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

Minutes of the meeting held on **Monday 14th June 2021** at **10:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Mr VI G Fenton-May
Professor N French
Ms S Hunneyball
Professor K Hyrich
Sir M Jacobs
Professor P J Lehner
Mr R Lowe[2]
Dr S Misbah
Professor Y Perrie
Professor C Robertson[1]
Professor T Solomon[2]
Professor K M G Taylor
Dr R Thorpe[3]
Professor M Turner
Dr S Walsh
Mrs M Wang
Professor C Weir

Apologies

Professor J Breuer
Professor G Dougan
Professor D Goldblatt
Professor H J Lachmann
Professor S Price
Dr A Riordan[3]

Observers

[redacted]
Professor WS Lim[4]
[redacted]

Secretariat

[redacted]

[1] joined during item 2
[2] left during item 3
[3] left during item 4
[4] Joined during item 3

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted] - VRMM

Presenters supporting specific items

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

MHRA Observers

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

[redacted]

4th February 2022

Key
LD = Licensing Division
VRMM = Vigilance & Risk Management of Medicines
NIBSC = National Institute for Biological Standards & Control
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 Professors Breuer, Dougan, Goldblatt, Lachmann, Price and Dr Riordan for this meeting.

1.5 The Chair welcomed the following observers:

[redacted] JCVI

[redacted]
Public Health Agency

Professor Wei Shen Lim
Chair of JCVI

[redacted]
Public Health Scotland

[redacted]
Public Health England

[redacted]
Head, Vaccine Preventable Disease Programme at Public Health Wales

[redacted]
NHS England and NHS Improvement (National)

1.6 The Chair congratulated Professor Tom Solomon for receiving a CBE award in the Queen's Birthday Honours List for his services to Neurological and Emerging Infections Research, including during the COVID-19 response.

2. COVID-19 vaccine AstraZeneca post authorisation effectiveness study protocol-COVIDRIVE

2.1 The EWG heard a summary of AstraZeneca's proposed post authorisation effectiveness study. The EWG commented that further clarification was required as to how the study will be conducted in terms of what aspects will be actively collected and what aspects will use secondary data and how they will define cases and outcomes.

2.2 The EWG considered that given the advanced stages many participating countries' vaccine roll-out are now at, the study may be initiated too late to be useful and informative. The EWG asked for clarification from the protocol authors if the Brighton Collaboration criteria will be used to define vaccine associated enhanced disease.

2.3 The EWG questioned whether it was appropriate to pool data across countries and considered that more meaningful results may be achieved by looking at each context individually.

2.4 In email comments, the EWG remarked on the fact that investigators will be allowed flexibility in terms of the type of controls used and in the numbers of control per case but stated that it will be important to make sure that these differences are accounted for in the analysis. They asked for more clarity on participating countries and also asked the authors to provide more specific information about sample size calculations.

3. Update on COVID-19 Vaccines and the risk of thromboembolic events with concurrent thrombocytopenia

3.1 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 9th June 2021.

3.2 The EWG reviewed the following publications: an article proposing a role for antiphospholipid antibodies in determining the severity of thrombosis with thrombocytopenia following Covid-19 vaccination; a pre-print report of an observational study describing the background incidence rates of 5 thrombosis with thrombocytopenia syndromes (TTS) from 6 European countries including the UK; and the effectiveness of adjunct intravenous immunoglobulin (IVIG) treatment in a small cases series of patients with PF4 antibodies. The EWG noted that the paper on potential mechanisms was highly speculative with no supportive clinical data and that there is no current evidence that the presence of antiphospholipid antibodies worsens the prognosis for those with TTS. The EWG advised that the dose of IVIG recommended in the Canadian case series paper is higher than that given in the current guidance issued by the UK Expert Haematology Panel.

3.3 An overview of the UK case reports associated with the AstraZeneca (AZ) COVID-19 Vaccine was presented including summary tables of the second dose cases. The EWG noted that a new confirmed case following a second dose has now been reported.

3.4 The UK and foreign cases associated with the Pfizer, Moderna and Janssen COVID-19 vaccines were summarised using the same case definition. A new non-UK confirmed case associated with the Pfizer COVID-19 vaccine was identified.

3.5 The estimated number of second AstraZeneca (AZ) COVID-19 vaccine doses administered has increased to 17.7 million whilst the number of first doses has increased slightly, in line

with the current deployment programme to 24.6 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 14.8 (13.3, 16.4) per million for first/unknown doses and the overall fatal incidence rate is also stable at 2.7 (2.1, 3.5) per million first/unknown doses. The age-stratified incidence rates associated with second doses were reviewed and the overall rate was stable at 1.5 (1.0, 2.2) per million doses. The case incidence rates per 100,000 patient years were also compared for first and second doses. The case incidence rates (per 100,000 patient years) within 28 days of dosing were 15.46 (13.9, 17.5) for the first or unknown doses and 2.6 (1.7, 3.7) for second doses. The risk estimates were then compared with the expected benefits of vaccine in age subgroups. The EWG noted that the reported CVST incidence rates following the first or unknown doses have increased slightly since the last data lock point, although the 95% confidence intervals are overlapping, while risk-benefit ratio remained relatively unchanged. The EWG commented that it is possible that the slightly increasing incidence rates are related to delayed reporting or over-reporting of typical thromboembolic events with mild thrombocytopenia or a longer latency time. The MHRA explained that there may have been case under-ascertainment early in the deployment programme and more younger people, possibly at higher risk, are now being targeted for vaccination. It is reassuring that the age-stratified risk estimates are stable. The EWG noted that the current estimates of the vaccine's beneficial effects are derived from second wave data for the SARS-CoV-2 Alpha variant. Emerging UK data indicates that the AZ COVID-19 vaccine is equally effective against the Delta variant although slightly fewer cases may be prevented. The EWG advised that the MHRA should use predicted third wave data for the Delta variant in its future benefit calculations to reflect the current situation.

3.6 The EWG then considered the following 3 questions:

3.6.1 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 significantly since it was reviewed on 7th June 2021.

3.6.2 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 reassuring the MHRA should continue to monitor second dose cases closely, particularly as younger patients will now be receiving their booster immunisations.

3.6.3 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.

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

4. Update on Capillary Leak Syndrome with COVID-19 vaccine AstraZeneca

4.1 The EWG heard that the European Medicines Agency's Pharmacovigilance and Risk Assessment Committee (PRAC) had recommended that warnings regarding a risk of capillary leak syndrome (CLS) should be added to the product information for the AstraZeneca vaccine. PRAC recommended a 4.3 contraindication, a 4.4 warning and listing of CLS in section 4.8.

4.2 The EWG considered that if they were to diverge from EMA's warnings, concrete evidence of patients with a history of CLS safely receiving the AstraZeneca vaccine, which is not available. The severity of the disease would also suggest a cautious approach would be warranted. The EWG therefore considered that the warnings should be included in the product information for the AstraZeneca vaccine in order to maintain alignment in Great Britain and Northern Ireland.

4.3 However, the EWG considered given the very small numbers and extreme rarity of the reported events, it was concerning to add warnings given the uncertainty around the causality of these events. The EWG considered inclusion of these warnings to be a pragmatic decision (in that the affected population is very small and there are alternative vaccines available to these patients) under circumstances where the evidence base was uncertain. The EWG did not wish for this inclusion to set a precedent for including warnings where such uncertainty exists, and the data is limited.

4.4 With regards to whether the introduction of these warnings warranted distribution of a Dear Healthcare Professional Communication (DHPC), the EWG considered that given the strong deployment framework within the UK, the NHS bodies within the 4 nations would be able to more effectively communicate the updates than a DHPC.

5. Any Other Business

None.

6. Date and time of next meeting

The next scheduled meeting is to take place **on Monday 21st June** at **10.30am**.

The Meeting today started at 10:32 and ended at 11:58.

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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 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 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 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 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] - 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 [redacted] has now left that role.

[redacted] - Other relevant interests in Pfizer & GSK- 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.