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

Minutes of the meeting held on **Wednesday 6th October 2021** at **16:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan
Mr VI G Fenton-May
Professor N French
Professor D Goldblatt
Ms S Hunneyball
Professor K Hyrich[1]
Professor H J Lachmann
Professor P J Lehner
Dr S Misbah
Professor Y Perrie
Professor S Price
Dr A Riordan
Professor K M G Taylor
Dr R Thorpe[2,3]
Professor M Turner
Professor S Walsh
Mrs M Wang
Professor C Weir

Apologies

Sir M Jacobs
Mr R Lowe
Professor C Robertson
Professor T Solomon

Observers

[redacted]

Secretariats

[redacted]

Professional Staff of MHRA Present

Principal Assessors

[redacted] - LD
[redacted] - VRMM

Presenters supporting specific items[4]

[redacted] - VRMM
[redacted] – VRMM
[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD

MHRA Observers

Dr S Branch - VRMM
Dr A Cave - Directorate
[redacted] - VRMM
[redacted] – MHRA Policy
[redacted] - VRMM
[redacted] VRMM
[redacted] – VRMM
[redacted] - Comms
[redacted] - VRMM
[redacted] – VRMM
Mr P Tregunno - VRMM

Key

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

[redacted]
16th February 2023

[1] left during item 5
[2] joind during item 2
[3] left during item 6
[4] supported specific items

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 Robertson, Solomon, Mr Lowe and Sir Michael Jacobs for this meeting.

1.5 The Chair welcomed the following observers:

[redacted] Public Health Wales

[redacted] NHS England Medical [redacted]

[redacted] Public Health Scotland

[redacted] UK Health Security Agency

[redacted] NHS England and NHS Improvement (National)

2. COVID-19 vaccines and risk of dizziness, vestibular disorders, and P.O.T.S

2.1 The EWG was presented with a review of the currently available evidence regarding dizziness, vestibular disorders and Postural Orthostatic Tachycardia Syndrome (POTS) in association with the COVID-19 vaccines currently deployed in the UK (AstraZeneca, Pfizer-BioNTech and Moderna COVID-19 vaccines). The EWG considered clinical trial and Yellow Card data (with a data lock point of 15 September 2021) as well as relevant published literature and data from the Yellow Card Vaccine Monitor.

2.2 The EWG noted the numbers of Yellow Card reports of dizziness, vestibular disorders and POTS received for the 3 deployed vaccines (9,491 cases with the Pfizer vaccine, 25,342 with AstraZeneca and 1,656 with Moderna). Approximately 80% of all the reports received were for the event of dizziness.

2.3 The EWG noted that dizziness is already included in the Summaries of Product Characteristics for the AstraZeneca, Moderna and Janssen vaccines but not for the Pfizer vaccine.

2.4 In considering the data presented, the EWG commented that dizziness is very common in the general population. It was noted that the median time to onset and median reaction duration of one day, derived from the spontaneous data, may indicate that dizziness occurred in the context of reactogenicity following vaccination.

2.5 The EWG did not consider that the possible biological mechanisms for dizziness and vestibular disorders post COVID-19 vaccination, proposed in the small number of available literature articles, were plausible, and that there was no clear mechanism to explain the reports.

2.6 With respect to POTS, the EWG noted the small number of Yellow Card reports received (17 cases with the Pfizer vaccine, 18 with AstraZeneca and none with Moderna) and that roughly one half of the patients had pre-existing POTS. The EWG noted that POTS was a difficult diagnosis to make and that the evidence supporting an association with COVID-19 vaccination was weak.

2.7 Overall, the EWG considered that the evidence presented did not confirm a signal of vestibular disorders or POTS for the 3 deployed vaccines and advised that dizziness should be kept under review for the Pfizer vaccine. No regulatory action was recommended.

3. Erythema Multiforme and mRNA COVID-19 vaccines

3.1 The EWG was presented with a review of the currently available evidence from clinical trials, literature and spontaneous sources (including Yellow Card data with a data lock point of 19th September 2021) regarding erythema multiforme (EM) following vaccination against COVID-19 with the Pfizer-BioNTech and Moderna COVID-19 vaccines. Company reviews of this issue were also presented.

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

3.3 The EWG heard that there was currently very little evidence for a risk of EM following vaccination with any of the COVID-19 vaccines reviewed. The EWG noted that the reported cases concerned EM minor, however there are reports of positive rechallenge with the Pfizer vaccine.

3.4 The EWG agreed that the number of Yellow Card reports and published literature cases of erythema multiforme was low in the context of usage.

3.5 The EWG considered that an opinion on the evidence should be sought from Dermatology experts, in particular with regard to the positive rechallenge cases seen.

3.6 No regulatory action was advised at this time.

4. AZ D8111C00010 Immunogenicity study protocol

4.1 The EWG considered a protocol for a study of immunogenicity and safety of the AZD1222 AstraZeneca vaccine. The study is an open-label, uncontrolled, multicentre, 52-week duration study. The primary objective is to characterise the immunogenicity of a 2-dose primary vaccination with AZ vaccine with a 4-week dosing interval in immunocompromised adults. The secondary objective is to characterise the reactogenicity and safety. There are also some exploratory objectives. The study aims to enrol a total of 360 patients within 5 cohorts of immunocompromised subjects and one immunocompetent group.

4.2 The EWG considered that the study was important but questioned the timing of it given that the majority of immunocompromised patients will have already been vaccinated in the UK and that other studies (such as Octave) are already ongoing with much larger sample sizes. The EWG commented that the study might be better conducted outside the UK as even with a small sample size, recruiting unvaccinated patients would be problematic.

4.3 The EWG questioned the generalisability of the study to the UK population as the study is to follow a 4-week interval between doses whilst the UK has implemented a 12-week interval.

4.4 The EWG also noted that there were some missing immunocompromised groups from the 5 proposed cohorts, e.g. patients on B cell depleting therapies. Furthermore, the EWG considered that the small sample size would not provide much immunogenicity data.

5. Update on myocarditis/Pericarditis with the COVID-19 vaccines

5.1 The EWG were presented with an update on reports of myocarditis and pericarditis following administration of COVID-19 vaccines. The EWG were informed that for the Pfizer/BioNTech vaccine, the reporting rate has remained similar between the first and second dose in adults. In the under 18-years age group, the reporting rate is higher for the second dose of the Pfizer/BioNTech vaccine compared to the first dose; however the second dose rate has reduced as vaccine exposure has increased. The EWG noted the first report of myocarditis following a booster dose of the Pfizer/BioNTech vaccine. For the Moderna vaccine, the reporting rates remain higher after the second dose compared the first dose and are highest in the younger age groups. The reporting rates for the Moderna vaccine remain higher than those for the Pfizer/BioNTech vaccine. The reporting rates for the AstraZeneca vaccine remain lower than those of the mRNA vaccines.

5.2 The EWG were presented with company data from Pfizer/BioNTech, which continued to show a similar pattern of reporting of myo/pericarditis as seen with international spontaneous reporting, with higher rates of myocarditis in younger males following the second dose of the Pfizer/BioNTech vaccine. The company data highlighted a small number of reports in the 12-15-years age group, with the pattern of higher proportion in males after second dose consistent with older age groups. The EWG noted that the majority of events were reported as recovered.

5.3 The EWG were presented with updated rapid cycle analysis which showed a higher than expected number of reports of myocarditis and pericarditis across both the first and second doses of the Pfizer/BioNTech vaccine. For the Moderna vaccine, the rapid cycle analysis showed a higher number of myocarditis reports following the second dose. The EWG noted the Moderna analysis was based on a small number of reports and so should be interpreted cautiously. For the AstraZeneca vaccine, the analysis no longer showed a signal for myocarditis or pericarditis following either dose.

5.4 The EWG were informed that Public Health Ontario had decided to recommend the Pfizer/BioNTech vaccine as the preference over the Moderna vaccine in the 18-24-years age group, due to higher rates of myocarditis for the Moderna vaccine. The EWG were also informed that public health bodies in Sweden and Denmark had restricted use of the Moderna vaccine in under 30 years and 18 years, respectively. The EWG noted that these were public health body decisions and no regulatory action to restrict use in certain age groups had been taken by the regulators in these countries.

5.5 The EWG concluded that the benefits still exceeded the risks overall for each vaccine and for all authorised subpopulations and that no regulatory action was required based on the data presented.

6. Summary of Yellow Card reporting

6.1 The meeting was presented with an updated version of the coronavirus vaccine weekly summary of Yellow Card reporting.

6.2 It was explained that as we've now reached a stage where primary immunisations have been completed, a large number of second doses have been given, and the roll out of boosters and vaccinations to children has begun, it would be timely to reformat the weekly summary of Yellow Card reporting in line with this.

6.3 Major revisions were highlighted to the group, including the splitting of Section 3 (analysis of reports) into two sections (population-based assessments and specific safety topics), the addition of information on boosters and under 18s, and the expansion of the section on myocarditis.

6.4 The EWG were supportive of the changes and commended the weekly summary of Yellow Card reporting.

7. For Information - Comirnaty / COVID-19 Vaccine BNT162b2 product information to include 6-month efficacy and safety data

7.1 The EWG heard that the 6-month efficacy and safety data have become available and consequently, an EU reliance variation has been submitted to update section 4.8 and 5.1 of the GB SmPC. An amendment request has also been submitted in parallel to include the same information in the Regulation 174 product information.

7.2 The EWG heard that, as of the new data cut-off of 13 March 2021, a total of 927 confirmed COVID-19 cases had accrued compared with 170 at the previous data cut-off date of 14 November 2020. In the updated efficacy analysis, efficacy of COVID-19 mRNA Vaccine in preventing first COVID-19 occurrence from 7 days after Dose 2 compared to placebo was 91.3% (95% CI of 89.0% to 93.2%) in participants in the evaluable efficacy population without evidence of prior infection with SARS-CoV-2. Similar efficacy point estimates were seen in subjects with or without evidence of prior infection with SARS-CoV-2 and across subgroups, e.g. participants at higher risk of severe COVID-19.

7.3 The EWG heard that efficacy was very high in participants with severe COVID-19 (95.3% [95% CI 70.9, 99.9]) 7 days after dose 2.

7.4 The EWG heard that 5 new adverse drug reactions have been identified all with a frequency designation 'Uncommon': decreased appetite, lethargy, hyperhidrosis, night sweats, and asthenia.

7.5 The EWG noted that no new safety concerns have been identified for inclusion in the Risk Management Plan based on the 6-month data.

8. Any Other Business

None.

9. Date and time of next meeting

The next scheduled meeting is to take place on **Wednesday 13th October** at **10:30**.

The Meeting today started at 16:33 and ended at 18:09.

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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.

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

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

[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.