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

Minutes of the meeting held on **Friday 17th September 2021** at **14:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer[1]
Professor G Dougan[1]
Mr VI G Fenton-May[2]
Professor N French[1]
Professor D Goldblatt[3]
Ms S Hunneyball
Professor P J Lehner
Dr S Misbah
Professor Y Perrie[4]
Dr A Riordan
Professor C Robertson[1]
Professor T Solomon
Professor K M G Taylor
Dr R Thorpe
Professor M Turner[3]
Professor S Walsh

Apologies

Professor K Hyrich
Sir M Jacobs
Professor H J Lachmann
Mr R Lowe
Professor S Price
Mrs M Wang
Professor C Weir

Visiting Experts

[redacted][5]
[redacted][6]
[redacted][7]

Observers

Professor WS Lim
[redacted]

Secretariat

[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted] - VRMM

Presenters supporting specific items[8]

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

MHRA Observers

[redacted] - VRMM
Dr S Branch - VRMM
[redacted] - VRMM
[redacted] - VRMM
[redacted] – MHRA Policy
[redacted] – VRMM
[redacted] – Comms
[redacted] - LD
[redacted] - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - VRMM

Key

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

[1] left during item 5
[2] joined during item 2
[3] left during item 6
[4] joined during item 2
[5] participated in item 6 only
[6] participated in item 5 only
[7] participated in item 2 only
[8] supported specific item

[redacted]
18th November 2022

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 Hyrich, Lachmann, Price, Weir, Mr Lowe, Mrs Wang and Sir Michael Jacobs for this meeting.

1.5 The Chair welcomed the following visiting experts:

[redacted] University of Cambridge
Participated for item 6.

[redacted]
Professor of Clinical Neurology and Consultant Neurologist. Participated for item 4.

[redacted] Bristol Heart Institute.
Participated for item 6.

[redacted] Imperial College Healthcare NHS Trust. Participated for item 2.

1.6 The Chair welcomed the following observers:

Professor Wei Shen Lim
Chair of JCVI

[redacted]
NHS England and NHS Improvement (National)

2. Observation time for mRNA COVID-19 booster vaccines

2.1 Advice was requested from the EWG on the need to retain a 15-minute observation period following mRNA vaccine booster doses.

2.2 The EWG were informed that Public Health England were considering an update to the Green Book advice to remove the requirement for the 15-minute observation period for homologous booster doses of the Pfizer/BioNTech and Moderna vaccines for patients that have not experienced any allergic reactions following the first and second doses.

2.3 The EWG noted the removal of the 15-minute observation period for homologous boosting would help to speed up the delivery of third doses and flu vaccines, which are planned to be administered together where the opportunity arises.

2.4 The EWG were presented with a summary of Yellow Card reports in the anaphylactic SMQ narrow. The EWG noted that reporting rates were higher following first dose compared to second dose. The EWG also noted reassuring data from Israel on third dose homologous boosting, which did not indicate any safety signals post-booster including for anaphylaxis.

2.5 The EWG considered that for individuals who do not experience an allergic reaction to a first and second dose of an mRNA vaccine, then it is unlikely that a third homologous dose will result in anaphylaxis. The EWG noted there was no data for heterologous booster doses and that this would be a new exposure to recipients who had not previously received that vaccine.

2.6 The EWG concluded that for those who are receiving a booster homologous dose of an mRNA vaccine and who have not experienced an allergic reaction or anaphylaxis with the primary doses, the requirements for the 15-minute observation period can be removed, including for third doses for immunocompromised patients. For those who are receiving a third or booster heterologous dose of an mRNA vaccine, the requirement for a 15-minute observation should be retained.

2.7 The EWG considered that the advice could be included in the Regulation 174 product information for Pfizer following endorsement from relevant bodies. For CMA products this can be applied via advice in the Green Book.

2.8 The EWG noted that careful communication would be required to explain why the 15-minute observation period for homologous third doses and boosting has been removed.

3. Update on AstraZeneca COVID-19 Vaccine and the risk of Human Leukocyte Antigen (HLA) sensitisation

3.1 The EWG was presented with the outcomes of a study on HLA sensitisation following a full two dose schedule.

3.2 The EWG was informed that the present study was included in the AstraZeneca Risk Management Plan (RMP) as a commitment to address the important potential risk of 'HLA sensitisation in transplant candidates and recipients'. This risk was theoretical in nature based on HLA sensitisation previously described following use of enveloped viruses; however, the chimpanzee adenovirus (ChAd) used for Covid-19 AZ is a non-enveloped virus. Patients who are highly sensitised face longer waiting times on organ allocation programmes (by reducing the options for selection of HLA-compatible donor organs), more graft rejection and therefore more side effects of immunosuppression, and poorer graft outcomes.

3.3 The EWG was informed that initial investigations showed no evidence for the presence of HLA proteins in the drug substance. Further, serum sample testing from vaccinated individuals showed no de-novo occurrence of anti-HLA antibodies following vaccination. Subsequently, the company was requested to conduct further analysis from a larger proportion of trial participants with comparison to samples from participants who received active control or placebo on the basis of a valid statistical plan.

3.4 The Group was presented with the data which did not indicate HLA sensitisation following vaccination with AstraZeneca vaccine compared to active control or placebo.

3.5 The EWG considered that the statistical model looked complex and that most of this was due to the study's design. Investigating gain or loss with each arm of these studies leads to interaction terms. The EWG noted that the sample size was reasonable to fit these models however, the precision may not be too high.

3.6 Despite the limitations of the study, members were reassured by the results the study provided.

3.7 The EWG advised that MHRA should communicate the outcome of the study to NHS Blood and Transplant (NHSBT).

3.8 The EWG agreed that based on the data provided, the important potential risk 'HLA sensitisation in transplant candidates and recipients' could be removed from the RMP.

4. Glomerulonephritis and nephrotic syndrome and COVID-19 vaccines

4.1 The EWG was presented with a review of the currently available evidence from non-clinical, clinical, literature and spontaneous sources (including Yellow Card data with a data lock point of 6th September 2021) regarding glomerular nephritis and nephrotic syndrome following vaccination against COVID-19 with the AstraZeneca, Pfizer-BioNTech and Moderna COVID-19 vaccines. Company reviews of this issue provided by Moderna and Pfizer were also presented.

4.2 The EWG was also informed of an ongoing review of this issue by the PRAC for Pfizer and Moderna COVID-19 vaccines.

4.3 The EWG heard that there was currently no evidence from non-clinical and clinical sources for a risk of these conditions following vaccination with any of the COVID-19 vaccines reviewed.

4.4 The EWG agreed that the number of Yellow Card reports and published literature cases of glomerular nephritis and nephrotic syndrome was low in the context of usage, including cases of acute kidney injury in the context of the background rate of this event in the population.

4.5 The EWG were reassured by the fact that the cases reviewed were heterogenous in terms of type of events reported (e.g. minimal change disease, IgA nephropathy etc.) and the range of associated background conditions reported, and that there were no reports of complement activation which could indicate an underlying immunological process.

4.6 It was noted that published studies in children with nephrotic syndrome had not shown a link between non-COVID-19 vaccination and a relapse of the condition; it was also noted that a large study of the meningitis C vaccine had also not shown a link to these conditions.

4.7 The EWG proposed that a non-specific activation of the immune system could potentially lead to a relapse of pre-existing glomerular nephritis or nephrotic syndrome and relapse may also be theoretically possible if vaccination occurs at the time of underlying active glomerular nephritis. The EWG therefore recommended that further expert opinion on the relevance of these factors should be sought.

4.8 No regulatory action was advised at this time pending additional expert opinion.

5. GBS and COVID-19 Vaccines

5.1 The EWG heard a presentation from Professor Michael Lunn describing a study conducted using linked data from the NHS England intravenous immunoglobulin (IVIG) database and the national immunisation management system to explore the risk of Guillain Barre Syndrome (GBS) following COVID-19 vaccination.

5.2 The EWG were informed that the number of GBS cases identified in the IVIG database in March and April 2021 was higher than the normal range for those calendar months. Analyses looking at the rate of GBS following vaccination showed a higher rate of GBS in the 6 weeks following a first dose of the AstraZeneca vaccine compared to the Pfizer vaccine, controlling for patient age. No difference in the rate was seen in the period 6-12 weeks following a first dose. It was estimated that this resulted in an approximately 6-8 additional cases per million first doses of the AstraZeneca vaccine.

5.3 The EWG noted that other influenza and adenovirus vaccines have been associated with an increased risk of GBS. The EWG discussed the potential for missing cases only with bilateral facial paralysis from this study as these would not receive IVIG and the potential impact of reduced availability of IVIG.

5.4 The EWG agreed that the study strengthened the evidence on an association between the AstraZeneca vaccine and GBS and recommended that the current AstraZeneca product information be reviewed with regards to the risk of GBS. They also recommended that for patients experiencing GBS following a first dose, an alternative vaccine should be offered for a second dose.

6. mRNA COVID-19 Vaccines and myo/pericarditis (Slides)

6.1 The EWG were presented an update on reports of myocarditis and pericarditis with the mRNA COVID-19 vaccines, focusing on data on exercise as a potential risk factor, reports of rechallenge in individuals who experienced myocarditis or pericarditis following their first dose and experience in individuals under the age of 18 years.

6.2 The EWG were informed that for the Pfizer/BioNTech vaccine, the reporting rates were similar between the first and second dose across all adult age groups. For the under 18-years age group, the reporting rate was higher for the second dose of Pfizer/BioNTech vaccine, but this was based on a small number of reports and limited exposure. For the Moderna vaccine, there has been an increase in the reporting rates in the 18-29-years age group and the reporting rates remain higher for the second dose compared to the first dose. The Moderna reporting rates have also remined higher than the Pfizer/BioNTech reporting rates.

6.3 The EWG were informed that there had been a total of 12 reports of myocarditis and pericarditis in individuals under 18 years for the Pfizer/BioNTech vaccine, with all of these occurring in 16-17-year-olds. The most common symptoms were chest pain and shortness of breath, and the majority were reported as having recovered. None of the reports of myocarditis or pericarditis had been confirmed by cardiac MRI.

6.4 The EWG were presented with international data on the Pfizer/BioNTech vaccine from Israel. Reporting rates have remained higher for the second dose compared to the first dose, with higher reporting rates in males compared to females. The EWG noted that the reporting rate in 12-15-year-olds was lower for both first and second dose compared to older age groups.

6.5 The EWG noted that there had been a small number of rechallenge reports, with the majority of these relating to aggravation of symptoms and did not include medical diagnosis of myocarditis. Reports of rechallenge from Israel have shown no recurrence of myocarditis or pericarditis with the administration of a second dose. The EWG considered that the available data does not suggest that individuals who had recovered from myocarditis or pericarditis following COVID-19 vaccine would be at a higher risk of experiencing myocarditis or pericarditis again with a second dose of vaccine. However, the EWG concluded that further research was required to be able to draw firm conclusions and the current Green Book advice to defer the second dose of COVID-19 vaccine if myocarditis or pericarditis have occurred after the first dose should be maintained.

6.6 The EWG were informed that there was a small proportion of reports that mentioned either onset of symptoms or aggravation of symptoms with strenuous exercise, and with these generally reported in younger males. The EWG concluded that the data did not support advice to rest following vaccination for individuals who do not have any symptoms. However, it was advised that patients with a diagnosis of myocarditis or pericarditis following COVID 19 vaccination should follow specific advice from their cardiologist to avoid exercise for a few months.

6.7 The EWG were informed that the Moderna risk management plan was being updated to include myocarditis and pericarditis as important identified risks. The ongoing post-authorisation studies have also been updated to include myocarditis and pericarditis as adverse events of special interest.

7. Any Other Business

None.

8. Date and time of next meeting

The next scheduled meeting is to take place on **Friday 24th September** at **10:30**.

The Meeting today started at 14:32 and ended at 17:12.

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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.

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).

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). Member of the independent Data Safety Monitoring Board for COV-BOOST trial.

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.

Observer

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.

Visiting Expert