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

Minutes of the Ad Hoc meeting held on **Monday 24th May 2021** at **17:15** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan
Mr VI G Fenton-May
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 T Solomon
Professor K M G Taylor
Dr R Thorpe
Dr S Walsh
Mrs M Wang
Professor C Weir

Apologies

Professor N French
Professor M Turner

Observers

[redacted]

Secretariat

[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted] - VRMM

Presenters supporting specific items

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

MHRA Observers

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

[redacted]

4th February 2022

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

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.

1.5 The Chair welcomed the following observers:

Dr [redacted], Public Health Agency

Dr [redacted]

Professor [redacted] JCVI

Dr [redacted] Public Health Scotland

Dr [redacted]

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 19 May 2021.

2.2 The EWG heard that the MHRA met with representatives of the Expert Haematology Panel (EHP) to discuss case definition for events associated with the AstraZeneca COVID-19 vaccine on 21 May 2021. The EHP are revising their case definitions for vaccine-induced thrombocytopenia (VIT) and vaccine-induced thrombosis and thrombocytopenia (VITT) and

are considering introducing threshold values for optical densities for PF4 antibodies in confirmed cases and are also reconsidering D-dimer threshold values. Platelet activation tests may be required in all cases or in those with negative PF4 antibodies if the clinical suspicion of VITT is high. The EHP also mentioned that some patients are experiencing recurrent thrombocytopenia on follow-up and thromboembolic events have occurred despite anticoagulation. Some patients are requiring rituximab treatment and PF4 antibodies have persisted in all cases on follow-up of up to 8 weeks. Additionally, the EHP commented that some confirmed cases associated with the Pfizer COVID-19 vaccine have also been reported with a longer time-to-onset than those following immunisation with the AstraZeneca (AZ) COVID-19 vaccine. The EWG agreed to keep the topic of case definition open for consideration as new evidence emerges.

2.3 The EWG was informed of the updated product information recommendations issued by the Committee for Medicinal Products for Human Use on 21 May 2021. The new contraindication and advice for expert haematology input are similar to UK guidance provided in the Reg 174 information for Healthcare Professionals.

2.4 The EWG was then presented with a summary of a recent publication describing a French case series of 9 patients with suspected VITT and the results of different tests for PF4 antibodies. A PF4-enhanced serotonin release assay was positive in 7 patients, but all of these patients tested negative in rapid immunoassays and the sensitivity of different ELISA tests varied with only the Lifecodes PF4 IgG Immunocor ELISA test identifying all patients with platelet activation. The EWG noted the therapeutic potential of imlifidase in patients with refractory VITT that has not responded to intravenous immunoglobulin therapy.

2.5 An overview of the case reports associated with the AstraZeneca COVID-19 Vaccine was presented including summary tables of the 17 reported probable and possible UK cases occurring after a second dose and a fatal cerebral venous sinus thrombosis case associated with thrombocytopenia in pregnancy from Brazil. The EWG was reassured by the clinical phenotypes of the second dose cases but advised that AstraZeneca should be requested to provide data on all foreign cases.

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 clinical details of 2 confirmed Pfizer cases reported from the UK were reviewed. The EWG commented that similar cases have not been reported from countries with much greater Pfizer vaccine usage but this could reflect differences in the effectiveness of post-marketing monitoring, adherence to national expert guidance on investigating VITT cases, different case definitions or different background event rates. The EWG advised that the MHRA should continue to closely monitor Pfizer cases.

2.7 The estimated number of second AstraZeneca COVID-19 vaccine doses administered has increased to 10.7 million whilst the number of first doses has increased slightly, in line with the current deployment programme to 24.2 million. Estimated case incidence rates for CVST and CVST plus non-CVST events were presented by age-stratified 10-year intervals and by gender. The overall incidence rate is stable at 13.0 (11.6, 14.5) per million for first/unknown doses and the overall fatal incidence rate is also stable at 2.4 (1.8, 3.0) per million first/unknown doses. The age-stratified incidence rates associated with second doses were presented and the overall rate was stable at 1.6 (0.9, 2.6) per million doses. The risk estimates were then compared with the expected benefits of vaccine in age subgroups. The reported incidence rates showed a small increase since the last data lock point, while the risk-benefit balance remained relatively unchanged.

2.8 The EWG was updated on ongoing work to ascertain background incidence rates of thrombosis with thrombocytopenia. It was noted that two presentations from different

research groups looking at the rate of thrombosis with thrombocytopenia with and without vaccination will be given at the next EWG meeting on 25 May.

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 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 17 May 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 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 second doses.

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 the Pfizer COVID-19 vaccine should continue to be closely monitored.

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

3. <u>Future Steps / Any Other Business</u>

None.

4. <u>Date and time of next meeting</u>

The next scheduled meeting is to take place on **Tuesday 25th May 2021** at **12.00pm**.

The Meeting today started at 17:18 and ended at 17:57.

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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 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).

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

Professor [redacted] - NPNS arises from the institution [redacted] University Hospitals NHS Trust) where Professor [redacted] works has received unrestricted investigator-initiated research funding from Pfizer for an unrelated prospective population-based cohort study of pneumococcal pneumonia in which Professor [redacted] is the Chief Investigator.

Dr [redacted] – Lapsed and NPNS - Regarding companies to declare interests for, prior to joining Public Health Scotland, Dr [redacted] worked for a company that provided epidemiological services to the pharmaceutical industry. Whilst working there, she supported respiratory vaccine development activities at Janssen (Johnson & Johnson). Dr [redacted] has now left that role.