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

Minutes of the meeting held on **Friday 22nd 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
Professor S Price
Dr A Riordan[1]
Professor C Robertson
Professor P Shah
Professor T Solomon
Dr R Thorpe
Mrs M Wang
Professor C Weir

Members of the CTBV Expert Advisory Group

Professor B K Park[1]
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

Observer

Professor S Ralston (Chair of CHM)

Secretariat

[redacted]

Professional Staff of MHRA Present

Principal Assessors[2]

Dr J Bonnerjea - LD
Dr P Bryan - VRMM

MHRA Presenters supporting specific items[2]

[redacted]
[redacted] - COMMS
[redacted]
Dr C Schneider - MHRA-NIBSC
[redacted]

MHRA Observers

[redacted]
Dr S Branch - VRMM
[redacted]
Mr K McDonald - LD
[redacted]
Dr J Raine - MHRA CEO
Ms N Rose - MHRA-NIBSC
[redacted] LD
Mr P Tregunno - VRMM
[redacted]

[1] Joined during item 3
[2] supporting specific items

[redacted]

[redacted]

19th July 2021

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
CHM = Commission on Human Medicines
MHRA CEO = Chief Executive
IE&S = Inspection, Enforcement & Standards
NIBSC = National Institute for Biological Standards & Control
COMMS = Deputy Director of News, Digital & Content

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 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.

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

CHM

Professor Ralston – NPNS – Sanofi, Pfizer, Janssen, AstraZeneca & Other relevant interests in NHS Lothian and Oxford University. Professor Ralston has an honorary consultant contract with NHS Lothian but has not been involved in any trials relating to COVID-19. He also has agreed to be an external examiner for Oxford University clinical trials MSc; however, this has not yet started.

1.4 MHRA Press Interaction

1.4.1 The EWG heard advice from the MHRA Communications Division regarding MHRA Press Interaction. MHRA advice remains that EWG members should not speak on behalf of or as a representative of the EWG/CHM or discuss EWG/CHM business. In these cases, EWG members are advised to pass these queries to the MHRA news centre. MHRA to circulate the contact details to EWG members post meeting.

1.4.2 The EWG were reminded of the code of practice for scientific advisory committees (communication with media is covered in paragraphs 139-142). MHRA to provide link to this document following the meeting.

1.4.3 The EWG heard that where information is already in public domain and decision or advice already been made or given when that advice is in the public domain then members can repeat the outcome to the press.

1.4.4 The EWG were informed that EWG members are not to interact with the press about any live issues that are under consideration or any other issues that could potentially come up in the future.

1.4.5 MHRA advised EWG members to avoid putting themselves in positions where they might get asked questions around COVID-19 vaccines and their role as an EWG member wherever possible. MHRA informed EWG members that the MHRA news centre staff are always available to discuss any press queries members receive with them and to provide support and advice and to agree what can and can't be said.

2. Minutes of the COVID-19 VBR EWG meeting held on Thursday 24th December 2020

2.1 The minutes were agreed as a true and accurate record of the proceedings.

3. Regulatory strategy for authorised Covid-19 vaccines in case of strain changes

3.1 The EWG heard a draft paper about the regulatory strategy for authorised COVID-19 vaccines in case of strain changes.

3.2 The EWG heard the difference between antigen drift and antigen shift, where antigen shift would mean a new gene assortment, and the regulatory concepts associated with both. The EWG heard that at present the coronavirus is mutating in line with what would be considered antigen drift.

3.3 The EWG heard how this antigen drift could be managed along the same lines as the annual flu vaccine updates. The EWG heard the quality requirements MHRA would expect to see in order to update the COVID-19 vaccines in this way.

3.4 The EWG heard that is not yet known if antibody response is a good indicator of a response, and that a challenge study with SAR-Cov2 would be required which would be time consuming. A hamster study would also be required in the post-marketing phase. Cross protection should also be evaluated to ensure any new vaccine would protect against previous versions of the virus as well as recent versions.

3.5 The EWG heard that immunogenicity data would be required as outlined in the draft paper.

3.6 The EWG discussed the human challenge model and whether it has a role to play in the path to rapid approval for new vaccine strains. The EWG heard there are some ethical concerns that may relate to how dangerous any new strain of the virus would be but could be looked at on a case by case basis. The EWG heard that challenge studies may not be necessary if it is possible to bridge via immunogenicity data and an occurrence of disease would not be required. The EWG agreed it would be useful to have a session on human challenge trials at a future meeting.

3.7 The EWG heard that the human challenge studies are a fairly quick process and could provide a route to understand correlates of protection and to measure escape processes of the virus. The EWG heard that already there are different variants in 3 different continents, and it is not known which strain should be targeted by an updated vaccine. Human challenge model may be the only way to find out. The EWG heard any strategy needs to be internationally regulated. The EWG heard there may be similarities between coronavirus and norovirus and how it changes in different continents.

3.8 The EWG discussed whether we have reached the trigger point for manufacturers to start thinking about creating new vaccines to combat the new variants.

3.9 The EWG heard that the live virus will show the full complement of the mutations occurring whereas a pseudovirus will only give some of the mutations but not necessarily any occurring outside the RBD domain.

3.10 The EWG heard that recipients of Pfizer vaccine are able to produce neutralizing antibodies against variant 501; however, the trigger point for production for new vaccine may almost be reached. The EWG also noted the level of IgG produced after vaccination with the Pfizer vaccine. The EWG noted that the role of cellular immunity is not yet fully understood.

The EWG discussed the use of the human challenge studies and their use to determine natural immunity to the virus as well as immunity to the virus following vaccination with a new vaccine.

3.11 The EWG discussed how a new vaccine to be used in challenge studies would be approved. The EWG heard it could be used at Phase II level and would not have to be a licensed vaccine.

3.12 The EWG heard discussion around a sample size of 300 participants being exposed to an updated vaccine and agreed it seemed reasonable that this number might meet adequate levels of precision and practicality.
The EWG discussed the use of multiple virus sequences in the same vaccine to combat variants.

3.13 The EWG discussed whether non-clinical or quality data could be used alone and did not agree that this could be the case.
The EWG discussed the minimum level of evidence required to develop an updated vaccine.
The EWG heard that the paper will be updated and that the next logical step would be to have discussions with WHO being mindful of the impact that any delay might have and any potential changes of the pandemic.

4. Update on fatal ADRs

4.1 The EWG heard an update on the safety data from fatal ADRs. The EWG heard a summary of the fatal cases in Norway following administration of the Pfizer/BioNTech COVID-19 vaccination in frail and elderly patients, and that no connection with the vaccine had been established.

4.2 The EWG heard that the majority of the fatal cases in the UK following vaccination with the Pfizer vaccine are in the 80+ age group. The ADR cases were also summarized and were largely in line with events expected considering the ages and comorbidities in the patients. There were also some cases reporting diarrhoea and vomiting.

4.3 The EWG heard a summary of fatal cases in the UK following vaccination with the AstraZeneca vaccine in those aged 65 – 96 years of age. The events reported in fatal cases for AstraZeneca COVID-19 vaccine were also considered expected due to the age and comorbidities in the patients.

4.4 The EWG heard that currently there is no evidence of an increased risk of fatal events in frail patients and the benefit/risk profile remains the same in these patients.

4.5 The EWG requested more information on the cases of toxic epidermal necrolysis and the fatal cases where the onset of symptoms occurred within 25 minutes of vaccination. The EWG heard that generally speaking the fatalities occurred within a week of vaccination.

4.6 The EWG agreed that there does not seem to be a signal for an increased risk of fatalities in the elderly and frail patients with either the Pfizer COVID-19 vaccine or the AstraZeneca COVID-19 vaccine. The EWG agreed that the regulatory procedures put in place by the MHRA currently seem adequate.

5. <u>Any Other Business</u>

None.

6. Date and time of next meeting

The next meeting scheduled to take place on Monday 25th January has been cancelled.

The next meeting is scheduled to take place on **Friday 29th January 2021** at **13:30**

The Meeting today started at 15:31 and ended at 17:37

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