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

Minutes of the meeting held on **Tuesday 9th March 2021** at **15:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan
Professor N French
Professor D Goldblatt
Ms S Hunneyball
Professor K Hyrich
Sir M Jacobs
Professor H J Lachmann
Professor P J Lehner
Dr S Misbah
Professor S Price
Dr A Riordan
Professor T Solomon
Dr R Thorpe
Mrs M Wang
Professor C Weir

Apologies

Mr R Lowe
Professor C Robertson
Professor P Shah

Member of the CTBV Expert Advisory Group

Professor M Turner

Members of the CPS Expert Advisory Group

Mr VI G Fenton-May
Professor Y Perrie
Professor K M G Taylor (Chair of CPS)
Dr S Walsh

Observers

[redacted]

Secretariat

[redacted]

Professional Staff of MHRA Present

Principal Assessors

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

Presenters supporting specific items

[redacted]

MHRA Observers

[redacted]
Dr S Branch - VRMM
[redacted]
Dr P Bryan - VRMM
[redacted]
Dr S P Lam - LD
[redacted]
Ms N Rose - MHRA-NIBSC
[redacted]
Mr P Tregunno - VRMM
[redacted]
Dr K Wydenbach - LD

Key
LD = Licensing Division
NIBSC = National Institute for Biological Standards & Control
VRMM = Vigilance & Risk Management of Medicines
CTBV = Clinical Trials, Biologicals & Vaccines EAG
CPS = Chemistry, Pharmacy & Standards EAG

[redacted]

13th April 2022

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 listed at **Annex II** to the minutes.

1.4 Apologies were received from Professors Robertson, Shah and Mr Lowe for the meeting today.

1.5 The Chair welcomed the following observers invited to observe the safety items discussed at the meeting today:

[redacted]

[redacted]
Public Health Scotland

[redacted] Public Health Wales

[redacted]

2. Moderna dosing interval

2.1 The EWG heard the Moderna COVID-19 vaccine was authorised under Regulation 174 of the HMRs 2012 on 08 January 2021. On 31 December 2020, in response to a DHSC request for specific guidance on an extended dosing interval, EWG and CHM advised that the recommended dosing interval should be at least 28 days. But, in subsequent discussions the manufacturer did not agree, and the product information for HCPs states that it is recommended to administer the second dose 28 days after the first dose and refers to

section 5.1 which provides an outline of the data on efficacy after the first dose and information about the dosing interval in the trial which was up to 42 days.

The EWG was reminded of the efficacy seen after 1 dose of Moderna and after 1 dose of Pfizer-BioNTech, as they are both mRNA vaccines with similar results in their clinical trials. Effectiveness data after one dose were presented mainly for the Pfizer-BioNTech vaccine.

2.2 The EWG were asked to consider, if a dosing interval of 'at least 28 days' for the Moderna vaccine could still be recommended, based on the currently available data.

2.3 The EWG noted recent discussions on the topic of vaccine dosing interval in the medical literature. The EWG noted an interval of 'at least 28 days' would be consistent with the outcome of the previous EWG discussion on the 31 Dec 2021, and the decision to make the specific recommendation of 'up to 12 weeks' is within JCVI's purview. The evidence on mRNA vaccine efficacy post first dose is reassuringly high ~80-90%. The real-world vaccine effectiveness data from Scotland, and Canada is also very encouraging, although the recent rate of infection in Canada has been lower. The EWG also noted the need to be consistent with the dosing interval between the two mRNA vaccines, or to be able to factually describe the basis for any inconsistencies, given the platforms are very similar.

2.4 The EWG noted that the most recent evidence available strengthens rather than undermines the rationale for an interval of at least 28 days. The EWG noted there is a reasonable basis to support extending the dose interval to at least 28 days. The precise implementation of the interval e.g. possibly to 12 weeks, in order to optimise population coverage falls within JCVI's purview.

2.5 The EWG noted the Pfizer and Moderna platforms use very similar but not identical technologies, and therefore, any comparison needs to be precisely constructed / grounded in science. Another caveat is that the landscape may change depending on the emergence of variants and as the present understanding of the disease matures.

2.6 The EWG noted it was of great benefit that high levels of efficacy have been shown against the primary virus, but as mentioned previously variants remain a potential concern. The scientific rationale that led to the extension of the AZ vaccine interval was based on fairly limited data, but this rationale was shown to be correct when cross-referring to real-world data. Therefore, applying the same thought process to the Moderna vaccine would not be unreasonable, but would need to be supported by immunogenicity data / other trial data such as the Oxford Vaccine Group heterologous prime-boost COVID-19 vaccination trial (Com-COV).

2.7 The EWG noted there is a need for more comparative immunogenicity data, but data emerging on the correlates of protection is promising for both for binding antibody to spike and viral neutralisation. The identical testing platforms are being used to test sera from cohorts of Moderna vaccine recipients and Pfizer vaccine recipients. The early comparative results show immunogenicity three weeks after one dose to be similar. The EWG noted that the recommended dosage of Moderna dose is larger than that of Pfizer/BioNTech.

2.8 The EWG asked about the process to handle the potential amendment to return the vaccine interval to that originally endorsed by the EWG. The Chair explained that the present meeting represents the first stage, the collation of the views of the expert committee, which will be followed by a CHM meeting, where a recommendation may be given. The recommendation will enable the MHRA to approach DHSC with the position of the CHM, and a discussion with the manufacturer will follow to reconcile the product information with an extended dosing

interval. A dosing interval of at least 28 days should permit the JCVI greater flexibility to facilitate wider Moderna first dose vaccine coverage.

2.9 The EWG requested information on the approach taken by the Canadian regulatory authority. The EWG heard a form of emergency-use authorisation has been granted and currently reflects the 28-day interval, reflecting an off-label approach that has been taken for the roll-out. The EWG noted that the dose interval of 4 weeks selected in the trials, was not based on exploratory clinical data.

2.10 The Chair concluded that the EWG share the perspective that the available data continue to support a dosing interval of at least 28 days for the Moderna vaccine, and that dosing interval recommendations should be consistent across both mRNA vaccines (Moderna and Pfizer/BioNTech).

3. Covid-19 Vaccines – Risk of Seizures

3.1 The EWG was informed of a cluster of 4 cases of seizures in patients with epilepsy who developed pyrexia and seizures within a few hours of receiving the AstraZeneca COVID-19 vaccine. The EWG noted that seizures/convulsions are included in the list of adverse events of special interest (AESI) for all COVID-19 vaccines and as such are closely monitored by the MHRA and the vaccines' authorisation holders. The EWG heard that although vaccines in general are not known to be causally associated with seizures in adults, seizures are included as an AESI as a precaution, because of the known but uncommon risk of febrile seizures in children following some immunisations.

3.2 The EWG considered an assessment of clinical trial data and individual case reports of seizure-related events reported via the UK Yellow Card Scheme for the Pfizer-BioNTech and AstraZeneca COVID-19 vaccines. For the Moderna vaccine, only clinical trial data and data from non-UK cases reported to the MHRA by the vaccine authorisation holder were considered; UK specific post-marketing data are not currently available as this vaccine has not yet been deployed in the UK.

3.3 The EWG agreed that the currently available data do not provide any evidence of a causal association between the COVID-19 vaccines and onset of seizure events in people without a prior history of seizure.

3.4 The EWG also agreed that the currently available data do not suggest a direct vaccine-specific increased risk of seizure and the COVID-19 vaccines in people with epilepsy or history of seizure.

3.5 The EWG discussed the small number of cases of seizure in people with a prior history of seizure reported alongside other known side effects of the COVID-19 vaccines. The EWG noted that intercurrent illness, feeling generally unwell, fever and fatigue can be triggers for seizures in some people with epilepsy and that some people do experience flu-like symptoms within 1-2 days of COVID-19 (and other) vaccinations. The EWG heard that the International League Against Epilepsy currently advises that fever developing after a COVID-19 vaccination could lower the seizure threshold in some people and that antipyretics, such as paracetamol, taken regularly after vaccination will minimise this risk.

3.6 The EWG noted that the UK information for the COVID-19 vaccines includes advice that, if required, paracetamol may be used after vaccination to provide symptomatic relief from post-vaccination adverse reactions and that advice about the use of paracetamol is also provided in the Green Book. The EWG agreed that there was no evidence available on whether

prophylactic paracetamol would reduce the risk of seizures in people with epilepsy following COVID-19 vaccination.

3.7 The EWG advised that based on the data currently available no updates to the product information for the COVID-19 vaccines are required, but that the risk of seizures should continue to be kept under close review.

4. Potential risk of Guillain-Barré syndrome GBS with Pfizer/BioNTech and AstraZeneca COVID-19 vaccines

4.1 The EWG was provided with an overview of Yellow Card reports of Guillain-Barré syndrome (GBS), an Adverse Event of Special Interest, up to and including 3 March 2021 with the Pfizer, AstraZeneca and Moderna vaccines. Clinical trial data and company data from Summary Monthly Safety Reviews were also provided.

4.2 The EWG heard epidemiological analysis which involved ecological, observed vs expected and rapid cycle analyses.

4.3 The EWG commented on the importance of following up GBS reports to gain sufficient detail to understand whether the cases meet the Brighton Collaboration Criteria for true Guillain-Barré syndrome.

4.4 The EWG and invited observers discussed ways to encourage healthcare professionals to provide more detail in Yellow Card reports and respond to follow up requests, including communicating with royal colleges and similar bodies, as well as medical directors of trusts.

4.5 The EWG noted that it was important to promote thorough reporting for all adverse events, rather than specific ones in order to avoid stimulating reporting and creating biases within the Yellow Card database.

4.6 The EWG stated that there was the potential of an increased signal of GBS, particularly with the AstraZeneca vaccine and that reports of GBS should be closely monitored but that a formal epidemiological study was not yet indicated at this stage.

5. Review of safety data for use of COVID-19 vaccines in patients with neuromuscular disorders

5.1 The EWG heard background information about a case of a patient with a neuromuscular disorder who had died shortly after receiving the AstraZeneca vaccine, as well as reports of patients with neuromuscular disorders experiencing more severe myalgia and creatinine kinase increases after vaccination with the Pfizer and AstraZeneca vaccines.

5.2 The EWG was provided with an overview of clinical trial data, Yellow Card reports and international reports regarding patients with underlying neuromuscular disorders who reported an aggravation of the underlying disease or renal damage, as well as reports of severe muscle damage in recipients regardless of their underlying disease status.

5.3 The EWG noted that the effects reported were broad but that no clear signal of vaccine association could be seen in the data.

The EWG requested that where possible, further details should be obtained for the most serious cases.

The EWG commented that creatinine kinase increases were difficult to interpret without knowing what the patient's baseline levels are.

5.4 The EWG concluded that these types of report should be kept under close monitoring but that no regulatory action was required at this stage.

6. Yellow Card Vaccine Monitor: Verbal Update

6.1 The EWG was provided with an update on enrolment of individuals to the Yellow Card Vaccine Monitor (YCVM), part of the MHRA pharmacovigilance surveillance strategy for the COVID-19 vaccines.

6.2 The EWG were reminded that individuals are recruited through the national call-recall process for vaccinations and receive a letter following the national call inviting them for vaccination.

6.3 The EWG heard that approximately 17,000 individuals have registered with the YCVM platform to date. Around 13,500 individuals have submitted data on their vaccination, of which around 5,700 individuals have submitted adverse reactions amounting to 11,500 adverse drug reactions reported to the YCVM.

6.4 The EWG also heard that a slightly higher proportion of women have registered compared to men, and women were also more likely to report an ADR.

6.5 The EWG heard that around 90% of individuals registered were of white British or white Irish ethnicity. The EWG considered the need to increase ethnic diversity and heard that engagement with the national call-recall process could increase ethnic diversity in specific areas.

6.6 The EWG heard that the top ten ADRs reported by vaccine type were consistent with the known short-term reactogenic effects of the COVID-19 vaccines.

6.7 The EWG considered that the presentation of data from the YCVM could be amended with stratification based on patient characteristics as opposed to the vaccine type in future updates to the EWG.

7. Any Other Business

7.1 None.

8. 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 15:33 and ended at 17:24.

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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 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 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 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.

Mrs Wang – Other relevant interest arising from family with several rare diseases and conditions, some of which result in epileptic fits as a consequence.

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

CTBV

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.

CPS

Mr V'lain Fenton-May – None

Professor Yvonne 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 Kevin Taylor – None

Dr Susannah Walsh – None

Observers for this meeting

[redacted] – [redacted]

[redacted]

[redacted] – [redacted]

[redacted] – [redacted]