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

Minutes of the Ad Hoc meeting held on **Tuesday 1st June 2021** at **15:15** via videoconference

Participants Present

Members

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

Apologies

Ms S Hunneyball
Sir M Jacobs
Professor Y Perrie
Professor T Solomon

Observers

[redacted]

Secretariat

[redacted]

Professional Staff of MHRA Present

Principal Assessors

[redacted] - VRMM

Presenters supporting specific items

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

MHRA Observers

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

[redacted]

4th February 2022

Key
LD = Licensing Division
VRMM = Vigilance & Risk Management of Medicines
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 Ms Hunneyball, Professors Perrie, Solomon and Sir Michael Jacobs for this meeting.

1.5 The Chair welcomed the following observers:

[redacted]
Public Health Scotland

[redacted]
Public Health England

[redacted]
[redacted] Public Health Wales

[redacted]
[redacted]
[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 26 May 2021.

2.2 The EWG reviewed the following publications: a summary of current hypotheses to explain thrombosis with thrombocytopenia following Covid-19 vaccination; a pre-print proposing that thromboembolic events are related to translation of alternatively spliced mRNA transcripts produced by adenoviral-vector vaccines; a small UK case series of ischaemic stroke; and an opinion piece describing initial Vigibase case reports by date from 1 February to 23 April 2021. The EWG commented that there is a lack of clinical data to substantiate any of the

emerging hypotheses and that the likely serum levels of Spike protein induced by a Covid-19 vaccine would not be sufficient to promote platelet aggregation.

2.3 An overview of the case reports associated with the AstraZeneca COVID-19 Vaccine was presented including summary tables of the 18 reported probable and possible UK cases occurring after a second dose. Follow-up information showed that the previously reported cerebral venous sinus thrombosis (CVST) probable case with severe thrombocytopenia was after the first dose and so there are no CVST cases following a second dose. Platelet factor 4 antibodies were identified in a case with isolated thrombocytopenia but none of the other new second dose cases were seropositive. The EWG was reassured by the clinical phenotypes of the second dose cases which are qualitatively different to those associated with first doses. The requested foreign case data from AstraZeneca are awaited.

2.4 The UK and foreign cases associated with the Pfizer, Moderna and Janssen COVID-19 vaccines were summarised using the same case definition. The EWG was informed that Belgium has announced the temporary suspension of the Janssen Covid-19 vaccine in individuals aged less than 41 years following the report of a fatal case in a 37-year-old female. The EWG advised that the MHRA should continue to closely monitor Janssen cases.

2.5 The estimated number of second AstraZeneca COVID-19 vaccine doses administered has increased to 13.4 million whilst the number of first doses has increased slightly, in line with the current deployment programme to 24.3 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 13.6 (12.2, 15.1) per million for first/unknown doses and the overall fatal incidence rate is also stable at 2.4 (1.9, 3.1) per million first/unknown doses. The age-stratified incidence rates associated with second doses were presented and the overall rate was stable at 1.3 (0.8, 2.1) per million doses. No deaths have been reported following a second dose in those aged less than 50 years. The risk estimates were then compared with the expected benefits of vaccine in age subgroups. The reported incidence rates showed a small increase since last data lock point, while risk-benefit ratio remained relatively unchanged. The EWG commented that follow-up duration for first and second doses could improve the interpretation of the incidence data.

2.6 The EWG was informed that an unpublished survey of initial platelet counts in patients admitted to University College London Hospitals (UCLH) with ischaemic stroke from 2018 to 2019 showed that 7% (n=170/2514) had thrombocytopenia with platelet counts < 150 x 10^9/L and 1% had more marked thrombocytopenia with values <100 x 10^9/L. 8% of those with intracranial haemorrhage had thrombocytopenia. UCLH plan to share their survey results with the MHRA. [redacted] will also share [redacted] epidemiological data on background rates of thromboembolic events with thrombocytopenia at an EWG meeting next week.

2.7 The Chair informed the EWG that a UK Covid-19 Consortium has received funding for a research group to investigate the underlying cause(s) of thrombosis with thrombocytopenia. The MHRA would be liaising with this Consortium, and it was suggested that researchers would be invited to present regular updates on this work for the EWG to consider.

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 reviewed on 24 May 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 is reasonably reassuring but limited, and so the MHRA should continue to monitor second dose cases closely, particularly as younger patients will now be receiving their booster immunisations.

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.

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

3. Any Other Business

3.1 None.

4. Date and time of next meeting

The next scheduled meeting is to take place on **Friday 4th June 2021** at **10:30am**.

The Meeting today started at 15:20 and ended at 15:59.

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:

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.

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 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

[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 J[redacted] has now left that role.

[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.