COMMISSION ON HUMAN MEDICINES (CHM)

COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Tuesday 2nd March 2021** at **12:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan[1]
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
Professor T Solomon
Dr R Thorpe
Mrs M Wang
Professor C Weir

Apologies

Professor S Price
Professor B K Park (Member of CTBV EAG)

Member of the CTBV Expert Advisory Group

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

Invited Experts presented Item 2[2]

[redacted]

Invited Experts for Items 2 & 5

[redacted]

Professional Staff of MHRA Present

Principal Assessors

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

Presenters supporting specific items[3]

[redacted] - LD
[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD

MHRA Observers

[redacted] – VRMM
[redacted] - VRMM
[redacted] - LD
Dr S Branch - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
[redacted] – VRMM
[redacted] - Devices
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - MHRA-NIBSC
Ms N Rose - MHRA-NIBSC
[redacted] - MHRA-NIBSC
[redacted] - LD
[redacted] - VRMM
[redacted] – Government Legal Team
[redacted] - MHRA-NIBSC
[redacted] - LD
[redacted] - LD
Dr K Wydenbach - LD

Observers

[redacted] (also participated in item 5)

[redacted]

Secretariat

[redacted]

23rd July 2021

[1] Joined during item 5
[2] Left after this item
[3] supporting specific items

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 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 Professor Price and Professor Park for the meeting today.

1.5 The Chair welcomed the following invited experts who presented item 2 - Analyses from REACT 2 study on vaccines. The experts left after the presentation of this item:

[redacted]

1.6 The Chair welcomed the following invited experts who participated for item 5 - Vaccination during Pregnancy & Breastfeeding.

[redacted], MD PRCOG

[redacted]

[redacted] **(also observed item 2)**
[redacted]

[redacted] **(also observed item 2)**
[redacted]

1.7 The Chair welcomed the following Observers who observed the meeting today and will be observing future meetings on the safety items:

[redacted]
Locum Consultant in Health Protection
Public Health Agency

[redacted] OBE - **Apologised**
[redacted]

[redacted]
Public Health Scotland

[redacted]

[redacted] MB ChB. FRCGP. FIMC (RCSEd), DUMC
[redacted]

2. Analyses from REACT 2 study on vaccines

2.1 The EWG viewed slides and heard a presentation by Imperial College London experts on the results of real-time assessment of community transmission 2 (REACT-2) programme, round 5, carried out on 26 January - 8 February 2021. REACT 2 is a community survey of adults in England that measures the prevalence of antibodies using the self-administered lateral flow immunoassay (LFIA) test. The survey comprised 172,099 participants, with valid immunoglobulin G (IgG) results from 154,417. The survey questionnaires collected demographic details, as well as clinical and COVID-19 vaccination histories.

2.2 The EWG heard a report on the overall prevalence of positivity for SARS-CoV-2 IgG antibodies in the community in vaccinated and unvaccinated individuals, the impact of vaccination on antibody status, and confidence in vaccination across the population. The EWG heard that antibody responses were detected after vaccination with Pfizer/BioNTech or AstraZeneca vaccines. However, the analysis was limited to those who received the Pfizer/BioNTech vaccine due to insufficient data for comparison with the AstraZeneca vaccine.

2.3 The EWG heard that antibodies to SARS-CoV-2 spike (anti S) protein and neutralisation were detected using the [redacted] (threshold value for positivity AU/ml). The results demonstrated the detection of antibodies on the LFIA correlated well with the threshold for neutralisation of live virus in in-vitro assays.

2.4 The EWG noted that the findings from REACT 2 study indicated higher prevalence of antibodies (37.9%) in the vaccinated population compared to the unvaccinated population (9.8%), which resulted from natural infections. The EWG heard that high level antibody positivity was seen following two doses of Pfizer/BioNTech vaccine across all age groups, with slightly higher levels in the younger population. It was also noted following a single dose of Pfizer/BioNTech vaccine high levels of antibody positivity were detected in those with previous infections compared to those with no history of COVID-19. The EWG heard that following a single dose of Pfizer/BioNTech vaccine lower antibody positivity was seen with increasing age. A high response was noted in those with previous or suspected COVID-19 across all age groups. The results on post vaccination indicated that the antibody response peaks around 30 days for all age groups.

2.5 The EWG heard that the uptake of vaccination by age was the highest in those aged 80 years and over (93.9%), followed by those aged 75-79 (64.9%). The data analysed also reported that 68.9% of healthcare workers and 59.7% of care home workers had received the vaccination. Further data was also received on 17,000 people who had reported having received one or two doses of the vaccine.

2.6 The EWG heard that confidence in the vaccine program was high with 92% of people being vaccinated or agreed to accept the offer. It was reported that vaccine confidence varied with age and ethnicity, with lower confidence in the higher prevalence groups (young people and those of Black or Asian ethnicity). It was noted that the reasons behind vaccine hesitancy were mainly related to the safety of the vaccine. Particular concerns were also identified around pregnancy, fertility, and allergies in all age groups.

2.7 The EWG heard the status and details of future plans, these included analysis of ongoing data, further modelling and comprehensive review of data, continuing to analyse digital images of completed LFIA tests, and conclusion of the pending rounds of REACT and linking the antibody results to cases, hospitalisations and mortality. The group are also awaiting confirmation that the blood testing services of [redacted] can be used to mount a larger scale analysis of the older cohort using [redacted] with the aim of subsequently linking results to clinical and hospital data.

2.8 The EWG asked whether qualitative or further quantitative assessments are being performed on the images. The EWG heard that the images are being read and checked by multiple individuals. However, a new method for automated reading is being developed and will be available in the future.

2.9 The EWG enquired if the apparent lower antibody response with age, may instead be due to an inadequate sensitivity or levels beyond the limit of quantification of the assay. The EWG heard that this was highly unlikely, because when using the same assay in older participants, post second dose, a far higher level of antibody was noted.

2.10 The EWG also heard that use of the [redacted] intends to focus on the older cohort and the assay should be capable of better characterisation of antibody responses when used in conjunction with a standard laboratory rush assay.

2.11 The EWG asked the invited experts about the binding kinetics of antibodies that have been afucosylated. The invited experts expressed a need to review the data on this topic before a response can be given.

2.12 The EWG enquired whether the WHO international standard will be used to calibrate the assay to an international unit to allow comparisons across other data sets. The external experts commented that calibration of assay quantification was based on previous inhouse

assays and information from published papers, and this was then aligned to [redacted]

2.13 The EWG asked the external experts whether people had reported of COVID-19 after receiving the vaccine and if this could be linked to the lateral flow positivity threshold. The expert stated that there are more data from previous study (REACT 1) which is under investigation. Further data are also being collected to link to the subsequent post vaccination hospitalisation, data on positivity and mortality.

3. COVID-19 Vaccine Moderna post authorisation study protocols: Post Authorisation Safety in the US and Observational Pregnancy Outcome Study

3.1 The EWG heard that Moderna had submitted protocols for a post authorisation safety surveillance (PASS) study to be conducted in the US, and for a pregnancy registry, to be conducted in centres in the US and in certain EU countries. The EWG heard that the US PASS proposes to further characterise the safety concerns of long-term safety and anaphylaxis with their COVID-19 vaccine, as included in the Risk Management Plan. The EWG noted that neither of the studies were proposed to be conducted in the UK, and that the protocols would be subject to approval by other regulators such as the US FDA and the EMA.

3.2 The EWG noted that the study design was a retrospective observational cohort study which will be conducted using a large US healthcare database. The EWG also heard that the study objectives were to estimate background rates for adverse events of special interest (AESI) prior to and during the pandemic, and since introduction of COVID vaccines, assess observed versus expected rates for AESIs and to estimate the relative risk for AESIs which meet prespecified evaluation threshold using a self-controlled risk interval (SCRI) analysis. The EWG noted that the proposed study timelines may be subject to change depending on protocol approval by various regulators, although interim updates are proposed every three months.

3.3 The EWG were informed that the MHRA intended to send some questions to the company for consideration, in relation to the power of the study to identify or exclude levels of risk for any AESI studied; also the design of the SCRI analyses will need to be AESI-specific and that use information on the UK deployment of the Moderna vaccine should be used to inform useful stratifications of data in the UK to understand the safety profile in the UK vaccinated cohort.

3.4 The EWG heard that a prospective, observational pregnancy exposure registry is proposed to collect primary data in the US and several EU countries from pregnant women who have received Moderna COVID-19 vaccine, and their healthcare providers. The EWG noted that the study proposes to estimate the proportion of major congenital malformations in the infants of women exposed to Moderna's vaccine and compare the proportion of major congenital malformations with the prevalence of birth defects in the general population in the EU and US (using European Surveillance of Congenital Anomalies [EUROCAT] and Metropolitan Atlanta Congenital Defects Program [MACDP], respectively. The EWG also noted the study also proposes to evaluate other adverse outcomes of pregnancy, and infant outcomes such as minor malformations.

3.5 The EWG agreed with the MHRA's assessment of the protocols and the proposed list of questions for the company. The EWG also recommended asking for some more specific details on other criteria for performing the SCRI analysis in the US PASS. Regarding the pregnancy registry, the EWG proposed asking the company to discuss the representativeness of the data collected in the pregnancy registry, and also whether the

choice of external comparators for the US and EU may introduce bias due to variations in the way that outcome data are collected.

4. COVID-19 Vaccine Moderna post authorisation study protocol: Safety and Immunogenicity of Moderna in Immunocompromised Patients

4.1 The EWG heard that a draft protocol for post authorisation study to characterise the use of SARS-CoV-2 mRNA-1273 vaccine in the subgroup of immunocompromised patients was submitted by Moderna. The protocol concerns a phase III, open-label, clinical trial comparing the safety and immunogenicity of the vaccine in uncomplicated solid organ transplant patients and healthy controls, aiming to monitor participants for 12 months after vaccination. The primary objectives are to evaluate safety and reactogenicity and to evaluate serum neutralising antibody response 28 days after first and second doses. Secondary objectives include evaluation of immune response persistence for a year and describing the incidence of COVID-19 in solid organ transplant (SOT) patients compared to healthy participants.

4.2 The EWG noted that the safety endpoints were assessed by clinical review of relevant parameters including adverse events (AEs), serious adverse events (SAEs), medically attended AEs (MAAEs), any reported adverse events of special interest (AESIs), and a biopsy-proven organ rejection.

4.3 The EWG heard the proposed humoral and cellular immunogenicity response endpoints and safety analyses are acceptable.

4.4 The MHRA has requested clarification from the company on the statistical comparison of the antibody responses of the transplant patients and the healthy participants, and on the method of selecting the antibody threshold from pivotal study mRNA-1273-P301.

4.5 The EWG heard that a request has been made for the company to confirm whether the subset of participants for exploratory cellular immunogenicity responses include both SOT recipients and healthy participants, to enable comparison. Justification was also requested to establish whether the sample size is large enough to achieve the aims of the study.

4.6 The EWG discussed further questions the MHRA will potentially raise with the company. The EWG noted that the immunocompromised subjects proposed in the study are uncomplicated SOT patients. The EWG was asked to comment whether the study population reflects the broader immunosuppressed population, if not, to comment on further suggestions for which other subgroups may be recruited and any potential recruitment sources.

4.7 The EWG agreed with the MHRA assessor that the patient population is very restrictive and is not representative of the wider immunosuppressed population. The EWG advised that the company's post authorisation study should include patient groups with both primary and secondary antibody deficiency, bone marrow transplant recipients, patients on immunosuppressant therapy, and patients with autoimmune disease or inflammatory disease. The EWG also recommended that an adequate sample for each of these groups can be obtained from the relevant scientific, or professional societies. The EWG also recommended having a broad spectrum of patients in these groups, including patients with combined secondary defects in terms of T-cell defects as well as antibody deficiency.

4.8 The EWG also heard about the company's proposal to measure cellular immunogenicity endpoints relating to B-cells and T-cells in a subset of participants at 7 days post second dose. Advice was sought from EWG whether the timing for sample collection is optimal.

4.9 The EWG noted in the phase I study conducted by Moderna, sample collection occurred at 14 days after the second dose, to align with the period for generation of T-cell response. At a minimum, it would be beneficial for the company to include a 14-day time point to allow comparison between the phase I immunogenicity data and the forthcoming post authorisation study data.

4.10 The EWG confirmed that the proposal for evaluation of more general safety endpoints as well as transplant rejection was generally acceptable. The EWG advised the MHRA to encourage the company to consider new data emerging and work closely with academic groups to produce a better-informed study protocol.

4.11 The EWG endorsed the list of questions to the company.

5. Vaccination during Pregnancy & Breastfeeding

5.1 The EWG heard that current COVID-19 vaccine trials within the UK do not allow inclusion of pregnant women but that there are plans from several companies to address this. Pfizer have announced a trial in pregnant women to compare the data to that from their pivotal trial, but as yet this will not involve the UK. Janssen have been in communication with the Clinical Trials Unit (CTU) and submitted an updated protocol for review for their planned phase II trial. The trial will evaluate women in the 2nd and 3rd trimester for safety and immunogenicity as well as parameters in the neonates. The CTU has also heard about a possible trial evaluating the deployed vaccines in pregnant women at 13 to 24 weeks gestation. The design will be similar to another ongoing trial of deployed vaccines but focusing on the doses and prime-boost regimen.

6. Any Other Business

6.1 None.

7. Date and time of next meeting

The next meeting is scheduled to take place on Tuesday 9th March 2021 at 15:30.

The Meeting today started at 11:31 and ended at 13:56.

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

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:

Apologies were received from Professor Price and Professor Park 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.

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 – Personal interests arising from being highly sensitive to insect stings, and plant products such as Hyacinth bulbs, which are recorded on Mrs Wang's medical records.

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

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

Observers for this meeting

[redacted]