball
Professor K Hyrich[2]
Professor H J Lachmann
Professor P J Lehner
Dr S Misbah
Professor Y Perrie
Professor S Price
Dr A Riordan
Professor C Robertson[1]
Professor T Solomon
Dr R Thorpe[3]
Professor M Turner
Dr S Walsh
Mrs M Wang
Professor C Weir

Apologies

Professor N French
Sir M Jacobs
Mr R Lowe
Professor K M G Taylor

Observers

[redacted]

Secretariat

[redacted]

[1] joined during item 3

[2] left during item 7

[3] joined during item 2

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] - LD
[redacted] - VRMM
[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
Dr S Branch - VRMM
[redacted] - VRMM
[redacted] – MHRA Policy
[redacted] - VRMM
[redacted] - Comms
[redacted] - LD
Mr P Tregunno - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - LD

[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, Taylor, Sir Michael Jacobs and Mr Robert Lowe for this meeting.

1.5 The Chair welcomed the following observers:

[redacted] JCVI

[redacted]
Public Health Agency

[redacted]
NHS England [redacted]

[redacted]
Public Health Scotland

[redacted]
Public Health England

[redacted] Public Health Wales

[redacted]
NHS England and NHS Improvement (National)

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 30 June 2021.

2.2 The EWG was presented with a summary of a publication of interest – a case report from the [redacted] concerning a patient who received their 2nd dose of the Moderna vaccine before experiencing a fatal thrombotic thrombocytopenia event. The EWG agreed that the case reiterated the need for continued vigilance across all vaccine types as well as after 1st and 2nd doses.

2.3 The EWG cited another publication of interest published after the data lock point for this update.[1] This was a multi-national, multi-centre, retrospective, descriptive analysis of the frequency of thrombocytopenia and platelet factor 4/heparin antibodies in patients with cerebral venous sinus thrombosis prior to the COVID-19 pandemic. The EWG highlighted the key message that of the 865 patients analysed, baseline thrombocytopenia was observed in 8.4% (n=73), and heparin-induced thrombocytopenia was diagnosed in 0.1% (n=1).

2.4 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 (399 cases) as well as summary tables of the 36 reported confirmed, probable and possible UK cases occurring after a second dose.

2.5 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).

2.6 Data from the weekly COVID-19 safety report published by the Therapeutic Goods Administration (TGA) was summarised for the EWG. Up to 27 June 2021 the TGA reported 69 thrombotic thrombocytopenia cases attributed to AstraZeneca COVID-19 vaccine exposure in Australia. This is a rise from the previously reported 64 cases up to 20 June 2021.

2.7 The UK and foreign cases associated with the Pfizer, Moderna and Janssen COVID-19 vaccines were summarised using the same case definition. The UK data were unchanged since the last EWG meeting and additional non-UK cases were presented for the Pfizer (n=4 possible), Moderna (n=3 possible) and Janssen (n=6, 1 confirmed, 5 possible) vaccines.

2.8 The estimated number of second AstraZeneca COVID-19 vaccine doses administered has increased to 21.5 million whilst the number of first doses has increased by 100,000 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 14.8 (13.3, 16.3) per million for first/unknown doses and to 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 increased to 1.7 (1.2, 2.3) per million doses. No new fatal cases following a 2nd dose have been reported up to the data lock point of 30 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)

[1] Sánchez van Kammen M, Heldner MR, Brodard J, et al. Frequency of Thrombocytopenia and Platelet Factor 4/Heparin Antibodies in Patients With Cerebral Venous Sinus Thrombosis Prior to the COVID-19 Pandemic. JAMA. Published online July 02, 2021. doi:10.1001/jama.2021.9889

were 15.5 (13.8, 17.4) for the first or unknown doses and 1.5 (0.9, 2.2) 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. Finally, a question on update of benefit-risk analysis was raised. The Group was informed that this will be considered for the next EWG presentation of thrombo-embolic events with thrombocytopenia.

2.9 The EWG then considered the following 3 questions:

2.9.1 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, 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 28th June 2021.

2.9.2 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 that NHS England has now circulated updated operational guidance on the use of the AstraZeneca vaccine under the age of 40 years. The guidance reiterates that those under the age of 40 years who are yet to have their first dose should be preferentially offered the Pfizer BioNTech or Moderna vaccines, unless there is a clinical reason that precludes the use of either of these alternative vaccines. e.g. PEG allergy. In addition, if there is a clinical reason for a person under 40 years to receive vaccination with AstraZeneca, informed consent following a discussion about risks and benefits to the individual must be obtained by the Senior Clinical Lead on duty. The MHRA should continue to monitor second dose cases closely, particularly as younger patients continue to receive their booster immunisations.

2.9.3 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. mRNA COVID-19 vaccine and anaphylaxis

3.1 The EWG were presented an updated review of Yellow Card reports of anaphylaxis following administration of mRNA COVID-19 vaccines. The EWG were informed that for the Pfizer/BioNTech vaccine, there was an overall reporting rate of 10.5 events per million doses. Reporting rates were higher in individuals aged under 60 years compared to over 60 years, however there was an even spread across the under 60 years age groups. The reporting rate was higher following the first dose compared to the second dose. For the Moderna vaccine, the overall reporting rate was higher (34.3 events per million doses), with all events after the first dose. The EWG noted the rate was likely to be imprecise due to the limited use of the Moderna vaccine in the UK so far.

3.2 The EWG were presented data from the US vaccine adverse event reporting system (VAERS) which showed similar reporting rates for anaphylaxis for Pfizer/BioNTech (5 per million doses) and Moderna (4.6 per million doses). The EWG noted the similarities with the UK data with the majority of reports following first dose and an even spread of reports across age groups. The EWG considered that the available data does not indicate an increased risk of anaphylaxis after the second dose of mRNA vaccine.

3.3 NHS England provided an update on their perspective of the 15-min observation period. The EWG were informed there had been some unproven infection control concerns of people having caught COVID-19 around the time of vaccination and whether the observation time contributed to this. NHS England also raised the JCVI guidance allowing concomitant administration of COVID-19 vaccine with flu vaccine. NHS England highlighted that the difference in observation requirements between the vaccines would reduce the volume of flu vaccines that could be administered as patients receiving concomitant administration would need observing for 15-minutes compared to no observation for flu vaccine alone.

3.4 The EWG considered that the data was reassuring with events of anaphylaxis remaining extremely rare and with the UK data comparable to that from the US. The EWG concluded that the 15-minute observation period following vaccination should be retained, as the current data were insufficient to support changing this safety risk minimization measure for anaphylaxis. The EWG suggested that NHS England should collect further data to support an evidence-based review of the requirement for the 15-minute observation period while the MHRA should continue to review reports of anaphylaxis for all COVID-19 vaccines.

4. Third review of myocarditis and pericarditis following administration of COVID-19 vaccines

4.1 The EWG were presented with an update of the Yellow Card reports for myocarditis and pericarditis with the Pfizer/BioNTech, Moderna and AstraZeneca COVID-19 vaccines as well as international data and analysis from Public Health England (PHE). The EWG were informed that the Commission of Human Medicines (CHM) had agreed the product information updates discussed at the previous EWG meeting and these were now included in the product information for the Pfizer/BioNTech and Moderna vaccines.

4.2 The EWG were informed that there has been an increase in reporting of myocarditis and pericarditis with the Pfizer/BioNtech vaccine, particularly in younger age groups and in males. Reporting rates were higher following the second dose with average onset time of 10 days after administration. For the Moderna vaccine, there has been an increase in the reporting of myocarditis and pericarditis. All reports followed the first dose, which is expected due to the deployment timing of the Moderna vaccine, and there was an even split of reports between males and females. The EWG noted that exposure to the Moderna vaccine remains low. For the AstraZeneca vaccine, it was noted that reports occurred in patients with an older average age than the mRNA vaccines and with a more even split between males and females.

4.3 The EWG were presented with the MHRA's updated observed vs expected analysis, which have shown a strengthening of the signal for myocarditis for the Pfizer/BioNTech vaccine assuming 50% reporting rate and for the Moderna vaccine assuming a 75% reporting rate.

4.4 The EWG were presented with an updated analysis of SUS hospital data from PHE, which has shown an increased risk of myocarditis in younger age groups (15-39 years) for the first dose of AstraZeneca vaccine and second dose of Pfizer/BioNTech vaccine in the 0-6 day risk window. The EWG noted that the attributed risk calculated for both the Pfizer/BioNTech and AstraZeneca vaccines was very small, at less than 5 additional cases per million vaccine doses.

4.5 The EWG were presented with international data from the US, which showed the peak of reporting of myocarditis and pericarditis was in the 16-24 years age group following second dose of an mRNA vaccine, with a lower reporting rate in the 12-15 years age group. Observed vs expected data from the vaccine adverse event reporting system (VAERS) showed a potential signal in younger males in the 7- and 21-day risk windows following first dose and a potential signal in males and females in the 7-day risk window following second dose of an mRNA vaccine. Rates were higher in males compared to females for both doses.

4.6 The EWG were informed that the FDA had updated the product information for mRNA vaccines to include similar warnings on myocarditis and pericarditis as had been introduced by the MHRA. The EWG were informed that other regulators including the European Medicines Agency, Health Canada and Israel were also investigating the signal of myocarditis and pericarditis.

4.7 The EWG discussed the MHRA proposal to include myocarditis and pericarditis as important identified risks in the risk management plans (RMPs) for the Pfizer/BioNTech and Moderna vaccines, with investigation of these signals in the post-authorisation safety studies. The EWG endorsed the inclusion of myocarditis and pericarditis as an important identified risk in the RMP for the mRNA vaccines. The EWG concluded that the signals of myocarditis and pericarditis should continue to be closely monitored.

5. COVID-19 vaccines and Guillain Barre syndrome – update on epidemiological analysis

5.1 The EWG were presented with an update on epidemiological analyses assessing the incidence of reported Guillain Barre Syndrome (GBS) following COVID-19 vaccination. The EWG heard updates on the observed vs expected analyses of Yellow Card reports and the rapid cycle analysis being conducted in the Clinical Practice Research Datalink (CPRD). Pre-print results from a study using Hospital Episode Statistics (HES) data by Patone et al. were also discussed.

5.2 The EWG discussed the results, in particular the observed changes in the recorded incidence rate of GBS since the start of the pandemic and the data that suggested an increased incidence of GBS following a first dose of the AstraZeneca vaccine. They noted the limitations of the different analyses, in particular the lack of validation of diagnoses in the CPRD and HES data and the high reporting of cases that did not meet Brighton Collaboration criteria.

5.3 The EWG agreed that, although there were limitations to the data, they supported an increased risk of GBS following administration of a first dose of AstraZeneca vaccine. It was noted that the results based on English HES data had been replicated using Scottish hospital admissions data. The EWG advised that available data did not suggest there were significant differences in the types or severity of GBS cases reported after vaccination compared to usual patterns, although they noted two papers suggesting an increased incidence of bilateral facial paresis. The EWG agreed that it was very important to further explore the risk of GBS with COVID-19 given the conflicting existing data.

5.4 The EWG supported the continued capture of data to inform further regulatory measures and noted the need to also consider international data.

6. Moderna vaccine and delayed injection site reactions

6.1 The EWG was presented with a review of the currently available evidence from clinical trials, literature and spontaneous sources (including Yellow Card data with a data lock point of 12th May 2021) regarding delayed skin reactions following vaccination the Moderna COVID-19 vaccine.

6.2 The EWG heard that there are a significant number of Yellow Cards for delayed skin reactions following vaccination with the Moderna vaccine and these reactions are more frequently reported for Moderna than for other COVID-19 vaccines. The EWG heard that whilst these reactions may be alarming for patients, they are self-limiting and not a contraindication for receiving a second dose of the Moderna vaccine.

6.3 The EWG agreed that the number of Yellow Card reports and published literature cases warranted an update of the product information and inclusion in the weekly publication on ADRs following COVID-19 vaccination.

6.4 The EWG considered that the company should be requested to review mechanisms as to why these reactions were more frequent with Moderna versus other COVID-19 vaccines.

7. COVID-19 Vaccines Safety Surveillance Strategy Review

7.1 The EWG were presented an update on the COVID-19 vaccine safety surveillance strategy, including the both the successes and challenges seen to date.

7.2 The EWG were informed that over 285,000 Yellow Card reports have been received, predominantly from members of the public (82%) and that these reports have supported signal detection and assessment. Resource challenges and the high volumes of reports have been managed through a combination of agile processes and technical solutions to ensure reports have been made available for signal detection within 48 hours.

7.3 The EWG were informed that Yellow Card Vaccine Monitor has nearly 30,000 individuals registered, including 1366 pregnant women due to collaboration with PHE. Challenges with the Yellow Card Vaccine Monitor have included low engagement within ethnic minorities.

7.4 The EWG were also updated on the implementation of observed vs expected analyses using the Yellow Card reports and the Rapid Cycle Analyses implemented using data from the Clinical Practice Research Datalink. The challenges in terms of ensuring timely access to data and the scale and complexity of the methods and the impact these have had on implementation of the analyses and their interpretation were discussed.

7.5 The EWG views were sought as to the next stages of implementation to ensure these systems were able to fully monitor second doses and the deployment of the Moderna vaccines and to start preparing for the rollout of additional doses.

7.6 The EWG discussed opportunities for increasing ethnic minority participation in the Yellow Card Vaccine Monitor. They advised working directly with faith and community groups and liaising with NHSE and PHE to understand their approaches with regards to vaccine uptake and to identify potential further opportunities.

7.7 The EWG agreed that the implementation of the surveillance strategy had been successful to date and supported ongoing development of the strategy to continue the rigorous monitoring of the safety of COVID-19 vaccines.

8. Any Other Business

None.

9. Date and time of next meeting

The next scheduled meeting is to take place **on Friday 23rd July** at **10.30am**.

The Meeting today started at 10:32 and ended at 13:05.

[redacted]

25th August 2022

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

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:

Apologies were received from Professors Lehner, Robertson, Solomon and Mrs Wang for this meeting.

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 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.

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.

Professor Robertson – PS interest in Oxford Study through a validation in Scotland. Professor Robertson was asked specific questions and did not volunteer any spontaneous comments.

Professor Solomon - Other relevant interests – Professor Solomon provides clinical care for patients with Covid-19; chaired the MRC/NIHR committee which awarded funding for development of the Oxford Vaccine.

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.

Observers

[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.

[redacted] - Other relevant interests 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.