COMMISSION ON HUMAN MEDICINES (CHM)

COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Wednesday 18th November 2020** 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 C Robertson
Professor T Solomon
Dr R Thorpe
Mrs M Wang
Professor C Weir

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 CTBV)
Dr S Walsh

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
Dr P Bryan - VRMM
[redacted] - LD

Supporting Specific Items

[redacted] - PHE
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD

MHRA Observers

[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
Dr S Branch - VRMM
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - VRMM
Dr S P Lam - LD
[redacted] - VRMM
[redacted] - LD
Mr K McDonald - LD

Observer

Professor S Ralston (Chair of CHM)

Apologies

Professor P Shah

Secretariat

[redacted]

[redacted]

[redacted]

Minute Taker

[redacted] - LD

[redacted] - LD

Dr N Rose - MHRA-NIBSC

[redacted] - LD

[redacted] - LD

Mr P Tregunno - VRMM

[redacted] - LD

[redacted] - LD

Dr K Wydenbach - LD

Key

LD = Licensing Division
NIBSC = National Institute for Biological Standards & Control
VRMM = Vigilance & Risk Management of Medicines
CHM = Commission on Human Medicines
CTBV = Clinical Trials, Biologicals & Vaccines EAG
CPS = Chemistry, Pharmacy & Standards EAG
PHE = Public Health England

[redacted]

18th January 2021

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.

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 declared interests and other relevant interests to date:

C19VBR EWG

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 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 reference 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 Lachman – 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.

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)

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 - Other relevant interest arising from link to the Lothian NHS Board. NHS Lothian R&D has partially funded Professor Weir's post at University of Edinburgh, since 2010, so that he could provide methodological advice on health services research studies and clinical trials.

CTBV EAG

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 Quantitatve 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 – Other relevant 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 EAG

Mr V'lain Fenton-May – None

Mr Robert Lowe – None

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 Kevin Taylor – None

Dr Susannah Walsh – None

CHM (Observer)

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.

The register of interests declared by participants had not been deemed to debar any other participation in line with the policy. No further interests were declared.

1.4 Apologies have been received from Professor Shah for this meeting.

1.5 The Chair welcomed the following:

Members of the Clinical Trials, Biologicals and Vaccines Expert Advisory Group (CTBVEAG)

- **Professor B Kevin Park**
- **Professor Marc Turner**

Members of the Chemistry, Pharmacy & Standards Expert Advisory Group (CPSEAG).

- **Professor Kevin Taylor**
- **Mr V'lain Fenton-May**
- **Mr Robert Lowe**
- **Professor Yvonne Perrie**
- **Dr Susannah Walsh**

Professor Ralston, Chair of CHM who joined as an observer.

[redacted] Consultant Epidemiologist, Public Health England, Immunisation and Countermeasures Division, who participated for item 7 to give an update on PHE Surveillance activities.

1.6 The Chair informed the Group that Members and Invited Experts who had declared personal interests (or potentially perceived interest) were not invited to this meeting and will not be participating in the future meetings.

2. Minutes of the meeting held on Tuesday 10th November 2020

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

3. Current status of rolling assessment of Pfizer/BioNTech mRNA vaccine (BNT162b2)

3.1 The EWG heard a high-level summary update of the rolling assessment of the Pfizer/BioNTech mRNA vaccine (BNT162b2). The EWG also heard high-level summary given by NIBSC on the planned controls for vaccine batch release.

3.2 The EWG heard that the planned controls for vaccine batch release centre on four parameters: product appearance, identity (encapsulation, RNA integrity), potency, and protocol review. Due to time constraints, it is unlikely that all of these controls will be in place at the time of first batch release; however, a risk mitigation based approach has been pre-defined to discern the various configurations of control measures which would be considered sufficient to ensure batch consistency.

3.3 The EWG heard MHRA are expecting to clarify if the first batches of the vaccine will be of the same specification as those used in the clinical trial. The EWG heard there would be a lower degree of risk associated with the 'clinical trial product' due to the availability of safety data from the trial. The EWG heard that data to aid with the qualification of the batches intended for the UK market has been requested.

3.4 The EWG noted that a data sharing approach between competent authorities could facilitate the rapid acquisition of batch data for instances where batches are divided between nations. The EWG heard that in this regard, MHRA are defining an approach to sharing data with the FDA and further options are being explored.

3.5 The EWG noted the sparse data and information on: flow, batch testing, protocols, and full details of the roll-out.

3.6 The EWG asked if the company are required to respond to the 36 questions posed by the MHRA. The MHRA confirmed that whilst there is no formal obligation to reply, key issues such as sufficient data / detail on: product stability, batch qualification and adventitious agents, e.g. TSE status, will be required prior to any form of authorisation being awarded.

3.7 The EWG asked about the EMA's rolling review of BNT162b2 and how it differs from the MHRA's review process for regulation 174 (temporary authorisation of the supply of an unlicensed vaccine). The EWG heard that the outcome of the EMA's assessment, if positive, is grant of a Marketing Authorisation (MA), either conditional or full MA. The MHRA's current review of BNT162b2 in line with regulation 174 is a risk-based evaluation in the context of emergency use and does not result in a MA for the product but a separate form of authorisation to supply. The emergency use review process seeks to confirm the absence of major issues or gaps in the data that could represent safety concerns, prior to the vaccine's deployment.

3.8 The EWG asked about the dimensions of the final presentation for the vaccine, in relation to the storage space needed and the feasibility of ensuring adequate control of the cold chain. The EWG heard the design of the presentation was envisaged for use in a mass vaccination programme, hence the pack size of 195 multi-dose vials. The EWG heard that the plans place reliance on networks of PCNs hiring larger venues such as community halls. The EWG heard representatives from NHS England and DHSC will be invited to a subsequent meeting of the EWG to outline the operational model. The EWG noted vaccination of care home residents will need to be considered within deployment operations and that further stability data are required to underpin the deployment model.

3.9 The EWG heard that based on currently available stability data, once the vials are removed from ultra-low temperature storage the shelf-life at 2-8^{o}C is 120 hours and once diluted with saline the shelf life is 6 hours; this is in line with WHO recommendations for unpreserved vaccines intended for use in mass vaccination campaigns. The EWG heard supply will include distribution via third party wholesalers, necessitating pack splitting, as such labelling will require precise guidance on storage and storage precautions.

3.10 The EWG noted it was summer in South America during the phase II/III trial. The EWG asked if data from the South American cohort could be used for comparative analysis with other trial regions to inform on the robustness of the cold chain. The EWG noted that the vaccine usage protocol should assure applicability to real-world scenarios including maintaining the safety profile of returning of vials to cold storage and acceptable in-use duration between isolating first dose and last dose from the vial. The EWG noted that assurance of sterility and the availability of sterilisation method data should also be assessed in detail. The EWG heard the multidose vial does not contain any preservatives.

3.11 The EWG asked if the lipid nanoparticle element of the vaccine possesses any adjuvant properties, aside from innate adjuvant activity. The EWG noted a separate evaluation of quality would likely be required if the nanoparticles have been included in the formulation to act as an adjuvant, in addition to their main role of delivering mRNA through the lipid bilayer. The MHRA confirmed that presently no specific data have been submitted on the nanoparticles as an adjuvant.

3.12 The EWG heard vaccine efficacy (VE) was evaluated versus placebo 2 weeks after vaccine dose 2: VE 95.5%, 90 cases of COVID-19 in placebo and 4 cases of COVID-19 in the treatment group (C.I 88.8 – 98.4).The EWG heard that the WHO state the point estimate of efficacy for a COVID-19 vaccine should be at least 50% (reduction in COVID-19 disease cases) and the lower bound of the 95% confidence interval (adjusted) should be >30%. The EWG noted that ~84% of the trial participants were Caucasian.

3.13 The EWG noted the current data are limited to establish efficacy of the vaccine in preventing severe COVID-19 illness with 7 severe cases, all in the placebo group; 5 cases were reported between Dose 1 and Dose 2 and 2 cases were reported at least 7 days after Dose 2. The EWG noted lack of data in those excluded from the phase II/III trial (pregnant women, people with worsening health, those immunocompromised). The EWG noted further data on VE versus placebo in subgroups at greater risk would be valuable.

3.14 The EWG heard 43% of trial participants were over the age of 55 years. The EWG noted that the exposure data are reassuring in over 65s, but there are limited data in those aged 85 and over. The EWG noted if a full breakdown of participants by age was available, calculations could help to understand VE versus placebo in the upper age brackets. The EWG noted that as a minimum, individual listing data on antibody response in the older age should be provided. The EWG also noted that data from subjects close to the threshold of obesity could be useful to assess VE versus placebo in overweight subjects.

3.15 The EWG heard the data cover a median duration of follow-up after the second dose of less than 2 months. The EWG expressed concern that the minimum median duration of efficacy and safety follow-up requirements specified by WHO (median 3 months follow-up) and FDA (median 2 months follow-up) to assess benefit-risk, may not be met in time for the decision on the Regulation 174 authorisation. The EWG also noted that the duration of follow-up data currently available could be insufficient to capture the development of adverse events. The EWG noted that the currently available interim data may not have sufficient duration of follow-up as protection through innate immunity or immediate post vax neutralization titres

of short duration may be incorrectly identified as secondary immune response (antibody mediated response) to the vaccine.

3.16 The EWG noted the preparations for roll-out for the NHS is the 30 November 2020.

3.17 The EWG heard that VE in seronegative + seropositive participants is the second co-primary end-point in the trial. The data on this end-point are expected to be included in the final analysis, however, the data may not be available at time of decision on authorisation within terms of regulation 174.

3.18 The EWG noted the absence of data on VE against transmission, and the importance of this for understanding the potential to reach herd immunity. The EWG heard the trial design was not configured to measure the vaccine's efficacy against disease transmission.

3.19 The EWG noted that the data indicate a highly reactogenic vaccine with levels of reactogenicity similar to those observed with the typhoid vaccine. The EWG heard the extent of data to support the reactogenicity profile is in line with WHO requirements. The EWG noted product information and communications will need to inform recipients of what to expect from the vaccine. The EWG heard that systemic reactions are more frequent and more severe after dose 2, and in younger recipients.

3.20 The EWG noted regarding vaccine associated enhancement of disease (VAED), T helper 1 (Th1) versus T helper 2 (Th2) cellular and humoral immunity data are reassuring. However, VAED may not be apparent until VE starts to wane.

3.21 The EWG asked about the death in the vaccine group. The EWG heard the subject was a 60-year-old male, obese, and taking two concomitant medicines for depression. The EWG heard that specific cardiovascular events are usually recorded as a cause of death rather than arteriosclerosis. However, this reflects the content of narrative provided.

3.22 The EWG noted that in the phase I trial, lymphopenia was reported in the vaccine group. The EWG heard the company confirmed the vaccine's mechanism of action is expected to induce lymphopenia, and all events of lymphopenia in phase I were transient and resolved completely. Testing for lymphopenia was not conducted in phase II/III of the trial.

3.23 The EWG noted the potential signal of lymphadenopathy from the clinical trial data, 44 events in the vaccine arm related to upper limb lymph nodes compared to 4 in the placebo group. The EWG noted a potential linkage to the 6 cases of appendicitis in the vaccine arm compared to one case in the placebo group should be explored further and monitored. The EWG heard that the MHRA are currently conducting a detailed evaluation these events. The EWG noted that a signal of lymphadenopathy was also observed in the non-clinical data, lymphadenopathy was reversible, and the literature suggest the signal was expected for vaccines. The EWG noted that non-clinical data on reproductive toxicity would be beneficial in particular, data on use in pregnancy, but it was appreciated that the non-clinical data are still being generated.

3.24 The EWG heard that historical incidence data suggests that Guillain-Barré Syndrome when associated with vaccine administration, usually occurs within 6 weeks of dosing, and highest risk is 2-3 weeks post-dose (Polakowski et al, 2013; American Journal of Epidemiology, Babazadeh et al, 2019; Journal of Translational Internal Med.). The EWG noted that gastrointestinal (G.I) AEs such as intussusception and G.I perforation should be carefully assessed.

3.25 The EWG noted that antipyretics given at the time of some other vaccines have been postulated to interfere with immune response. The EWG heard antipyretics were not recommended to be given as a prophylaxis in the clinical trial protocol. The EWG heard clinical trial data is available on dosing and administration of antipyretics and this will likely inform the phrasing of the SmPC i.e. to suggest use only for pain and fever experienced from Day 2 post-vaccination.

3.26 The EWG noted the Pfizer's press release from today stated that the trial limit of 170 evaluable cases of COVID-19 has been reached and VE is confirmed in both those with or without previous COVID-19 infection. The EWG heard that these data are expected to be submitted to the MHRA in due course. The EWG heard in this package data on 15,000 subjects covering a median follow-up above 2 months post dose 2 is likely to be included.

3.27 The EWG heard the number of trial subjects given the vaccine in Germany, Turkey and South Africa was limited as recruitment to these sites was only beginning when the required number of COVID-19 clinical cases had been reached in the US, Argentina and Brazil.

3.28 The EWG noted the potential importance of vaccine failure data from the 8 participants that were vaccinated but still contracted COVID-19. Data should include the clinical features of their disease including symptomatic status, viral load, pathogenesis and immunogenicity. The EWG noted that the data should be requested. The EWG heard in the package of interim data, the case narratives of the subjects that experienced vaccine failures have been provided and none of these cases were severe.

3.29 The EWG noted the importance of stratified data on symptomatic seropositive trial participants to help inform expectations when vaccinating exposed individuals in the community. The EWG heard that the primary analysis only includes seronegative subjects and that the information in seropositive patients is not yet available. The EWG heard that there is no excess of COVID-19 cases in the active arm vs the placebo arm in those cases not included in the primary analysis, which would include cases in seropositive subjects.

3.30 The EWG also enquired about cases occurring before the second dose of the vaccine. The EWG heard that there appears to be protection even after only the first dose is received, with preliminary analyses by the assessors based on the case narratives showing fewer cases before dose 2 is received in the active arm compared to placebo.

3.31 The EWG heard case studies outside of the period of interim review indicate fewer COVID-19 infections in the vaccine arm prior to the second dose (32 vaccine versus 75 placebo group) suggestive of protective effect of the vaccine after first dose. The EWG noted an extreme imbalance would be worth investigating, but lesser imbalances should be protected by the processes of blinding and randomisation, and there is presently nothing to suggest a lapse in blinding or inadequate randomisation.

3.32 The EWG noted the background attack rate data in table 16 shapes the subgroup analysis. Approximately a third of COVID-19 cases in the placebo group were in Argentina, which is half of the number of COVID-19 cases reported in the US subjects; however, the majority of subjects were in the US (12,500 versus 2500). It was asked whether adjustments have been made for this in the analysis. It was confirmed that the analysis was not stratified by country. The EWG noted the relatively higher number of COVID cases in US subjects was most likely to be due to the differences in COVID-19 incidence rates in the US compared to Argentina. The EWG heard the MHRA will explore this data further.

3.33 The EWG requested future access via the portal to the presentation slides and the statistical analysis plan. The EWG commented that the read-only functionality of the assessment

report documentation, prevents the ability to highlight relevant data and make comments electronically. The EWG heard this step was taken to enhance data security.

3.34 The MHRA acknowledged the potential safety concerns over the limited duration of follow-up, and that information to draw robust conclusions on safety was currently insufficient. The EWG heard a specific date for receiving additional data is not yet available, but assessment will continue on any incoming data, and details of further data / assessment will be presented to EWG and/or CHM as appropriate.

4. Pharmacovigilance / Update on PHE Surveillance activities

4.1 The EWG received a summary of MHRA vaccine pharmacovigilance and the progress towards implementation. The EWG subsequently received a summary of PHE plans for post marketing vaccine surveillance.

4.2 The EWG noted that the MHRA and PHE must endeavour to ensure that pharmacovigilance data is rapidly shared between all nations of the United Kingdom.

4.3 The EWG noted that traceability needs to be established in terms of vaccine failures in order to conduct root cause analyses. The EWG heard vaccine failure data will be obtainable as part of base line and convalescent (recovered patients) enhanced surveillance, but gathering this information is not currently possible through surveillance of data from blood banks. The EWG noted that the power calculation for vaccine failures should be re-visited to ensure the sample size is sufficient.

5. Any Other Business

5.1 The MHRA secretariat proposed an extraordinary EWG meeting on Saturday 21 November 2020 at approximately 2pm, for an explanatory session of the Pfizer vaccine assessment report.

6. Date and time of next meeting

The next meeting is scheduled to take place on **Friday 20th November 2020** at **2.30pm**.

Date and time of future meetings:

- **Tuesday 24th November 2020** at **2.30pm**.
- **Monday 7th December (10.30am - 1pm)**
- **Tuesday 22nd December (11.30am - 2pm)**

The Meeting started at 15:30 and ended at 18:20.

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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.