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

Minutes of the Ad Hoc meeting held on **Monday 7th June 2021** at **17:15** 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[1]
Professor P J Lehner
Mr R Lowe
Dr S Misbah
Professor S Price
Dr A Riordan
Professor K M G Taylor
Dr R Thorpe
Professor M Turner
Dr S Walsh
Mrs M Wang
Professor C Weir

Apologies

Professor Y Perrie
Professor C Robertson
Professor T Solomon

Visiting Expert

[redacted]

Observers

[redacted]
[redacted]
Professor WS Lim
[redacted]
[redacted]
[redacted]
[redacted]
[redacted]

Secretariat

[redacted]
[redacted]

Professional Staff of MHRA Present

Principal Assessors

[redacted] - VRMM

Presenters supporting specific items

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

MHRA Observers

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

[redacted]

4th February 2022

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

[1] Joined during Item 2

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 visiting expert:

[redacted]
[redacted]BHF Data Science Centre

1.5 The Chair welcomed the following observers:

[redacted]
[redacted] JCVI

[redacted]
[redacted]
Public Health Agency

Professor Wei Shen Lim
Chair of JCVI

[redacted]
NHS England [redacted]

[redacted]
Public Health Scotland

[redacted]
Public Health England

[redacted]
[redacted] Public Health Wales

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

1.6 Apologies were received from Professors Perrie, Robertson and Solomon for this meeting.

2. Analyses on thrombosis and thrombocytopenia using data from the BHF TRE

2.1 The EWG was presented with the latest analyses using data from linked electronic medical records from healthcare settings including 54.4 million people alive and registered with general practitioners on 1 January 2020. These analyses calculated adjusted hazard ratios for pre- (baseline) and post-COVID-19 vaccination periods with follow-up from 8 December 2020 to mid-March 2021 without any adjustment for time-varying confounders. The analyses adjusted for all potential variables with available data. Data was presented for the Pfizer and AstraZeneca (AZ) COVID-19 vaccines.

2.2 For the risks of any venous or arterial thrombosis, the adjusted hazard ratios were reduced following vaccination, especially for those aged at least 70 years. An analysis of the risk of lower limb fractures showed a similar protective effect in older people and so the observed reduction in risk may reflect residual confounding in older individuals. The confounding factors could include changes in behaviour such as social distancing after vaccination or exclusion of frail individuals at higher risk of vascular events.

2.3 For the risk of cerebral venous sinus thrombosis, the adjusted hazard ratio was increased following the administration of the AZ COVID-19 vaccine in those aged under 70 years, but this risk estimate was based on a small number of events. A protective effect was apparent after immunisation with the Pfizer vaccine. The CVST incidence rate in 2019 was 0.5 - 1.5 cases per million per month but only a handful of adult cases were associated with thrombocytopenia in that year. The reported rates of thrombocytopenia are underestimated and the absolute risk of thrombosis with thrombocytopenia following vaccination may only increase the background rate by 1 case per million per month. However, the association of thrombocytopenia with thrombosis appears real and sensitivity analyses are ongoing. The EWG noted that CVST cases are likely to be recorded accurately although specific investigations are required to ascertain cases. Those vaccinated are also likely to be very different to unvaccinated individuals.

2.4 Further analyses will explore the association between COVID-19 vaccines and thrombotic thrombocytopenia events beyond March 2021.

2.5 The EWG thanked [redacted] for [redacted] presentation and commented that it would appreciate any updates on [redacted] team's work in assessing safety signals for the COVID-19 vaccines.

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 2 June 2021.

3.2 The EWG reviewed the following publications: three articles proposing hypotheses to explain thrombosis with thrombocytopenia following Covid-19 vaccination; and a report of the detailed post-mortem findings from 2 confirmed cases associated with the first dose of the AstraZeneca COVID-19 vaccination. The EWG noted that the descriptions of potential causal mechanisms were not supported by any clinical data.

3.3 An overview of the UK case reports associated with the AstraZeneca (AZ) COVID-19 Vaccine was presented including summary tables of the 23 reported probable and possible UK cases occurring after a second dose. The EWG noted that a possible fatal case with cerebral venous sinus thrombosis (CVST) and severe thrombocytopenia was reported but the time-to-onset of 2 days was implausible and platelet factor 4 antibody testing was negative. The working diagnosis was endocarditis and further follow-up information is awaited. Two reported cases were in the 40 to 49 age group.

3.4 The EWG was informed that the MHRA has received data on Australian cases of thrombotic thrombocytopenia associated with COVID-19 vaccines from the Therapeutic Goods Administration (TGA). They appear to have adopted the UK's case definition and all reports, where specified, followed dosing with the AZ COVID-19 vaccine. The clinical phenotype appears similar to the UK cases in terms of gender, age range, time-to-onset, absence of risk factors, sites of thromboses and nadir platelet counts. It was not possible to compare cases reported after first doses with second dose cases. The TGA website gives estimated case incidences of 3.1 per 100,000 doses in those aged under 50 years and 18 per million doses in older people. The EWG commented that these higher estimated incidences may be a result of better case ascertainment derived from the UK experience, ethnic factors or more effective post-marketing pharmacovigilance. The EWG was also informed that AstraZeneca has submitted their foreign case data to the MHRA, and this information will be presented at the next EWG meeting on 14 June 2021. The EWG commented that a summary table of estimated case incidences by country would be useful.

3.5 The UK and foreign cases associated with the Pfizer, Moderna and Janssen COVID-19 vaccines were summarised using the same case definition. No new confirmed cases were identified.

3.6 The estimated number of second AstraZeneca COVID-19 vaccine doses administered has increased to 15.7 million whilst the number of first doses has increased slightly, in line with the current deployment programme to 24.5 million. 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 is stable at 14.2 (12.8, 15.8) per million for first/unknown doses and the overall fatal incidence rate is also stable at 2.6 (2.0, 3.3) per million first/unknown doses. The age-stratified incidence rates associated with second doses were presented and the overall rate was stable at 1.5 (0.9, 2.2) per million doses. No deaths have been reported following a second dose in those aged less than 50 years, but 2 cases were identified in the 40 to 49 age group. The case incidence rates per 100,000 patient years were also compared for first and second doses. The case incidence rates (per 100,000 patient years) were 15.4 (13.7,17.3) for the first or unknown doses and 1.7 (0.9, 2.7) for second doses. The risk estimates were then compared with the expected benefits of vaccine in age subgroups. Overall, the reported incidence rates showed a small increase since the last data lock point with overlapping 95% confidence intervals, while the risk-benefit ratio for the AZ COVID-19 vaccine remained relatively unchanged.

3.7 The EWG then considered the following 3 questions:

3.7.1 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, depending on the status of the COVID-19 pandemic, its severity and impact on hospitalisation. The benefit-risk assessment has not changed since it was reviewed on 1st June 2021.

3.7.2 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 is reassuring but the MHRA should continue to monitor second dose cases closely, particularly as younger patients will now be receiving their booster immunisations.

3.7.3 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.

3.8 In conclusion, the EWG did not identify any potential trigger for regulatory action.

4. Any Other Business

None.

5. Date and time of next meeting

The next scheduled meeting is to take place on **Monday 14th June 2021** at **10:30am**.

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

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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 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.

Observers

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. 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.

[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]. [redacted] has now left that role.