COMMISSION ON HUMAN MEDICINES (CHM)

COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Tuesday 24th November 2020** at **14:30** 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
Professor H J Lachmann
Professor P J Lehner
Dr S Misbah
Professor S Price
Dr A Riordan
Professor C Robertson
Professor T Solomon[1]
Dr R Thorpe
Mrs M Wang
Professor C Weir

Apologies

Sir M Jacobs
Professor P Shah

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

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted] - LD

Supporting specific items

[redacted] - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - LD
[redacted] - Government Legal Team
Professor Van-Tam - DMO[2]
[redacted] - LD

MHRA Observers

[redacted] - Government Legal Team
Ms R Arrundale - Policy
Dr M Bailey - MHRA-NIBSC
[redacted] - LD
[redacted] - LD
[redacted] - LD
[redacted] - LD
Dr S Branch - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - MHRA-NIBSC
[redacted] - LD
[redacted] - LD
[redacted] - Policy
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - LD
Dr SP Lam - LD
[redacted] – Government Legal Team

Observers - CHM

Professor S Ralston (Chair of CHM)
Ms S Bradford
Dr J Fraser
Professor J Friedland
Professor R Gilson
Professor M Macleod
Dr R Mann
Professor S Meredith
Dr M Wilson
Mrs H Ward (Invited Expert of CHM)

Secretariat

[redacted]
[redacted]
[redacted]

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
PHE = Public Health England
CHM = Commission on Human Medicines
DMO = Deputy Medical Officer
IE&S = Inspection, Enforcement & Standards
MHRA CEO = Chief Executive

Mr K McDonald - LD
[redacted] - IE&S
Dr M O'Kane - LD
[redacted] - LD
Dr J Raine - MHRA-CEO
Dr N Rose - MHRA-NIBSC
Dr C Schneider - MHRA-NIBSC
[redacted] - LD
[redacted] - IE&S
[redacted] - LD
Mr P Tregunno - VRMM
[redacted] - LD
[redacted] - Government Legal Team
[redacted] - LD
Dr K Wydenbach - LD

Minute Takers

[redacted] - LD
[redacted] - LD

[redacted]
18th January 2021

[1] Left during item 4 & returned during item 5

[2] Left after the presentation of his item 2

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 invited experts and observers declared interests and other relevant interests for this meeting:

C19VBR

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.

Professor Lachmann – Other relevant interest as a volunteer participant in the Oxford vaccine study and no other involvement in the study.

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 - 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

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. Certainly I don't 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.

Professor Friedland – NPNS - GlaxoSmithKline, Sanofi, Pfizer

Professor Gilson – NPNS - Pfizer, GlaxoSmithKline, Novavax, Janssen, Oxford University

Professor Macleod – NPNS - Sanofi, Pfizer, Janssen

Dr Mann – NPNS - Sanofi

Professor Meredith – NPNS - Janssen, GlaxoSmithKline, Pfizer, AstraZeneca, Sanofi The Unit in which Professor Meredith works at University College London is coordinating the Imperial Covid Vaccine trials, however Professor Meredith is not involved.

Professor Patel – NPNS - Pfizer & NPNS – University of Nottingham have a scientific collaboration with Astra Zeneca who are providing free compound (a p38- small molecule inhibitor for the University to use in a dendritic cell caner trial the University is working on. AZ have also agreed to a donation to the University's scientific team for covering cost of reagents for the immune assays in the trial.

1.4 Apologies have been received from Sir Michael Jacobs and Professor Shah for this meeting.

1.5 The Chair welcomed:

Professor Van-Tam, Deputy Chief Medical Officer to present Epidemiological Data.

Chair and Members of the Commission on Human Medicines (CHM)

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

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

The following members of the Government legal team: [redacted], [redacted] and [redacted].

2. Professor Van-Tam, Deputy Medical Officer to present Epidemiological Data

2.1 The EWG heard a presentation from Professor Van-Tam. Professor Van-Tam agreed to follow up with a letter to the Chair to detail data on age-related COVID-19 mortality. The EWG noted that there were very few deaths in under 16s in England due to COVID in the first wave.

2.2 The EWG noted that some seasonality of coronavirus has been observed but was not as pronounced as seen with influenza virus and RSV. A stable signal cannot be observed for COVID-19 due to isolation measures and pharmaceutical intervention.

2.3 The EWG heard that the priorities for vaccination are residents in care homes for older adults and their carers and then all those 80 years of age and over, and frontline health and social care workers. With regard to pregnancy and women of childbearing age, information is currently being prepared for the JCVI PHE green book. It is not yet known that vaccines are unsafe for pregnant women. However, there are also no data to show that they are safe. The initial position in the green book is do not administer the vaccine to pregnant women but, there could be individual cases where there is extreme clinical vulnerability in a pregnant woman and decision would be made on a case-by-case basis with the respective clinician.

2.4 The EWG considered whether HCPs require vaccination in order to protect themselves or to protect the patient / elderly public. The EWG heard that vaccination of frontline health and social care workers is recommended as they are at increased personal risk of exposure to infection with COVID-19, and also of transmitting that infection to susceptible and vulnerable patients in health and social care settings. Apart from the risk of severe disease in HCW (albeit low in the younger age groups), there is a risk of long-COVID, the precise prevalence of which is unclear. Vaccination of HCPs will also help to maintain resilience in the NHS and for health and social care providers. There is evidence that infection rates are higher in residential care home staff than in those providing domiciliary care or in healthcare workers. Care home workers are therefore considered a very high priority for vaccination.

3. The EWG heard a summary on the legal aspects of Regulation 174

3.1 The EWG heard of other examples where Regulation 174 had been employed such as Flublok Quadrivalent vaccine.

3.2 The EWG heard that the timeline during which authorisation for distribution of a vaccine under Regulation 174 can be used is context specific. The EWG can implement any timeline that it considers appropriate, for example, temporary approval for an undisclosed time, limit approval to the season where coronavirus is expected to be prevalent, or until coverage is reached in a particular sub-set of the population.

4. The EWG heard an update on the non-clinical aspects of the assessment of the COVID-19 vaccine BNT162b2

4.1 The EWG heard that responses to non-clinical questions due from the company have not yet been received. It was also noted that the non-clinical pharmacokinetics were not performed in a conventional way. There is no information provided whether the vaccine, or elements thereof, cross the placenta, enter nodes of lactating mammals, crosses blood/brain barrier, or whether lipid nanoparticles bind to cell membranes, or travel to thymus or spleen. It is not clear whether the company will perform these studies.

4.2 The EWG discussed the lack of developmental and reproductive toxicity and histopathology data. Data to validate the choice of animal model is also awaited.

4.3 The EWG heard that in terms of the data observed so far there are no toxicological findings that would prevent the use of the vaccine. However, it was agreed that clear exclusions and exceptions for pregnant women, women of childbearing age and lactating women will need to be defined. Information is also required regarding the 23 incidental pregnancies that occurred in the clinical study in the pre-and post-vaccination window. The duration of this window also needs clarification.

4.4 The EWG noted the clinical trial exclusion criteria is expected to be followed during deployment, unless the non-clinical data become available and support expanding use to pregnant women and women of childbearing potential not taking dual birth control measures.

4.5 The EWG discussed inclusion of a contraindication in pregnant women in the SmPC and agreed if there is evidence of harm, a contraindication may be appropriate. However, at present the animal study is not complete and information is lacking. Women of childbearing potential could be included in the vaccination programme, provided effective contraceptive measures are being used for an appropriate period before and maintained for a period after vaccination, in addition to a negative pregnancy test result before vaccination. Information provided to women of childbearing age needs to be as informed and explicit as possible for facilitate informed decision. The EWG noted the most recent version of product information states the vaccine should not be used in people who are breastfeeding. The EWG requested a review of the data of RNA absorption through the infant gastrointestinal tract, and any evidence the company have used to support excluding women who are breastfeeding. The EWG noted the broad impacts and disadvantages to many women & children.

4.6 The EWG discussed whether the novel lipid nanoparticles distribute to a foetus and whether they are teratogenic. This information is required and the lack of it is a concern when considering the vaccination of younger healthcare and social care workers.

4.7 The EWG agreed it is not known whether mRNA would have unexpected negative consequence to an embryo or foetus, and it may be the case that a pregnancy test is integrated into the health system as part of the vaccination.

4.8 The EWG agreed that lung histopathology has not been provided but may be available; this information will be requested from the company as a high priority.

4.9 The EWG noted that data on carcinogenicity is not a requirement for the antigenic component of a vaccine due to the short exposure of the vaccine. Likewise, genotoxicity data have not been provided which is in line with the regulatory framework for a vaccine. The EWG discussed the potential risks associated with a mRNA vaccine, for example, modulation of gene expression and the potential for off-target mutations, in addition to the risk of potential toxicity of the novel lipid nanoparticles. The EWG agreed these risks need to be balanced against the degree of risk associated with COVID-19 disease across age-ranges and groups.

5. The EWG heard a presentation on the quality assessment of BNT162b2

5.1 The EWG heard there were no major quality objections. The issues remaining relate to the lack of experience with the novel format of the vaccine and the wide specifications set for batches, in particular the drug product. The EWG heard that some responses from the company had been received shortly before this meeting but some issues remain outstanding. It remains to be seen whether the responses raise any more issues.

5.2 The EWG heard that the labelling is complete now and cannot be amended. Any further information required would have to be made available via the information for use and other product information that will be provided to those people to be vaccinated.

5.3 The EWG heard that of the 2 specific batches that had been identified for supply in the UK; one has been used in a study from which the risk benefit profile was established. However, this batch was only used in 5 US centres and the doses used are not known. Despite this, that batch may fulfil criteria to be clinically qualified which addresses some of the uncertainties.

5.4 The EWG heard that batch CTM12 consists of 67665 vials and batch CTM consists of 67470 vials.

5.5 The EWG discussed mRNA degradation, the low limits set and the lack of explanation from the manufacturer. Given the good immune response observed with the vaccine, a question on the criticality of mRNA integrity was discussed by the EWG.

5.6 The EWG also noted that the limits for in vitro cell expression were also wide being set at 30% or above. This could lead to large differences across batches.

5.7 The EWG noted the difficulties in estimating potency of a vaccine where the antigen production is driven by mRNA. The effect of the cold chain was also discussed. A mechanism may be required (in a small population in each devolved area) to test the vaccine as it is administered to patients in order to provide early serological information. Data could also be returned to NIBSC for potency validation and cell transfection to see if antigens are being generated.

5.8 The EWG heard that NIBSC will be releasing the product in line with the specification in place and will not be adopting an in-house specification. It was noted that particle size, although a critical attribute, is not being evaluated by NIBSC. The current timeframe prevents this step being available.

5.9 MHRA informed the EWG that there is a stipulation for batches to be released that are in conformity with the limits specified in the clinical studies.

5.10 The EWG discussed how to monitor the timeline of 2 hours for mixing of the vaccine at room temperature when this is performed in the community. The stability of the vaccine should be maintained. It was noted that it might be better for the vaccine to be administered via mass vaccination and therefore the vaccine will not need to go in and out of the fridge repeatedly. Ideally the vaccinee should be identified beforehand and vaccinated together.

5.11 The EWG noted that in general, the stability of the product seems acceptable although there is some concern remaining with regard to the vaccine being thawed and then transported.

6. The EWG heard a presentation on the clinical assessment of BNT162b2

6.1 The EWG heard that MHRA has now received everything they can reasonably expect for an application under Regulation 174.

6.2 The EWG discussed the need for information on the use of analgesia and whether it would interfere with the immune response, comorbidities in older patients and the number of patients aged 70/80 years in the trial. MHRA agreed to check the patient listings. The EWG discussed fatigue as a symptom of vaccination and agreed that any mention of it in the SmPC will require quantification with regard to the onset and duration.

6.3 The EWG discussed the exclusion of immunosuppressed patients in the trial. MHRA agreed to check the protocol for the definition of immunosuppressed, and to gain full breakdown of the data on immunomodulators and immunosuppressants to gain insight for label.

6.4 The EWG discussed the number of protocol deviations that were excluded from the primary efficacy endpoint but included in 'all efficacy' endpoint. However, it was noted that these exclusions did not affect the efficacy which was reassuring.

6.5 The EWG discussed whether the vaccine could be recommended in those with a history of symptomatic Covid-19 illness.

6.6 The EWG noted there was no indication of enhanced disease in the clinical trial. It was noted that data on seropositive patients were included in terms of efficacy but not available in terms of safety. However, this may be available in the latest submission.

6.7 The EWG considered the age group the vaccine should be indicated for and noted that the manufacturer is currently proposing to include 16-17 year olds. The EWG agreed that the most clear benefit is observed in the >50 years age group. However, it was noted that limiting the age group for vaccination would have to be based on data. Efficacy data is available in all age groups and is equivalent in the different age groups identified in the data supplied.

6.8 The EWG raised concerns with the lack of longer-term safety data. Any potential rare side effects will become apparent as the numbers vaccinated increase. Post-authorisation safety data will be collected and will inform on any potential safety issues.

6.9 The EWG discussed whether it would be possible to defer a decision on vaccinating the younger population until more data is received.

6.10 The EWG heard that the full line listings were received the night before the meeting and the assessment team requires time to review these and report back to EWG.

7. The EWG heard a presentation on the RMP assessment of BNT162b2

7.1 The MHRAs core RMP for COVID-19 vaccines has been shared and discussed with the company previously. It was noted that it would be the company's responsibility to fulfil the conditions and content set out in the agreed RMP.

7.2 The EWG heard about the clinical studies included in the applicant's pharmacovigilance plan. The applicant is planning to conduct these studies. Geographically these are in Europe and the US, but the UK could be specified. The EWG heard that in the MHRAs core RMP, it has been highlighted that MHRA would accept studies performed outside of the UK if they contain a relevant population.

7.3 The EWG discussed the importance of brand and batch recording and their impact on traceability. The MHRA informed there is much discussion around this issue. PHE is intending to record batch data with linkage to patient records where possible. Where the vaccine is given outside of primary care it can be captured in the new NHS system; however, it will not automatically flow into CPRD data sets. MHRA informed that this is being addressed with the NHS. There is a push to record patient data and it is being worked on.

7.4 The EWG queried whether vaccine failures and a deeper dive (immunological, host genomic, viral genomic) into these will be included in post-authorisation studies. MHRA informed that PHE plan to carry out post-authorisation effectiveness studies and this would be a valuable source of information.

8. The EWG discussed product information for the vaccine

8.1 The EWG heard that the PIL and SmPC are being reviewed and the company will be made aware of comments on a rolling basis.

9. Future Steps / Any Other Business

9.1 The EWG was unable to review data received today. The next meeting of the EWG is to be arranged.

The Meeting started at 14:33 and ended at 18:15.

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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.