NOT FOR PUBLICATION

COMMISSION ON HUMAN MEDICINES (CHM)

COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Thursday 4th February 2021** at **10:30** 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[2]
Professor K Hyrich
Sir M Jacobs[2]
Professor P J Lehner
Dr S Misbah
Professor S Price
Dr A Riordan
Professor C Robertson
Professor P Shah
Professor T Solomon[3]
Dr R Thorpe
Mrs M Wang
Professor C Weir

Apologies

Professor H J Lachmann

Member of the CTBV Expert Advisory Group

Professor B K Park

Members of the CPS Expert Advisory Group

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

Invited Expert

[redacted][4]

Secretariat

[redacted]

MHRA Observers continued

[redacted] - LD
[redacted] - LD

[1] Joined during item 2
[2] Left after item 5
[3] Left during item 4
[4] Presented item 2 & left after this item

Professional Staff of MHRA Present

Principal Assessors[5]

Dr J Bonnerjea - LD
Dr P Bryan - VRMM

MHRA Presenters supporting specific items[5]

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

MHRA Observers

[redacted] - VRMM
[redacted] - LD
[redacted] - LD
Dr S Branch - VRMM
[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - LD - Medical Writer
[redacted] - VRMM
[redacted] – VRMM
[redacted] - VRMM
[redacted] - LD - Medical Writer
[redacted] - LD
[redacted] - LD
[redacted] - VRMM
Ms N Rose - MHRA-NIBSC
[redacted] - LD
[redacted] - LD
[redacted] - VRMM
Mr P Tregunno - VRMM
[redacted] - Government Legal Team
[redacted] - MHRA-NIBSC

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

[5] supporting specific items

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 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 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.

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 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.

CPS

Mr V'lain Fenton-May – None
Professor Kevin Taylor – None
Dr Susannah Walsh – None

1.4 The Chair welcomed [redacted] from ZOE, Kings College London

2. ZOE App and suspected adverse events

2.1 The EWG heard from [redacted] on the preliminary analysis of the occurrence of adverse effects and reduction of SARS-CoV-2 positivity rate, based on the data provided by contributors to the ZOE/KCL COVID Symptom study. On 4th December 2020, questions on vaccination were made available to users of the app. Most of the ~4.5 million users are located in the UK. 1.5 million log data each week, and many of these have been reporting via the app since April 2020.

2.2 ~300,000 users had logged their vaccine; most were white and BAME populations were underrepresented. A high number of healthcare professionals reported regularly (45,000). Post vaccination PCR tests have been reported from 51,763 contributors while a much smaller proportion had antibody tests (1,654).

2.3 The first analysis focused on data from 40,000 mainly healthcare professionals who had received the Pfizer/BioNTech vaccine - at cut off ~23,000 first dose only (65%), and ~12,000 (35%) first and second dose. Local and systemic adverse effects were studied. Systemic effects were more frequent after the 2nd injection, (~11.1% reported at least one systemic adverse effect after the 1st dose versus ~19.7% same reporting measure after the 2nd dose). Systemic adverse effects were headache, fatigue, chills, shivering, diarrhoea, fever, arthralgia, myalgia, and nausea. The data were fairly consistent with the clinical trial data for the vaccine. Contributors who had COVID in the past were more almost twice as likely to have at least one systemic adverse effect (~33% vs ~19%). Younger users <55 years also reported more systemic effects (~25% vs ~13% in those >55 years), possibly due to a reduced immune response in older people. The most frequent adverse effects are fatigue and headache, and aftereffects tend to resolve after 2-5 days, although ~2% continued for longer.

2.4 Local adverse effects were pain that is localised, swelling, tenderness, redness, itch, warmth, proximal lymphadenopathy; these effects were short lasting (most lasting 3 days or less) and highly similar in both rate and type to those reported in the clinical trial. Local effects were more common after the 2nd dose. It should be noted that check box lists of adverse events were displayed to users, and the list was developed in collaboration with virologists and the Pfizer BioNTech clinical trial investigators. A free text box was also included under the category of other, to enable reporting of effects outside of the predefined list. Female contributors reported more adverse effects (both local and systemic).

2.5 The re-infection rates post Pfizer/BioNTech vaccination increased during the period 5-12 days after vaccination. The increase was suspected to be due to the window where there is no protection as the immune response has not had time to develop combined with a potentially higher risk of exposure, on travelling en route to and from vaccination centres / clinics, and possibly increased socialisation due to a false perception of immediate protection. After 12 days and adjusted for the background decrease in cases, an approximate reduction in infections in the vaccinated group of contributors of approximately 50% was observed.

2.6 Future analyses are planned to investigate similar parameters for the AstraZeneca vaccine and compare these to the Pfizer/BioNTech data. Questions to be explored included if past COVID may remove the need for a 2nd dose, the biological vaccine response in long COVID and responses in BAME vaccine recipients, to work with the MHRA to enhance reporting of rare side effects, and to explore the duration of protection through natural exposure and vaccine-based protection. In the invited experts closing remarks, attention was drawn to the limited NHS promotion of the app, for example at vaccination centres and other NHS platforms, despite Chief Medical Officer (CMO) support.

2.7 Questions and Answers

2.7.1 The Commission heard it will be explored if there is a relationship between the time interval from natural infection to vaccination, and if this affects the likelihood of developing systemic side effects. There is a hypothesis that vaccine recipients with a longer interval between natural infection and vaccination may experience reduced vaccination side effects, which may be attributed to waning immunity.

2.7.2 The Commission heard the vast majority of healthcare workers tested for COVID-19 post vaccination were symptomatic according to the app's symptom criteria which includes a greater list of symptoms compared with that used by Public Health England (PHE). The Commission noted that the post vaccination infection rate was similar to that observed in vaccine effect studies conducted in Scotland, and Professor Tim Spector requested access to any other relevant epidemiological data sets.

2.7.3 The Commission noted it may be beneficial on a precautionary basis, to calculate the number contributors that reported (resolved) infection prior to vaccination as a positive control when analysing the 5-12 day post vaccination infection data. If the proportion who had prior infection is high, there would be expected to be a degree of immunity, this could help to eliminate social factors and other routes of elevated exposure as causes.

2.7.4 The Commission heard messaging at the point of vaccination seems to focus on managing of common aftereffects, and perhaps, neglects to reinforce the message that no additional protection against infection will be acquired until at least 12 days after vaccination.

2.7.5 The Commission heard the Zoe app currently does not request information on use of analgesics including paracetamol by contributors to manage vaccine aftereffects, but this could be potentially added.

2.7.6 The Commission asked if any contributors have reported anaphylaxis or severe systemic reactions. No events have been seen so far, although the review of the other column is still incomplete. There is also another limitation that contributors may be unlikely to report severe systemic reactions due to their condition and perhaps due to the knowledge that the healthcare professional should report via the Yellow Card Scheme. Contributors might also report once they have recovered, so there could be a time lag. Data on localised allergic reactions is being collected and can be provided in due course. Professor Tim Spector was also keen for the MHRA to highlight any potential side of effects of special interest or rare side effects that could be investigated further using the app's data sets. Data from the CDC and MHRA indicate rates of anaphylaxis to be ~1 in 100,000 for PfizerBioNTech vaccine recipients.

2.7.7 The vaccinated cohort appear well motivated and drop-out rates from the app are low, users consistently and frequently engage with the app, and other materials on the affiliated website, e.g. a webinar with 100,000 attendees; frequent feedback also helps retain contributors. Complete data is preferred and generally contributors that drop-out are not included in the analyses.

2.7.8 The app includes a system to permit reporting on behalf of elderly relatives: ~300,000 users are in this group. The median age of contributors is ~55 years so the coverage of the JCVI priority list is relatively good, although a full proportional analysis is needed. The Commission heard that symptoms and severity of symptoms could be further defined / sub-divided in the app's checklist, where the MHRA feels it may be useful, e.g. in line with emerging signals to improve granularity of the data. The need to gather more detailed information needs to be balanced against the risk of dissuading users / lowering compliance if reporting takes too long, for example if symptom lists are too exhaustive. An alternative option would be to email all contributors reporting a specific symptom and ask them to provide a detailed narrative.

2.7.9 MHRA and [redacted] agreed that continued liaison between the VRMM and the King's College team is beneficial and should be continued, including to discuss data linkage.

2.7.10 The MHRA was asked to assist with facilitating promotion of the app through the NHS.

2.7.11 The Chair gave thanks [redacted] for the valuable contributions Kings College and ZOE are making to increase data collection and analysis to help further understanding of COVID-19.

3. Bell's palsy and myocarditis rapid cycle analysis and observed vs expected

3.1 The EWG discussed a paper which presented summaries of the most recent epidemiological analyses of the incidence of Bell's palsy and myocarditis or pericarditis following COVID-19 vaccination. The EWG heard updates on the observed vs expected analyses of Yellow Card reports and the rapid cycle analysis being conducted in the Clinical Practice Research Datalink (CPRD).

3.2 The analyses specific to Bell's Palsy were described and the EWG discussed the inconsistent results. In particular, they discussed the finding within the rapid cycle analysis which suggested a higher observed number of cases of Bell's Palsy in the 42 days following the first dose of the Pfizer/BioNTech vaccine than expected based on age-specific background risks of Bell's Palsy calculated in the CPRD primary care data.

3.3 The EWG agreed that there were limitations to the analyses and as such they did not provide evidence of an increased risk of Bell's Palsy and should be treated with caution. However, they were broadly supportive of the initiation of a more robust epidemiological study to further explore the issue. They noted that such a study would allow for more careful case definition and identification and advised that sensitivity analyses should be conducted around the risk window. The EWG agreed that monitoring of Bell's Palsy should also continue with further consideration of incidence rates following the second dose of the vaccine.

3.4 The analyses specific to myocarditis/pericarditis were also described and the EWG discussed the statistical signal of an increased incidence in the 42 days following the first dose of the Pfizer/BioNTech vaccine in the rapid cycle analyses. It was noted that this was based on a small number of cases.

3.5 It was agreed that this was likely to be a chance finding given the body of evidence but that monitoring of myocarditis should continue given the overlap with multisystem inflammatory syndrome seen predominantly in paediatric patients with COVID-19 infection.

4. Trends in reactogenic adverse reactions with the Pfizer and AZ vaccines

4.1 The EWG was presented with a summary of Yellow Card data for the Pfizer/BioNTech and AstraZeneca COVID-19 vaccines focusing on cases capturing one of the relevant serious criteria available; hospitalised, life threatening, fatal, disability/incapacitation and "other" medically significant such as affecting everyday activities. The meeting commented on how subjective these categories can be for recording the severity of reactions.

4.2 The meeting heard that a higher proportion of cases reporting any serous criteria was identified for the AstraZeneca COVID-19 vaccine compared to the Pfizer/BioNTech vaccine, and that this difference was largely related to the more moderate "other" serious criteria. The types of events most commonly reported for both of the COVID-19 vaccine related to reactogenicity side effects known to be associated with the vaccines. It was noted that a higher proportion of cases are reported in females compared to males, and the meeting commented that this has been seen with other vaccines too and the potential biases behind this were discussed.

4.3 Compared with Yellow Card data available on the flu vaccine for the past 10 years, there is higher proportion of serious reports for the flu vaccine compared to the COVID-19 vaccine. The nature of the events reported in the serious categories was similar between the flu vaccine and the COVID-19 vaccines. The frequency and nature of events reported for the Pfizer/BioNTech COVID-19 vaccine was also similar to data provided by the ZOE COVID Symptom Study and US data published by the CDC.

4.4 The meeting was presented with the reporting rates broken down by age groups based on usage data of both COVID-19 vaccines, which showed a higher proportion of serious events reported in younger age groups, particularly in the "other criteria" and largely representing reactogenicity events. Similarly, clinical trial data for both vaccines showed a higher proportion of reactogenicity events being reported in the younger age groups. In comparison with the flu vaccine data, there is not such a pronounced difference in younger age groups. The meeting discussed which reporting biases may be contributing to this difference.

4.5 The meeting was also presented with Yellow Card data suggestive of a higher proportion of serious events reported following the second dose of the Pfizer/BioNTech vaccine compared to that reported with any dose. This is similar to data from the clinical trials and that reported from the ZOE COVID Symptom Study and US data published by the CDC. There is limited data to conduct a similar analysis with the AstraZeneca vaccine; a higher frequency of events with the second was not observed in the clinical trials.

4.6 The meeting discussed the available data on use in those with prior-COVID-19 infection and it was noted by the meeting that the MHRA were engaged with PHE on how best to gather further data on this topic. The meeting also considered the need for a second dose of the COVID-19 vaccines in those with prior-COVID infection and that further data was needed before any conclusions could be drawn.

4.7 The meeting agreed with the conclusions presented in the paper and that the data did not indicate any new safety concern for either of the COVID-19 vaccines currently in use.

5. General safety update for the AZ vaccine

5.1 The meeting heard an overview of the safety of the AstraZeneca Covid-19 vaccine as described by Yellow Card reports. The meeting heard that up to the end of 31st January 2021, an estimated 3,098,605 doses of COVID-19 Vaccine AstraZeneca have been given

in the UK. Up to 28th January 2021, the MHRA has received a total of 9681 reports of suspected ADRs in association with COVID-19 Vaccine AstraZeneca.

5.2 The reactions reported most frequently are common reactogenicity reactions seen with all vaccines as well as in the AstraZeneca clinical trials. These terms, or associated umbrella terms are labelled in the product information.

5.3 63 fatal cases were received, with most occurring in patients aged 80+ and with underlying comorbidities.

5.4 The meeting heard that cases of Bell's Palsy and transverse myelitis, which are adverse events of special interest, had been received. These are being monitored closely and Observed vs Expected and Rapid Cycle analyses are also being performed.

5.5 Overall, the ADR data was broadly in line with the safety profile seen in clinical trials. Review of the cumulative data does not identify any new safety signals.

5.6 The EWG found the safety data reassuring.

5.7 The EWG commented regarding anaphylaxis that a recent case had been identified of a patient who experienced anaphylaxis with a biological medicine and had a strong reaction upon skin testing to both polysorbate and PEG.

5.8 Regarding transverse myelitis, the meeting commented that we may not see all cases of transverse myelitis reported via the Yellow Card Scheme and that these may be seen in hospital. Observed vs Expected and Rapid Cycle analyses will also be important to pick up additional cases, but hospital admission and discharge data could be important in identifying cases.

5.9 The meeting suggested that use of prophylactic paracetamol could be proposed to reduce the number of adverse events experienced. However, it was recalled that the data regarding use of prophylactic paracetamol in clinical trials was limited and this was only recorded in a small number of participants. This data therefore could not be used to recommend prophylactic use.

6. Verbal update on Yellow Card Vaccine Monitor

6.1 The EWG was provided with an update on enrolment of individuals to the Yellow Card Vaccine Monitor (YCVM), part of the MHRA pharmacovigilance surveillance strategy for the COVID-19 vaccines.

6.2 The EWG heard that individuals are recruited through the national call-recall process for vaccinations and receive a letter following the national call inviting them for vaccination. The EWG heard that many individuals also receive invitations through local call-recall processes that the MHRA is considering linking into.

6.3 The EWG heard to date approximately 120,000 invites to register with the YCVM platform have been posted with the aim of enrolling 10,000 individuals in total.

6.4 The EWG heard that approximately 8,000 individuals have registered with the YCVM platform to date. The EWG also heard that an equal proportion of men and women have registered and 92% are aged 70 years and over. The EWG noted the proportion of younger people registered should increase once the priority groups have been vaccinated.

6.5 The EWG heard that around 92% of individuals registered were of white British or white Irish ethnicity and that consideration is being given to increasing the representation of other ethnic groups.

6.6 The EWG heard that of the 8,000 individuals registered, approximately 4,000 have entered details regarding their first vaccine dose and that an equal proportion have received the Pfizer-BioNTech or Oxford AstraZeneca vaccines as their first dose.

6.7 The EWG heard that a small proportion of immunocompromised individuals have registered, and it is anticipated this number will increase as this group is called in for vaccination.

6.8 The EWG considered the importance of this data collection and promotion of the YCVM platform could occur at the point of vaccination and continue throughout the vaccination programme to maximise numbers contributing to the platform.

6.9 The EWG noted that epidemiological studies and rapid cycle analyses form will enable linkage to hospital admission data with the YCVM data important as an additional data source providing long-term follow-up.

7. Verbal update on Janssen Vaccine Quality issues

7.1 The Commission heard two rolling review cycles have been undertaken in order to review the data on the Janssen vaccine provided so far. The data reviewed was of high quality, and no unresolvable issues are currently envisaged by the quality assessment team. Certificates of Analysis for small commercial-scale process performance qualification (PPQ) batches are not expected until after the 22nd February 2021. The February data package is also expected to include details of manufacturing scale-up. Comprehensive comparability data for scaled-up supply is not expected until early March and is intended to be assessed by variation to the conditional marketing authorisation, if given. There are no concerns presently in relation to the finished product stability data, and preliminary data showed that the product is stable to at least 6 weeks at room temperature.

7.2 In terms, of resolvable issues, an out-of-date GMP certificate dated 2017 has been provided for the drug substance manufacturing site, likely due to COVID related delays to the next planned inspection. Some key release potency acceptance criteria are also wider than those specified for the clinical trial material, and therefore an in-depth clinical justification of the wider limits will be required. The company have requested that no questions are to be sent by the MHRA, until the MHRA have been sent the questions/assessment reports from the European Medicines Agency (EMA).

7.3 The Chair conveyed to members that data package would likely be available to be seen by the EWG by late February/early March 2021, depending on when the data have been submitted and assessed (and potentially when the EMA's assessment has been received).

8. Any Other Business

8.1 None.

9. Date and time of next meeting

The next meeting is scheduled to take place on Monday 15th February 2021 at 10:30.

The Meeting today started at 10:34 and ended at 12:51

[redacted]

19th July 2021

Members are reminded that the content of papers and proceeding of the meetings are to be treated as 'Official – sensitive commercial'. Members are also reminded that, in accordance with the Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members must also declare any other matter which could reasonably be perceived as affecting their impartiality. Detailed guidance is set out in the Code of Practice