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

Minutes of the meeting held on **Friday 23rd July 2021** at **10:30** via videoconference

Participants Present

Members

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

Apologies

Professor D Goldblatt
Professor H J Lachmann
Professor P J Lehner
Professor C Robertson
Professor M Turner

Visiting / Invited Experts

[redacted][3]
[redacted][3]
[redacted]
[redacted][5]

Observers

[redacted]

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

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
[redacted] - VRMM

MHRA Observers

[redacted] - VRMM
[redacted] - LD
Ms A Cave - Directorate
[redacted] - VRMM
[redacted] – MHRA Policy
[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - LD
[redacted] - Comms
[redacted] - VRMM
Mr P Tregunno - VRMM
[redacted] - LD
[redacted] – VRMM
[redacted] - VRMM

Secretariat

[redacted]

[redacted]

4th February 2022

[1] left after item 6
[2] left during item 6
[3] Participated for items 3 & 4 only
[4] Participated for item 2 only
[5] Participated for item 6 only

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 Goldblatt, Lachmann, Lehner, Robertson and Turner for this meeting.

The Chair welcomed the following visiting / invited experts:

[redacted]
Edinburgh Medical School

[redacted] University of Aberdeen

[redacted]
University Hospital Bristol NHS Foundation Trust

[redacted]
Professor of Clinical Neurology and Consultant Neurologist

1.5 The Chair welcomed the following observers:

[redacted] JCVI

[redacted] JCVI [redacted], [redacted] Joint Committee on Vaccination and Immunisation, Public Health England

[redacted]
Public Health Agency

[redacted]
Public Health England

[redacted] Public Health Wales

[redacted]
NHS England and NHS Improvement (National)

2. Presentation: ComFluCov trial

2.1 The EWG was presented with details of the ComFluCov trial which is coordinated by University Hospitals Bristol and Weston. The trial commenced in March 2021 and is sponsored by the National Institute for Health Research (NIHR). The trial objective was to gain a greater understanding of the tolerability and safety of concomitant vaccination (COVID-19 vaccine & influenza vaccine). The trial included COVID vaccines: AstraZeneca vaccine, or Pfizer vaccine and influenza vaccines: Fluad, or Flucelvax, or Flubloc.

2.2 The EWG noted that due to the urgent need to generate data ahead of the 2021/2022 flu season, second doses rather than booster doses were used. This also aligned with the stage of the UK vaccine campaign at the time that the trial data were collected.

2.3 The EWG asked if there was a biological basis to suspect that a difference in immunogenicity could occur with single schedule versus a concomitant schedule (COVID and influenza vaccine). The EWG heard previous studies of concomitant use have generated mixed results. For example, studies of pneumococcal vaccines have shown immunogenicity to be preserved; however, the pre-print results of a study of the Novavax vaccine given concomitantly with influenza vaccine showed a reduction in immunogenicity in response to vaccination with Novavax, although clinically the reduction was not estimated to hold significance.

2.4 The EWG noted that a key area of interest is the degree of protection afforded against variants of SARS-CoV-2 and influenza viruses. The EWG heard there are plans to complete immunogenicity evaluations against the SARS-CoV-2 alpha strain whereas, in terms of flu vaccines, to avoid the need for unblinding testing will be completed against all four strains for all samples. The EWG heard that a serendipitous consequence of this will be the availability of data on Fluad vaccine against the B strain—a strain not included in this vaccine formula.

2.5 The EWG heard that in line with the authorised route of administration the vaccines were given by intramuscular (IM) deltoid injection in opposite arms, in other instances where this was not possible the upper thigh was selected.

2.6 [redacted]

2.7 The EWG noted that also undertaking concomitant studies of Fluenz Tetra would likely be useful given the probable roll-out of the COVID vaccines to children. The invited expert agreed to share this opinion with the paediatric team.

2.8 The EWG noted that, as a consequence of the trial's timing it was not able to include concomitant COVID-19 booster doses (third doses) and the flu vaccine. Without such data decisions can only rely on observational data, that is, unless data from other trials generated outside of the UK become available.

3. Menstrual disorders and COVID-19 vaccines

3.1 The EWG was informed of the MHRA's previous reviews (June 2021) of reports of menstrual disorders following the COVID-19 vaccines, including reports of heavy and/or painful periods, delayed or absent bleeding, changes in menstrual cycle patterns, and post-menopausal bleeding. The EWG had been informed during these reviews that the number of Yellow Card reports of menstrual disorders had increased alongside the usage of the vaccines and escalating media coverage relating to this issue. The EWG noted at that time the number of reports was small in the context of the vaccine usage and it was agreed to continue to monitor reports.

3.2 The EWG considered an assessment of non-clinical and clinical trial data, as well an updated review of spontaneous reports of menstrual disorders reported via the UK Yellow Card Scheme for the AstraZeneca, Pfizer-BioNTech and Moderna COVID-19 vaccines with a data lock point of 14 July 2021. The EWG also considered data from the Yellow Card Vaccine Monitor (YCVM) and the ZOE App. Invited experts included [redacted] of the University of Edinburgh and [redacted] of the University of Aberdeen (chair of MWHEAG) and written comments were provided by [redacted], Specialist in menopause and gynaecology, Meanwood Group Practice and Spire Hospital, Leeds.

3.3 It was noted that although there was no evidence for effects on the menstrual cycle from pre-clinical or clinical trial data, non-clinical models used were generally not very predictive for humans and the collection of data on the menstrual cycle during clinical trials tends to be poorly standardised.

3.4 The EWG agreed that the updated evidence presented did not suggest a causal association between the COVID-19 vaccines and the menstrual events reported and it considered that the data from the YCVM and the ZOE app were reassuring. It was noted that reports of menstrual disruption (which can be considered as 'symptoms' rather than 'diagnoses') were very common (reported by up to 1 in 3 women over their lifetime) since the endogenous mechanisms that control the menstrual cycle are highly susceptible to stressors and other factors. In line with the patterns of Yellow Card reporting described in the paper, it was agreed that women most commonly seek medical attention for menstrual problems such as fibroids in the age band 30-49 years. The EWG noted that menstrual changes may be associated with factors such as undiagnosed underlying conditions, conditions such as long COVID, with the extraordinary stress associated with the pandemic, and with bleeding irregularities associated with use of hormone preparations. The EWG heard that it was in fact noted that some women have been temporarily stopping hormone replacement therapy with the aim of reducing the perceived risk of vaccine related venous thromboembolism. The invited experts highlighted a study which compared the incidence of menstrual disturbances pre- and post- COVID-19 pandemic, which identified a higher frequency of these during the pandemic.

3.5 The EWG noted that many women reporting menstrual changes are concerned that the changes may be permanent or may potentially affect their fertility. The EWG advised that fertility was a complex process, susceptible to many factors beyond changes in the menstrual

cycle. The EWG highlighted that short-term effects on the menstrual cycle would not generally indicate a potential change in fertility. It was noted that although up to 40% of Yellow Cards reported an outcome of recovered or recovering, without more complete longitudinal data, it will be difficult to estimate time to recovery with confidence.

3.6 To address increasing current public interest, the EWG advised that clear positive communication will be especially important to emphasise the absence of causal association with the vaccines and that the menstrual changes being reported are usually transient with no evidence that they will affect fertility. The EWG requested a further update on this issue in 6 weeks' time once the younger age groups have received their second dose of vaccine.

4. Review of the safety data for COVID-19 vaccines in pregnancy

4.1 The EWG considered the latest safety information regarding COVID-19 vaccines in pregnancy, including data from the spontaneous Yellow Card reports and the Yellow Card Vaccine Monitor (YCVM) received up to and including 9th July 2021.

The EWG noted written comments from [redacted]

4.2 The EWG noted that since its last reviews of these data in March and April 2021, the advice on use in pregnancy from the Joint Committee on Vaccination and Immunisation (JCVI) had been amended to include offering vaccinations to those who are pregnant at the same time as non-pregnant individuals based on their age and clinical risk group. It was noted that the Pfizer-BioNTech and Moderna vaccines are currently the preferred vaccines for use during pregnancy.

4.3 Up to 9h July 2021, 810 spontaneous Yellow Card reports have been received for reports related to possible exposures during pregnancy. Of these, 726 reported suspected ADRs associated with exposures during pregnancy via maternal vaccination. In addition, the Yellow Card Vaccine Monitor included information from 1366 participants who reported maternal exposures during pregnancy up to 30th June 2021, of whom 565 participants had reported suspected ADRs following vaccination up to 9th July 2021. This is in the context of at least 55,000 women in England and Scotland who reported they were or might be pregnant at the time of vaccination.

4.4 The data reviewed comprised 264 spontaneous reports and 124 reports from YCVM participants who had received the Oxford-AZ vaccine (total n = 388 reports), 383 spontaneous reports and 383 reports from YCVM participants who had received the Pfizer-BioNTech vaccine (total n = 766 reports), and 79 spontaneous reports and 58 reports from YCVM participants who had received the Moderna vaccine (total n = 137 reports).

4.5 The EWG noted that reports of miscarriage, especially first trimester losses, constitute a large proportion of the spontaneous Yellow Card reports related to early pregnancy exposures. Some miscarriages were reported as gestational age of fetal demise as detected by scans and some by onset of bleeding. As far as can be ascertained from this information, there is no clear pattern for the miscarriages with respect to time to onset, gestational age or presence or absence of non-pregnancy related ADRs, including pyrexia, fever or chills.

4.6 The EWG noted that first trimester miscarriage is estimated to occur in 20 to 25 of 100 UK pregnancies outside of the pandemic. The EWG considered that the reports of first trimester miscarriages reported did not raise concerns in light of these considerations.

4.7 The EWG considered that it was important to continue to collect these data and suggested that communications on the use in pregnancy should be placed in context of the background risk and any risks potentially associated with COVID-29 infections.

4.8 The EWG noted a small number of reports have been received for each of stillbirth, transient decreases of fetal movements, premature rupture of membranes, premature birth and term births. The EWG considered that these reports did not raise concerns at this time and in light of published international evidence of safety in pregnancy for the Pfizer-BioNTech and Moderna vaccines.

4.9 The EWG noted that further data on pregnancy outcomes, including data from studies in Scotland (the COPS study) and England (OpenSafely) are expected to add to knowledge of safety of the COVID-19 vaccines in pregnancy in due course.

5.10 The EWG noted that vaccine hesitancy is a concern amongst pregnant women, especially for vaccinations in their first trimester. The EWG recommended that these data supported that there are no concerns for using the COVID-19 vaccines during pregnancy and suggested working with the Royal Colleges of Obstetrics and Gynaecology (RCOG) and Midwives (RCM) to deliver this message.

5. COVID-19 Vaccines and risk of thromboembolic events with concurrent thrombocytopenia

5.1 The EWG was presented with a proposal to cease the weekly updates for thrombosis with thrombocytopenia syndrome (TTS) to the VBR EWG. This follows the EWG conclusion over the last month that the data has remained reassuring and without major changes.

5.2 The background and timeline of events was summarised for the reference of the EWG.

5.3 Weekly presentation of the data has resulted in no regulatory action for this issue since the product information updates provided to healthcare professionals and the public on the 7th and 15th April 2021. Since 10th May 2021 the EWG has consistently 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.

- that the risk of thromboembolic events occurring with thrombocytopenia following second doses remains reassuring.

- that the risk associated with the Pfizer and Moderna COVID-19 vaccines appears lower than that associated with the AstraZeneca COVID-19 Vaccine.

5.4 The EWG heard that all other relevant processes will continue. These include the review & analysis of relevant reports as part of the signal detection processes in the MHRA. If a new concern arises then this will be brought to the attention of the EWG. In addition, the latest breakdown of all cases concerning thromboembolic events with concurrent thrombocytopenia will continue to be published as part of the weekly coronavirus vaccine summary of yellow card reporting.[1]

5.5 The EWG agreed that the weekly updates for TTS can be ceased. The EWG requested an update in 4 weeks' time which would inform the decision as to whether full transition to an ad-hoc update system can take place.

[1] https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting

6. Update on COVID-19 Vaccines and Guillain-Barre Syndrome

6.1 The EWG was presented with up to date information on Guillain-Barre syndrome (GBS) concerning AstraZeneca, BioNTech/ Pfizer and Janssen including vaccine usage and Yellow Card data, clinical trial data, data from company monthly summary update reports and epidemiological analyses.

6.2 Following the combined evidence for the AstraZeneca vaccine, the EWG considered that there was now more evidence to suggest a potential causal relationship between AstraZeneca vaccine and GBS. It was highlighted, that the mechanism remained unclear as there is no known molecular mimicry with either the adenoviral vector or the spike protein, however not all epitopes and associated glycosylation's were known. It was considered more likely that there was a non-specific immunological switch in people prone to inflammatory demyelinating neuropathy similar to that seen post-natural infection.

6.3 The EWG recommended that the product information for AstraZeneca should be updated to include GBS as an Adverse reaction, using cautious wording, perhaps similar to the EU product information, as a causal association has not been fully established.

6.4 Concerning the BioNTech/Pfizer and Moderna COVID-19 vaccines, there was still limited evidence of an association and the EWG did not recommend any actions other than to continue to monitor the emerging data very closely.

6.5 The EWG recommended to update the GBS statement currently included in the Coronavirus Weekly Summary of Yellow Card Reporting and to include a reassuring statement that the risk of developing GBS with the AstraZeneca vaccine is considerably smaller compared with the lifetime risk of GBS due to other pathogens.

6.6 The EWG concluded that, with regards to the second dose following a GBS event after the first COVID-19 vaccine dose, the data were extremely limited. It was highlighted that GBS is a monophasic condition and that there is no evidence of an increased risk of recurrent GBS on rechallenge with either an infectious cause or post-vaccination, with a study on a flu vaccine given as an example. However, it appears that clinical practice locally was to recommend a second dose of different vaccine to the index vaccine where there were symptoms of GBS after the first dose. The EWG concluded that this advice should be considered more widely.

6.7 The EWG was also informed of cases of Functional Neurological Disorder (FND) following COVID-19 vaccination which has been mentioned in social media posts. The reporting rate was low compared to the background rate in the general population and there were no fatal cases. It was stated by the committee members that this disorder was very difficult to diagnose as it required a host of tests to exclude other causes; and there was no clear definition of FND in the neuroscience community which would make it very hard to establish causality, especially based on the small number of cases received to date. The EWG supported inclusion of a statement in the Coronavirus Weekly Summary of Yellow Card Reporting to communicate that there is no association between vaccines and FND.

7. Update on Myocarditis and Pericarditis with mRNA COVID-19 Vaccines

7.1 The EWG was presented with an update on reports of myocarditis and pericarditis with the COVID-19 vaccines. The EWG heard that there had been a substantial increase in Yellow Card reporting since the regulatory action to include myocarditis and pericarditis in the mRNA vaccine product information.

7.2 The EWG was informed that for the Moderna and Pfizer/BioNTech vaccines, reports remained consistent with the previous reviews, with a higher number of reports following the second dose, particularly in males in the younger age groups. The majority of reports still described mild events which have recovered. Observed vs expected analysis for the mRNA vaccines showed a similar pattern to the Yellow Card cases, with higher observed cases in younger age groups, especially males under 40 years, which is consistent with previous reviews of myo/pericarditis and mRNA COVID-19 vaccines.

7.3 The EWG was informed that for the AstraZeneca vaccine, the reporting rates remained low compared to the mRNA vaccines. There was a higher proportion of pericarditis reports and reports were evenly distributed between first and second dose. Observed vs expected analysis did not raise a signal for myo/pericarditis with the AstraZeneca vaccine.

7.4 The EWG was informed that reports of sudden death and other serious cardiac events have also been reviewed. Reports of these events remained low across all three vaccines considering current exposure. There were particularly low numbers of cases in patients aged under 40 years and many of these reported co-morbidities or alternative explanations for the events. The EWG considered that these cases did not have a similar pattern to the myo/pericarditis cases and no safety concern was identified with these events.

7.5 The EWG considered that based on the available evidence, no regulatory action was required for the AstraZeneca vaccine and no further regulatory action was required for either the Moderna of Pfizer/BioNTech vaccines.

8. Minutes of the meeting held on Tuesday 2nd March 2021

8.1 The minutes were approved as a true and accurate record of the proceedings.

9. Any Other Business

None.

10. Date and time of next meeting

The next scheduled meeting is to take place on **Tuesday 3rd August** at **12:30pm**

The Meeting today started at 10:35 and ended at 13:09.

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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

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.

Dr Misbah - NPNS - Holds honorary Senior Lectureship with University of Oxford & Oxford University Hospitals NHS Foundation Trust. Other relevant interest in AstraZeneca arising from being part of a collaboration in which the epidemiology and therapeutic approaches to Vaccine associated Thrombosis-Thrombocytopenia (VITT).

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). 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.

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 Experts

[redacted]

[redacted]

[redacted]

Observers

[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.