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

Minutes of the meeting held on **Tuesday 23rd March 2021** at **15:30** 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[2]
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
Professor M Turner
Dr S Walsh
Mrs M Wang
Professor C Weir

Apologies

Professor P Shah

Invited Experts

[redacted] (presenter of specific item)

[redacted]

Observers

[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD

Presenter supporting specific item

[redacted] - VRMM
[redacted] - VRMM

MHRA Observers

Ms R Arrundale - MHRA-Policy
[redacted] - VRMM
[redacted] - LD
Dr S Branch - VRMM
[redacted] - MHRA-NIBSC
[redacted] - VRMM
[redacted] – MHRA-Policy
[redacted] - VRMM
[redacted] - VRMM
[redacted] - MHRA-NIBSC
[redacted] - COMMS
[redacted] - VRMM
[redacted] - VRMM
[redacted] - VRMM
Dr J Raine - MHRA CEO
Ms N Rose - MHRA-NIBSC
[redacted] - VRMM
[redacted] - VRMM
Mr P Tregunno - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - VRMM

Secretariat

[redacted]

[redacted]

4th February 2022

Professor W S Lim

[redacted]

Professor Van-Tam

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

[1] left during item 8
[2] joined during item 7

1. Introduction and Announcement

1.1 The Chair reminded Members and invited Experts 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 Shah for this meeting.

1.5 The Chair welcomed Invited Expert, Dr [redacted], [redacted] of Public Health England who presented item 7 - Vaccine benefit by age group and analysis of risk of events of thrombosis with thrombocytopenia at the meeting today.

1.6 The Chair welcomed the following Invited Haematology Experts for the meeting today:

Dr [redacted] **-** Imperial Healthcare College NHS Trust
Dr [redacted] **-** [redacted]
Dr [redacted] **-** Oxford University Hospitals
Dr [redacted] **-** University Hospital Birmingham
Professor [redacted], University of Oxford
Professor [redacted] **-** University College London Hospitals
Dr [redacted] **–** [redacted]

1.7 The Chair welcomed the following Observers for the meeting today:

Professor Jonathan Van-Tam - Deputy Chief Medical Officer
[redacted] **-** Public Health England **(**Scientific Secretariat to JCVI)
Dr [redacted] **-** Public Health England (Head of JCVI Scientific Secretariat)
Professor [redacted]
Dr [redacted] **-** HSCNI
Dr [redacted] **-** HSCNI
Dr [redacted] **-** LSHTM
Dr [redacted] **ry -** PHS
Professor Wei Shen Lim - COVID-19 Chair for JCVI
Dr [redacted] **-** Public Health England
Dr [redacted] **-** PHW
Dr [redacted] **-** NHS England & NHS Improvement
Dr [redacted]

Ms [redacted] **-** Public Health England
Dr [redacted] Public Health England
Dr [redacted] **-** Imperial College London

2. Minutes of EWG meeting of 17th March 2021

2.1 The minutes were subject to one comment on the reporting rate being addressed. This comment was actioned. The amendment was revisited by the Chair who then approved the minutes as a true and accurate record of the proceedings on 22nd June 2021.

3. Update on communications since 17 March 2021

3.1 MHRA had published a statement on 18 March which communicated the findings of the EWG so far, that the currently available evidence does not suggest that blood clots in veins (venous thromboembolism) are caused by COVID-19 Vaccine AstraZeneca, and that a further, detailed review into a very rare and specific type of blood clot in the cerebral veins (sinus vein thrombosis) occurring together with lowered platelets (thrombocytopenia) is ongoing. The EWG was informed that the MHRA advice remained that the benefits of the vaccines against COVID-19 continue to outweigh any risks and that the public should continue to get their vaccine when invited to do so.

3.2 The meeting heard an update on the PRAC review of thrombocytopenia and thromboses, and subsequent communications from the EMA. The meeting also heard that pending further review, PRAC had recommended introducing warnings in the product information for AstraZeneca COVID-19 vaccine to inform of a potential risk of DIC or CVST with thrombocytopenia. The meeting was given an overview of several media articles reporting on studies performed in Germany and Norway, which discuss potential mechanisms for the reported events. It was highlighted that there was no peer reviewed published evidence to date. It was also commented that a collection of cases may be published in the Lancet shortly. The experts noted that while there was a difference in wording between the communications released by the EMA and MHRA, both had stated in press briefings that no causal association with the AZ vaccine had been confirmed.

4. Update on COVID-19 Vaccine AstraZeneca and risk of thromboembolic events with concurrent thrombocytopenia

4.1 The EWG were presented with a summary of the cases available to date of thromboembolic events with concurrent thrombocytopenia following vaccination with AZ, both from the UK and worldwide. A potential case definition was also presented to the EWG.

4.2 Experts commented that many of the cases lacked important information for assessment but noted that the overall benefit:risk of the vaccine was still considered positive for the entire currently vaccinated population. The age groups reported in the cases were considered, and it was noted that older patients may present with different thromboses (such as PE and cardiac) due to variable risk factors. The experts noted that a number of cases in their records had tests for antibodies against heparin/platelet factor 4 (anti-PF4 antibodies) carried out, and that a number of these were positive. There was a discussion of the potential mechanism, including if it could be related to the spike protein which would not be specific to AZ. The EWG advised caution in assuming a link to the vaccine without establishing a mechanism as this had led to erroneous associations in some past cases.

4.3 The possible case definition was discussed, and it was proposed that this could be graded into three categories of diagnostic certainty in a similar way to Brighton Collaboration criteria: possible cases which report thrombosis alongside thrombocytopenia; probable cases which

also report D-dimer >4000 and confirmed cases which also include identified anti-PF4 antibodies. The experts suggested that platelet functional test should be considered in cases with strong clinical correlation if anti-PF4 testing was ambiguous.

4.4 The meeting considered whether there could be any relation to vaccine storage or delivery issues; the MHRA confirmed that there was no evidence to support this at present and also no evidence of a batch-related issue.

5. Updated proforma for case report collection – for agreement

The EWG were provided an overview of the proforma developed between MHRA and haematology experts to aid in gathering important case details on reports submitted to the MHRA. The EWG agreed that this could be refined and that comments should be provided to the MHRA so a final version could be agreed.

6. Risk management proposals including draft treatment guideline

6.1 The meeting considered what information could be gathered to further define risk factors in cases and potentially determine at risk groups. The MHRA also summarised future plans for a call to reporting of cases of interest and collaboration with PHE on data collection including serological testing. The meeting also heard of considerations for studies which could be conducted to further assist in the investigation of this potential risk.

6.2 The meeting discussed the lack of risk factors in many of the cases and highlighted that cases in older patients may not have raised suspicion to trigger full investigation and reporting of the events.

6.3 It was also considered what advice could be provided to advise patients on when to seek help, particularly around symptoms of headache and bruising. It was considered that advice to professionals on treatment protocols should be co-ordinated with NHSE and devolved administrations and ensure that it reaches key stakeholders in a co-ordinated way, while avoiding causing unnecessary concerns on the use of the vaccine.

7. PHE: vaccine benefit by age group and analysis of risk of events of thrombosis with thrombocytopenia

7.1 The meeting was presented with updated analysis from PHE of the events of interest associated with the AZ and Pfizer vaccine in the UK. The presentation highlighted that there was no indication of a raised risk of thromboembolic events with either of the vaccines and of the new terms included there were small numbers of events identified. There was no increased risk identified with the exception of 'Intracranial and intraspinal phlebitis and thrombophlebitis' for which there was indication of a small increased risk for AZ in the under 65 year age group; it was noted that unadjusted confounding could be present and that the numbers were small.

7.2 PHE also presented an analysis of the benefit of COVID-19 vaccination. It was shown that younger age groups required higher number of vaccinations to reduce deaths, hospitalisation and long-COVID, and that this effect of age was less pronounced for hospitalisation and long-COVID prevention. It was also noted that risk factors within age groups could impact this effect. A risk analysis of MHRA cases of CVST and CVST concurrent with thrombocytopenia was also provided, and showed that if causality was assumed, there would be a lower number of doses of AZ needed in the younger age group for an event of CVST with thrombocytopenia to occur, compared with older age groups.

7.3 The EWG discussed the uncertainties of the risk analysis and that due to the rarity of the events, these estimates would likely have wide confidence intervals. The EWG commented that an accurate number of cases is also unknown. The meeting highlighted that a case definition would assist in investigating this further.

8. AstraZeneca: presentation from company on cases received, potential mechanisms and discussion on studies planned

The Chair welcomed the following representatives from AstraZeneca for the meeting today:

8.1 AstraZeneca presented a summary of the cases they had received to date. The meeting heard that the majority of cases were female and younger age, and where dose was reported, these were all first dose. Many of the cases had important information missing. AstraZeneca provided an overview of potential mechanisms and discussed whether these would be specific to the AstraZeneca vaccine and its vector or common to all COVID-19 vaccines and associated with the spike protein. AstraZeneca commented on the challenges of epidemiological study of the combined event of thromboses with thrombocytopenia and stated that the company was engaged with NHSE to develop a protocol to study the potential association further.

8.2 The EWG discussed whether there would be any differences in the spike protein in the AZ vaccine compared to that produced with other vaccines. The company also confirmed to the meeting that no invitro assays had been conducted at present and that it was in contact with international investigators regarding cases too.

9. Next steps / Recommendation

9.1 The EWG discussed the information presented at the meeting. Members commented that the cases lacked significant information at present, that there was insufficient evidence to establish causality at present, and that the events that have been reported are rare. The EWG highlighted that information needed to be gathered on possible risk factors in cases.

9.2 The meeting also noted that there had been potential cases of thromboembolic events with thrombocytopenia reported with the Pfizer vaccine and that this information was important to consider. The meeting concluded that details on these reports should be obtained and presented for further discussion could be given at the next EWG meeting (24 March 2021).

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

None.

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

The next meeting is scheduled to take place on Wednesday 24th March 2021 at 13:30.

The Meeting today started at 15:32 and ended at 19:01.

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).

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.

Professor Turner - NPNS interest. Professor Turner is a Non Executive Director (non-remunerated) on the Board of the Cell and Gene Therapy Catapult (CGT) until the end of March. CGT have been tasked by UK Government with re-purposing a factory in Braintree to manufacture either a vaccine or a therapeutic mAb. No decision has been made as to whether or what product CGT Braintree may be asked to manufacture and that decision will be made by UK Government. Professor Turner does not believe that CGT Board will have any material input into the decision as to what product may be manufactured. Rentschler have signed a contract with the Cell and Gene Therapy Catapult (CGT) to rent one of the manufacturing clean room suites at the Stevenage Centre. Professor Turner understands that this will be for contract AAV manufacture.

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.

Invited Haematology Experts for this meeting

[redacted]

[redacted]

[redacted]

Dr Will Lester - PNS in Pfizer and Sanofi – no interests were declared in relation to vaccines

[redacted]

[redacted]

[redacted]

[redacted] - None

Observers for this meeting

[redacted]

[redacted]

[redacted]

Professor Wei Shen 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]