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

Minutes of the meeting held on **Wednesday 13th January 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
Dr A Riordan
Professor C Robertson
Professor P Shah[1]
Dr R Thorpe
Mrs M Wang[1]
Professor C Weir

Apologies

Professor S Price
Professor T Solomon

Members of the CTBV Expert Advisory Group

Professor B K Park
Professor M Turner

Members of the CPS Expert Advisory Group

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

Secretariat

[redacted]

Minute Taker

[redacted] - LD - Medical Writer

[1] Joined at item 2
[2] supporting specific items

Professional Staff of MHRA Present

Principal Assessors[2]

Dr J Bonnerjea - LD
Dr P Bryan - VRMM

Presenters supporting specific items[2]

[redacted] - VRMM
[redacted] - VRMM
[redacted] - VRMM
Dr N Rose - MHRA-NIBSC

MHRA Observers

[redacted] - VRMM
[redacted] - VRMM
[redacted] - MHRA-NIBSC
[redacted] - LD
Dr S Branch - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
[redacted] - MHRA-NIBSC
[redacted] - LD
[redacted] - VRMM
[redacted] - VRMM
Mr P Tregunno - VRMM
[redacted] - Government Legal Team
[redacted] - MHRA-NIBSC
[redacted] - LD
[redacted] - 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

1. Introduction and Announcement

1.1 The Chair reminded Members 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 The following members and invited experts declared interests and other relevant interests for this meeting:

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 joining 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.

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)

Mrs Wang – Other relevant interest arising from being highly sensitive to insect stings, and plant products such as Hyacinth bulbs, which are recorded on Mrs Wang's medical records. This declared interest is only specific for this meeting.

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 Park - NPNS in GSK Research & Development Ltd. and in Janssen as I received a research grant in the past two years. The grant has been handed over to a colleague in 2020 and the grant is due to finish in 2020. Professor Park received no direct payment. In addition, Professor Park have two active IMI grants for Transbioline and Quantitative Systems Toxicology, he is the PI on the TransBioline grant for the University of Liverpool. Both grants are paid directly to the University of Liverpool.

Professor Turner – NPNS interest. Professor Turner is a Non Executive Director (non-remunerated) on the Board of the Cell and Gene Therapy Catapult (CGT).
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.

CPS

Mr V'lain Fenton-May – None

Mr Robert Lowe – 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

1.4 Apologies have been received from Professor Price and Professor Solomon for this meeting.

2. mRNA COVID-19 vaccines – Safety data in those with prior COVID-19 infection

2.1 The EWG heard a paper on safety in those with prior COVID-19 infection.

The EWG discussed the potential for increased reactogenicity, particularly with the Pfizer vaccine, in those who have previously had COVID-19 infection. The EWG agreed that although there may be a theoretical reason to anticipate a lower magnitude of antibody response in the AZ vaccine compared with the Pfizer vaccine, at present both vaccines can be considered similar in this respect. The EWG noted the lack of standardised assays and head to head studies to evaluate whether the vaccines induce a different magnitude of antibody response. The EWG also noted that a small percentage of individuals in clinical trials were seropositive at baseline and data from clinical trials did not indicate an increased risk of reactogenic events in these individuals.

2.2 The EWG noted that immune-complex type reactions, including serum sickness and vasculitides, were also theoretical and no risk was observed in the clinical trials. The EWG noted that the risk of immune-complex deposition was unlikely and would be more likely to occur in the event of prolonged antigen production, for example with a live vaccine.

2.3 The EWG discussed possible approaches for continued monitoring and noted that patients with previous COVID-19 infections may have a higher immune response with symptomatic disease than with asymptomatic disease.

2.4 The EWG agreed that given the evolving landscape with COVID-19 to enhance current monitoring, the MHRA should include immune-complex events as Adverse Events of Special Interests (AESIs). These would include events such as glomerulonephritis and vasculitis.

2.5 The EWG considered that the correlates or the true biological markers of protection are still unknown. The EWG noted the need for ongoing studies in order to understand if the immune response to each individual batch is the same and a baseline blood sample would be useful to carry this out and to link the subsequent reactions in those with pre-existing antibodies. The EWG considered that such a study might be coordinated by PHE and would likely have a number of individuals with pre-existing antibodies.

2.6 The EWG briefly discussed long COVID-19 and noted it would be useful to know if individuals are collecting data on this.

2.7 The EWG noted the issue of antibody enhancement of disease. There EWG heard there is potential concern that poor levels of neutralising antibodies may lead to enhancement of

disease when individuals encounter COVID-19 if they are naïve at the time of vaccination. In cases where the second dose is delayed in mRNA vaccines, high levels of IgG are observed post dose 1; however, the levels of neutralising antibodies stay low which theoretically is a situation that could lead to enhancement.

2.8 The EWG heard that approximately 300000 individuals have had the second dose and noted a proportion of them would have had a prior infection. The EWG discussed whether the second dose could induce the same kind of immune complex disease in those individuals that have not previously had COVID-19. The EWG also considered that a greater antibody response might be expected after two doses. The EWG noted that there is some evidence, i.e. from the Moderna study, that the second dose induces more of a response.

2.9 The EWG were relatively reassured for the present time by the results of the clinical trial data in terms of both reactogenicity and immune-complex events in individuals who were seropositive at baseline who have received the vaccine but noted the need for continued vigilance.

3. Risk of anaphylaxis with Pfizer/BioNTech and Moderna COVID-19 vaccines

3.1 The EWG heard a paper of the risk of anaphylaxis with Pfizer/BioNTech and Moderna COVID-19 vaccines. The EWG were reassured that the rate of anaphylaxis remained similar to that previously reported. The EWG agreed the 15-minute observation period should be maintained.

3.2 The EWG noted that the patient group directions (PGDs) for Oxford/AstraZeneca and Pfizer vaccines should be the same with respect to contraindications due to pre-existing allergies and that some patients have been incorrectly refused vaccination due to, for example, penicillin allergy. MHRA agreed to raise this with PHE.

4. Update on the Safety Data for the Pfizer/BioNTech COVID-19 vaccine
Example Publication to get view on structure

4.1 The EWG heard a paper on an update on the safety data for the Pfizer/BioNTech COVID-19 vaccine. The EWG agreed that the data were broadly reassuring.

4.2 The EWG were assured that low levels of lymphadenopathy were observed, and this event is listed in Section 4.8 of the SmPC.

4.3 The EWG heard there were no cases of appendicitis.

4.4 The EWG heard there are risk windows for each of the adverse events of special interest. For Bell's Palsy the window is between 7- and 42-days post dose 1 vaccination. These windows are then compared to the rates of Bell's Palsy in unexposed populations.

4.5 The EWG discussed the risk of lack of care in individuals following their first dose of vaccine has led to a number of cases of COVID-19 disease. The EWG also noted that some cases of COVID-19 could be contracted in the vaccine centre.

The EWG discussed individuals who contract a fever post vaccination. The EWG heard that most were healthcare professionals, and some did report symptoms of fever and joints aches/pains. A proportion of these did report positive COVID-19 tests.

4.6 MHRA informed 500 yellow cards have been received concerning the AZ vaccine which do not indicate any signals.

The EWG reviewed an example COVID-19 vaccine adverse reaction summary publication.

The EWG gave advice to MHRA on the language, content and structure of the example publication. Some members of the EWG offered their time to input further on the publication, including lay members, to ensure the publication is understood in the context of the number of doses of vaccine administered.

5. Future Steps / Any Other Business

5.1 Update on Independent Batch Release

5.1.1 The EWG heard an update on Independent Batch Release from NIBSC on Pfizer (12 batches) and AZ vaccines (5 batches) of which 10 Pfizer batches and 3 AZ batches have been certificated.

5.1.2 The EWG heard that approximately 7 million doses of COVID-19 vaccines have now been certificated. The number of doses that have been batch tested and are awaiting manufacturers testing data to allow certification is approximately another 6 million.

5.1.3 The EWG heard that by the end of January 2021 batches representing approximately 5.5 million doses are expected to have been submitted to NIBSC for testing.

5.1.4 Overall, the number of batches tested and released by the end of January by NIBSC will represent between 15 and 20 million doses in total, depending on the manufacturers' data (Lot Release Protocol) submission dates.

5.1.5 The EWG heard that the duration of the longest test is 4 days for the AZ vaccine, and 5-6 days for the Pfizer vaccine.

5.2 Members were reminded that:

The content of papers and proceeding of the meeting are strictly confidential and should not be disclosed.

All enquiries, approaches, interview requests and requests for comments made directly to the members from the media or stakeholders, verbal or written, should be declined and referred to the agency's news centre in the first instance.

6. Date and time of next meeting

The next meeting is scheduled to take place on Monday 18th January 2021 at 10:30

The Meeting today started at 15:34 and ended at 16:58

[redacted]

24th March 2021

Members are reminded that the content of papers and proceeding of the meetings are to be treated as 'Official – sensitive commercial'. Members are also reminded that, in accordance with the 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 must also declare any other matter which could reasonably be perceived as affecting their impartiality. Detailed guidance is set out in the Code of Practice