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

Minutes of the Ad Hoc meeting held on **Monday 17th 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 N French
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 K M G Taylor
Dr R Thorpe
Professor M Turner
Dr S Walsh
Mrs M Wang
Professor C Weir

Apologies

Professor T Solomon

Observers

[redacted]
Professor W S Lim
[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] - MHRA-Policy
[redacted] - VRMM
[redacted] - VRMM
[redacted] - VRMM
[redacted] - Comm
[redacted] - VRMM
[redacted] - VRMM
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.

1.4 Apologies were received from Professor Tom Solomon for this meeting.

1.5 The Chair welcomed the following observers:

Dr [redacted]
[redacted], Public Health England

Professor [redacted]
[redacted] JCVI

Dr [redacted]
Locum Consultant in Health Protection, Public Health Agency

Dr [redacted]

Professor [redacted]
[redacted] JCVI

Dr [redacted]
Public Health Scotland

2. Update on the review for major thrombotic events associated with 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 12 May 2021.

2.2 The EWG was informed of the updated recommendations issued by the [redacted] on 3rd May 2021.

2.3 The EWG was then presented with a summary of recent publications concerning the AstraZeneca COVID-19 vaccine including: interim reactogenicity and safety data results from the COM-CoV study of heterologous prime-boost COVID-19 vaccines; a review of 20 published cases of vaccine-associated immune thrombosis and thrombocytopenia; a review of COVID-19 vaccine platforms that included a proposed causal mechanism to explain observed events of thrombosis with thrombocytopenia; and a small study reporting the frequency and platelet-activation properties of PF4 antibodies detected in healthy volunteers after immunisation with the AstraZeneca and Pfizer COVID-19 vaccines.

2.4 An overview of the case reports associated with the AstraZeneca COVID-19 Vaccine was presented including summary tables of the 15 reported cases occurring after a second dose.

2.4.1 It was noted that a female of unknown age had experienced cerebral venous sinus thrombosis and deep vein thrombosis with severe thrombocytopenia at 8 days after her second dose although her PF4 antibody status was not known.

2.4.2 Another case was reviewed in detail: an elderly female with localised lymphoma in remission developed an incidental hepatic vein thrombosis with mild thrombocytopenia about 28 days after her first dose of the vaccine. She experienced an acute occipital arterial infarct associated with moderate thrombocytopenia and PF4 antibodies (optical density 2.46). The events following the second dose were confounded by recent COVID-19 infection. The EWG advised that this was probably a positive rechallenge case confounded by COVID-19 infection. It also noted that second doses are contraindicated in patients who have experienced major venous and/or arterial thrombosis occurring with thrombocytopenia following vaccination with any COVID-19 vaccine which seems to be supported by this particular case.

2.4.3 The EWG advised that the emerging data on second dose cases might have identified a different clinical phenotype to early first dose cases but is based on an older group. More data on the risks associated with second doses in younger people is required and so this issue should remain under close monitoring as the vaccine programme moves into younger patients. It also requested that age-stratified second dose incidence rate data should be presented at future weekly meetings.

2.5 The UK and foreign cases associated with the Pfizer, Moderna and Janssen COVID-19 vaccines were summarised using the same case definition. The EWG noted that the case incidence rates for the Janssen COVID-19 vaccine reported by the [redacted] are gradually increasing and are now comparable to those for the AstraZeneca COVID-19 vaccine.

2.6 The estimated number of second AstraZeneca COVID-19 vaccine doses administered has increased to 9.0 million whilst the number of first doses has increased slightly, in line with the current deployment programme to 23.9 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 12.3 (10.9, 13.7) per million for first/unknown doses and the overall fatal incidence rate is also stable at 2.3 (1.7, 3.0) per million first/unknown doses. The incidence rate associated with second doses has increased slightly from 1.1 to 1.7 (0.9, 2.7) per million doses but the 95% confidence intervals are overlapping. The risk estimates were then compared with the expected benefits of vaccine in age subgroups. The EWG noted that all new fatal cases have cerebral venous sinus thromboses. The reported incidence rates showed a small increase since last data lock point, while risk-benefit ratio remained relatively unchanged.

2.7 The EWG then considered the following 3 questions:

2.7.1 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 10 May 2021.

2.7.2 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 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. The case of positive rechallenge reported after the second dose of the AstraZeneca COVID-19 vaccine, although confounded, validates the contraindication in those with thrombotic events associated with thrombocytopenia after a first dose of any COVID-19 vaccine.

2.7.3 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.

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

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

None.

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

The next scheduled meeting is to take place on **Friday 21st May 2021** at **2.30pm**.

The Meeting today started at 17:17 and ended at 18:03.

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.

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).

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 - University of Oxford employee (with no involvement in research or clinical trials related to Oxford AZ vaccine)
[redacted] JCVI

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.