COMMISSION ON HUMAN MEDICINES (CHM)

COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Wednesday 17th March 2021** at **15:00** 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
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 T Solomon
Professor K M G Taylor
Dr R Thorpe
Professor M Turner
Dr S Walsh
Mrs M Wang
Professor C Weir

Apologies

Professor K Hyrich
Professor C Robertson
Professor P Shah

Invited Experts

[redacted]

Observers

[redacted]
Professor W S Lim
[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted] - LD (& for CHM)

Presenters supporting specific items

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

MHRA Observers

Ms R Arrundale - MHRA-Policy
[redacted] - Directorate
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - LD
Dr S Branch - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - MHRA-NIBSC
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - VRMM
[redacted] - MHRA-NIBSC
[redacted] - LD
[redacted] - Medical Writer
[redacted] - Comms
[redacted] - LD
[redacted] - LD
[redacted] - VRMM
[redacted] - LD - Medical Writer
[redacted] - LD
[redacted] - LD
[redacted] - MHRA-NIBSC
[redacted] - LD
Dr J Raine - MHRA CEO
Ms N Rose - MHRA-NIBSC
[redacted] - VRMM
[redacted] - LD
[redacted] LD
[redacted] - VRMM
Mr P Tregunno - VRMM

[redacted]

[redacted] - LD
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - VRMM
Dr K Wydenbach - LD

Secretariat

[redacted]

[redacted]

22nd June 2021

Key
LD = Licensing Division
NIBSC = National Institute for Biological Standards & Control
VRMM = Vigilance & Risk Management of Medicines
Directorate = Director of Operational Transformation
MHRA CEO = Chief Executive

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 at **Annex II** to the minutes.

1.4 Apologies were received from Professors Hyrich, Robertson and Shah for this meeting.

1.5 The Chair welcomed the following invited experts for the meeting today:

[redacted] Professor of [redacted] University of Oxford

[redacted] Imperial Healthcare College NHS Trust

[redacted] at Oxford University Hospitals

[redacted] at University Hospital Birmingham

[redacted] University College London Hospitals

According to the Conflict of interest Policy invited experts are permitted to participate in discussions and do not contribute to conclusions and recommendations. At the chair's discretion, Professor Scully, Dr Cooper and Dr Lester was permitted to participate by answering specific questions from the chair, but not raise spontaneous comments or questions.

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

[redacted] Public Health England

[redacted]
Immunisation, Hepatitis, Blood Safety and Countermeasures Response
National Infection Service
Public health England

[redacted]

[redacted]
Professor of Primary Care and Director of Graduate Studies
[redacted]

[redacted]
Locum Consultant in Health Protection
Public Health Agency

[redacted]
Public Health England

[redacted], NIHR Health Protection Research Unit in Immunisation
London School of Hygiene & Tropical Medicine

[redacted]
Public Health Scotland

Professor Wei Shen Lim
COVID-19 Chair for JCVI

[redacted]
Public Health England

[redacted] Public Health Wales

[redacted]
Clinical Workstream [redacted]
National COVID-19 Vaccination Programme
NHS England and NHS Improvement (National)

[redacted]
Immunisation, Public Health England

2. Review of venous thromboembolism and thrombosis with thrombocytopaenia reported following vaccination with AstraZeneca COVID-19 vaccine

2.1 Introduction

2.1.1 The Chair welcomed the invited experts in haematology to the ad hoc Expert Working Group which had been convened to advise on reports of venous thromboembolism and thrombosis with thrombocytopaenia following vaccination with the AstraZeneca COVID-19 vaccine.

2.1.2 The Chair indicated that there were three questions to consider:

a. Is there an increased risk of peripheral VTE associated with the Pfizer and AZ vaccines?

b. Is there an increased risk of thrombocytopaenia with the Pfizer and AZ vaccines?

c. What is the expert view on cases of thrombosis with thrombocytopaenia associated with the AZ vaccine?

2.2 Peripheral Venous thromboembolism

2.2.1 The meeting heard data presented by MHRA and Public Health England in relation to peripheral venous thromboembolic events. Combined epidemiological evidence from multiple data sources including the MHRA's Yellow Card database, CPRD and the Secondary Uses Service consistently indicate that the incidence of venous thromboembolic events is not at a higher level than expected when compared to historical background rates and when other risk factors such as underlying conditions were taken into account. The Group concluded following discussion that the available data indicate there was no signal of these events occurring with either COVID-19 vaccine currently deployed in UK, Pfizer/BioNTech and AstraZeneca COVID-19 vaccine.

2.3 Immune thrombocytopaenia

2.3.1 Observed/ expected analyses indicate the number of observed spontaneous reports of ITP received through the Yellow Card scheme remains substantially below the expected.

2.4 Thrombosis with thrombocytopaenia

2.4.1 There were no cases noted for the Pfizer vaccines. Case report details were presented for the Astra Zeneca vaccine. The meeting noted a small cluster of 7 thrombotic events (5 CVST and 2 PE) occurring in conjunction with thrombocytopenia predominantly in younger patients (range 19-73, mean 41.7, median 32 years) following vaccination with AstraZeneca COVID-19 vaccine. This was agreed to be a challenging issue to investigate: due to the combination of events, it would extremely be difficult to evaluate this using epidemiological analyses alone, and detailed examination of the clinical characteristics of the cases would be needed.

2.4.2 The meeting heard evidence relating to a signal of thromboembolic events occurring with thrombocytopaenia that had been raised by the EMA following suspension of the AstraZeneca vaccine in several EU member states including Ireland, Norway, Iceland, Austria, Estonia, Lithuania, Luxembourg, Italy, Latvia, and most recently, France, Spain and Germany. There appeared to be a pattern of Cerebral Venous Thrombosis with thrombocytopaenia. Some cases were apparently confounded, e.g. by concomitant hormonal oral contraceptives. There were 5 cases in Norway (4 CVST plus 1 portal venous

thrombosis, three of whom were on Oral Contraceptives or Nuvaring) and 7 cases in Germany all in young women (three with potential risk factors for thrombosis, oral contraceptives, unspecified genetic disorder and pre-existing thrombophilia with von Willebrand disease type 1, Factor V Leiden mutation and anticardiolipin antibody).

2.4.3 The meeting noted anecdotally that there were likely other similar cases that had not yet been received by the MHRA. Experts agreed there was a need to rapidly gather data on these cases, including previous COVID-19 infection, with clinical input from a panel of clinical experts as the data emerged to keep pace with the dynamic nature of the signal. It would also be helpful to put out a call for reporting via the British Society for Haematology, not only of cases occurring in relation to the vaccine but also those which occur naturally.

2.4.4 Experts noted that the co-existence of a prothrombotic state with thrombocytopaenia is rare. Although this is seen to occur rarely with certain conditions, at present it is unclear if a causal association exists with the vaccine. Nevertheless, given the close temporal association and the rare nature of the event, the meeting concluded this should be promptly evaluated further as a signal.

2.4.5 To date, thrombosis occurring with thrombocytopenia has not been noted with the Pfizer vaccine from UK Yellow Card reports. The Centres for Disease Control's rapid cycle analysis for events of venous thromboembolism, pulmonary embolism and disseminated intravascular coagulation has not identified a statistically significant increased risk for any of these events for the mRNA vaccines in use in the USA (Pfizer and Moderna).

2.4.6 Immune thrombocytopenia can occur with vaccines, for example, it has been noted to be associated with the MMR vaccine at a risk of approximately 1 per 25,000. Further literature analyses of the occurrence of thrombocytopaenia together with thrombosis for any vaccine needs to be undertaken.

2.5 Conclusion

2.5.1 The Group agreed that there was no evidence of an increased risk of peripheral venous thromboembolism. The group also agreed that the evidence did not support an increased risk of thrombocytopaenia alone.

2.5.2 Although the numbers of cases of thrombosis with thrombocytopaenia were small, the Group advised that since this was a very serious condition further information should be rapidly gathered.

2.6 Advice

2.6.1 The meeting advised that the benefit-risk of the vaccine was still positive overall, although it may vary in different age groups and clinical vulnerability. Further data on the risk of COVID-19 stratified by age needs to be evaluated (not only with respect to mortality, but also hospitalisation) to provide a better assessment of benefit-risk in different age groups.

2.6.2 The meeting agreed on the further next steps:

a. To work with expert haematologists on a proforma to rapidly gather more relevant clinical details on cases of thrombosis with thrombocytopaenia

b. To work with a panel of experts to obtain expert review of cases, understand their nature and whether there is a causal association.

c. To work with clinical groups including the British Society for Haematology to encourage pro-active reporting of cases to the Yellow Card scheme in as much

detail as possible. This would include reporting of COVID-19 serology, and also of similar events not associated with vaccination.

d. Along with experts, to carefully establish appropriate risk minimisation strategies to enable patients and non-specialists to be able to detect the occurrence of these events at an early stage.

e. Ongoing review at a rapid pace to be discussed with the Expert Working Group at subsequent meetings.

2.7 Communications

2.7.1 The meeting noted that public messaging around the signal would need to be very carefully handled to maintain public confidence.

3. Any Other Business

None.

4. Date and time of next meeting

The next meeting is scheduled to take place on Thursday 18th March 2021 at 10:30.

The Meeting today started at 15:01 and ended at 17:10.

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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.

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.

Professor Weir - NPNS - Imperial College and Other relevant interest arising from his department collaborates with Imperial College on a number of clinical trials.

Invited Experts for this meeting

[redacted]

Observers for this meeting

[redacted] - None

[redacted] - None

[redacted] - None

[redacted]

[redacted] – None

Professor Lim - NPNS interest as the institution he works for (Nottingham University Hospitals NHS Trust) has received unrestricted investigator-initiated research funding from Pfizer for an unrelated prospective population-based cohort study of pneumococcal pneumonia in which WSL is the Chief Investigator.

[redacted]

[redacted]

[redacted]

[redacted] – None

[redacted] – None

[redacted] – None