COMMISSION ON HUMAN MEDICINES (CHM)

COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Tuesday 29th September 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
Sir M Jacobs
Professor P J Lehner
Dr S Misbah
Dr A Riordan
Professor C Robertson
Professor P Shah
Dr R Thorpe
Mrs M Wang
Professor C Weir

Invited Experts

[redacted]

Apologies

Professor I J Douglas (Invited Expert)
Professor H J Lachmann
Professor T Solomon

Secretariat

[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted] - LD

Supporting Specific Items

[redacted] - LD
[redacted] - LD
Dr P Bryan - VRMM
[redacted] - LD
[redacted] - LD
Dr N Rose - MHRA-NIBSC
Dr C Schneider - MHRA-NIBSC
[redacted] - LD

MHRA Observers

[redacted] - VRMM
Dr S P Lam - LD
[redacted] - LD
Dr M O'Kane - LD
[redacted] - LD
Dr K Wydenbach - LD

[redacted]

15th October 2020

Key

LD = Licensing Division
VRMM = Vigilance & Risk Management of Medicines
NIBSC = National Institute for Biological Standards & Control

1. Introduction and Announcement

1.1 The Chair reminded Members that the papers and proceedings are confidential and should not be disclosed.

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:

Professor Sir Munir Pirmohamed - NPNS AstraZeneca - Research grant to UOL to support PhD in drug interactions.

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.

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.

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 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.

Invited Experts of the COVID-19 Vaccines Benefit Risk Expert Working Group declared the following interests:

[redacted] - Personal Specific interest, [redacted] is a member of a DSMB for clinical trials of a COVID-19 vaccine developed by CUREVAC, Germany - receive DSMB fees for this work.
At the chair's discretion, [redacted] was permitted to remain for the discussion and to answer direct questions from the chair and other members, but not raise unsolicited comments or questions.

[redacted] - Personal non-specific interest in AstraZeneca who provide [redacted] department at the London School of Hygiene and Tropical Medicine with an unrestricted research grant covering the period 2016-2021. The grant partially contributes to funding [redacted] salary. [redacted] research and employment is not dependent on this funding and AstraZeneca have no influence on the nature of [redacted] research, or on reporting or dissemination of results. Other relevant interest, [redacted] is working on a [redacted] paper and some of the co-authors are statisticians at AstraZeneca in Cambridge. It's an academic paper on [redacted] and is not related to the business side of the company or products.

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

1.4 Apologies have been received from Professor Douglas, Professor Lachmann and Professor Solomon for this meeting.

2. Minutes of the meeting held on Tuesday 25th August 2020

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

3. Update on Vaccine Manufactures' Submission Plans (verbal update only)

3.1 The Expert Working Group (COVID-19 VBR EWG) were updated on the MHRA's discussion with vaccine manufacturers and their plans for regulatory submissions. For confidentiality reasons code names will be used for the different vaccines in the future except where this is not possible, e.g. where information is received uncoded from third parties. The MHRA also informed the COVID-19 VBR EWG that the MHRA had withdrawn from the government's Vaccine Task Force to avoid any perceived conflict between the MHRA's role in evaluating the quality, safety and efficacy of candidate vaccines and the Task Force's work on the procurement and deployment of vaccines in the UK.

3.2 Initial schedules of the vaccine companies' rolling submissions were presented, emphasizing that these timings could change as the companies further developed

their submissions. The MHRA agreed to update the COVID-19 VBR EWG regularly as further information on the submission timings was obtained.

4. COVID-19 Vaccine Pharmacovigilance and Risk Management Plan standards

4.1 The COVID-19 VBR EWG considered a proposal on the core requirements of a pharmacovigilance system and risk management plans (RMP) for COVID 19 vaccines in the UK.

4.2 It was noted that the legal obligations for pharmacovigilance systems and RMPs are described in Part 11 of The Human Medicines Regulations (2012). This requires, amongst other specific requirements, the recording and reporting of suspected adverse reactions (ADRs), signal detection activities, continuous monitoring of risk-benefit balance based on all data sources, submission of periodic safety update reports (PSURs) and the operation of a risk management system (in accordance with an RMP).

4.3 The COVID-19 VBR EWG heard that the RMP consists of a 'safety specification', a 'pharmacovigilance plan' and a 'risk minimisation plan'. The purpose of the 'safety specification' is to outline what is known about the safety and efficacy of a product at the time of authorisation and any important risks, uncertainties in risk or gaps in knowledge. Based on the specification, the purpose of the 'pharmacovigilance plan' 'risk minimisation plan' is to have in place a scientific strategy to continuously evaluate risk-benefit balance, to address the important risks, uncertainties and gaps in knowledge and to mitigate risks.

4.4 The COVID-19 VBR EWG agreed that there are aspects and specific challenges of the pandemic situation, and the potential mass deployment of a COVID-19 vaccine over a relatively short time period, that require a rigorous approach to pharmacovigilance. It therefore agreed that compliance with the existing scientific standards of pharmacovigilance guidance is required but should also be strengthened and tailored where appropriate.

4.5 The COVID-19 VBR EWG noted and endorsed the proposals outlined in the paper that, in addition to routine pharmacovigilance activities, all applicants should additionally:

- Conduct signal detection activity as close to real-time as possible, and no less than at a weekly interval
- Conduct 'observed vs expected' (as outlined in section P.I.B.4.5 of the EMA's GVP module on vaccines) analysis of suspected ADRs and adverse events of special interest (AESIs) on a routine basis
- Adopt of a list of AESIs (as defined by MHRA) for tailored pharmacovigilance and conduct 'observed vs expected' analyses and targeted follow up of such events.
- Conduct batch-specific surveillance in accordance with the principles outlined in section P.I.B.5 of the GVP vaccines guidance.

- Supplement the existing PSUR requirement with a monthly 'simplified PSUR' approach

Commit to regular (e.g. two-weekly) video-telecon with MHRA to discuss the sPSUR content, ongoing observed vs expected analysis of adverse events of special interest, and any other emerging safety data and signals.

4.6 The COVID-19 VBR EWG agreed that, in addition to these core requirements, there may be additional requirements for individual applicants based on the safety specification and characteristics of individual products, particularly in relation to the need for post-authorisation safety studies (PASS) and post-authorisation efficacy studies (PAES). The COVID-19 VBR EWG heard that, where required, a PASS is intended to further characterise the safety profile, which can include confirmed or potential risks identified from the clinical trials, and important missing information such as safety in groups excluded from pre-authorisation trials. The COVID-19 VBR EWG also heard that PAES could be used to further evaluate important vaccine characteristics, such as long-term protection and the ability of the vaccine to prevent viral acquisition, carriage and transmission.

4.7 The COVID-19 VBR EWG advised that if a well-designed and feasible PASS or PAES study (or other form of proactive surveillance) in a non-UK territory is proposed, then MHRA should consider accepting that in fulfilment of a UK RMP.

4.8 The COVID-19 VBR EWG also agreed that as relevant national public health authorities will be actively co-ordinating all NHS and public-facing communications relating to a COVID-19 vaccine programme, there should not be a default requirement for additional risk minimisation material, and this should be considered on a case by case basis.

5. Efficacy Measures being used in COVID-19 Vaccine pivotal trials

5.1 The COVID-19 VBR EWG reviewed a summary table comparing and contrasting the main efficacy parameters of 4 pivotal trial protocols for 3 COVID-19 vaccines (Oxford/AstraZeneca ChAdOx1 Vector Vaccine, Pfizer BioNTech SARS-COV-2 RNA vaccine and Moderna mRNA-1273 SARS-CoV-2 Vaccine). [redacted] The COVID-19 VBR EWG heard how the COVID-19 vaccines will be determined to be effective. The WHO and FDA guidance on the development of vaccines to prevent COVID-19 was highlighted.

5.2 It was noted that, at the time of the efficacy assessment for the Oxford/AstraZeneca vaccine in the UK, results from the US trial are not anticipated to be included. The assessment will be based on pooled data from 4 trials (UK phase I/II and phase II/III, Brazil phase III and South Africa phase I/II) with approximately 20,000 subjects enrolled. The COVID-19 VBR EWG endorsed this approach.

5.3 It was noted that the method of calculating Vaccine Efficacy (VE) and the approach to statistical analysis differed between all the trials presented. It was agreed that all the methods used are approaches seen previously in vaccine applications and that

they were all acceptable. The results from each of the approaches would be expected to be consistent and the COVID-19 VBR EWG concluded that it would be reasonable to assess each trial based on its pre-specified methodology. For one of the trials a Bayesian analysis was planned so results would be impacted by the choice of prior distribution, however the estimate of VE and associated confidence interval would come from standard frequentist methodology, permitting consistent interpretation with the other trials.

5.4 The differences between the trials with respect to the number of patients targeted for recruitment in different age categories was noted. The COVID-19 VBR EWG noted that this would be an important aspect to consider when assessing the trials.

5.5 The COVID-19 VBR EWG were asked to consider what impact, if any, differences in the clinical definition of symptomatic COVID-19 could have on the primary efficacy endpoint assessment, while all cases would have to be PCR-confirmed. It was noted that sensitivity and specificity of the PCR test is likely to impact on the assessment of the primary endpoint. The COVID-19 VBR EWG considered that case identification and case definition would have an impact, particularly for any comparisons across trials. It was also highlighted that in most of the protocols reviewed, COVID-19 cases were identified by symptoms with subsequent confirmatory PCR testing, rather than also by routine PCR testing.

5.6 The COVID-19 VBR EWG heard that vaccine efficacy with regards to protection against asymptomatic COVID-19 infection, determined by serological testing, was a secondary endpoint in the studies.

5.7 The COVID-19 VBR EWG were concerned that with infrequent serological testing, asymptomatic cases may no longer be seropositive at the time of testing. They highlighted that regular PCR testing would provide additional information about asymptomatic cases. The COVID-19 VBR EWG welcomed the fact that weekly PCR testing was being carried out in a subset of subjects enrolled in the UK Oxford/AstraZeneca phase II/III trial.

5.8 Currently only adult patients have been enrolled into the clinical trials. The COVID-19 VBR EWG recommended that if/when children are included in studies the clinical symptoms of COVID-19 are amended to reflect the disease presentation in this population e.g. diarrhoea and vomiting are common, and sometimes the only, clinical symptoms in children.

5.9 Regarding the success criteria for the primary endpoint in the trials, while there is no strong scientific argument for any particular cut-off, it was considered that the WHO/FDA requirement that the lower bound of the confidence interval for VE should be above 30% with a point estimate of 50% was clinically reasonable. The COVID-19 VBR EWG noted that simply achieving a lower bound above 0% was not sufficient. A lower bound of 20% was discussed and may be acceptable depending on the supporting data and safety information available at the time. A limit for the lower bound of confidence interval of 30% was the preferred option. The COVID-19 VBR EWG also expressed concerns about the success criteria for the primary endpoint, in the context of the importance of public confidence in the vaccines and the scale of vaccination. With this in mind, while study success criteria are defined

in terms of lower bounds of the confidence interval, the COVID-19 VBR EWG recommended the study reports include appropriate emphasis on the point estimate for VE, rather than focussing on the lower bound which represents a worst case.

5.10 The COVID-19 VBR EWG also highlighted that ultimately the decision on whether to license each vaccine will be determined by the overall benefit-risk decision, including the adverse event profile.

6. COVID-19 Vaccine-Specific batch release testing

6.1 The COVID-19 VBR EWG was presented with a paper laying out the Agency's proposal for independent batch release testing of COVID-19 vaccines, both in the scenario of a regular Marketing Authorisation (which is the preferred route), and under a Regulation 174 opinion.

6.2 The MHRA proposed a view that independent batch release should be the default for all vaccines under any scenario; and under Regulation 174, such a requirement would be imposed on the manufacturers. However, this requires that technology transfer of methods to the Official Medicines Control Laboratory (NIBSC) is complete. The Expert Group enquired how a situation would be handled in case such method transfer would not yet be completed at the time of authorisation. The Agency will in such case take a decision based on a multidisciplinary assessment of data on pharmaceutical quality and its robustness, the potency tests involved, review of the manufacturer's data and protocols etc. In such a scenario, batch release may or may not be deferred, which cannot be pre-empted because it will depend on the particular case.

6.3 The Commission for Human Medicines will take these considerations into account when advising on the benefit and risk of a particular vaccine. The COVID-19 VBR EWG was very supportive of the Agency's default position and noted that the Agency's independence from the manufacturers was a key aspect for public confidence and governance. It was noted that not all manufacturers are familiar with vaccine development. It was concluded that the next step will be to put the paper to the CHM for information and endorsement.

7. Paper for information - AZD1222 toxicology

7.1 Members of the COVID-19 VBR EWG noted the paper presented and the potential issue that general and reproductive toxicity studies with AZD1222 are ongoing and may not be completed until after an anticipated licence application, reflecting urgency of vaccine development in this pandemic. The approach of the company to base evaluation of safety of AZD1222 on studies with other vaccines [redacted] but with different [redacted] was noted; however this does not apply to testing in pregnant animals, where no data with other such vaccines are available.

7.2 The COVID-19 VBR EWG discussed that other companies have adopted a similar approach to cross reference studies with other vaccines in order to expedite development. The contribution of a general toxicity study in animals to establishing

safety in the context of several thousand healthy human volunteers dosed was also discussed.

8. Any Other Business

8.1 None.

9. Date and time of next meeting

9.1 The next meeting is scheduled to take place on **Wednesday 14th October 2020** at **10.30am** to **1pm**.

Date and time of future meetings:

- **Wednesday 28th October (1.30pm - 4pm)**
- **Tuesday 10th November (2.30pm - 5pm)**
- **Tuesday 24th November (2.30pm - 5pm)**
- **Monday 7th December (10.30am - 1pm)**
- **Tuesday 22nd December (11.30am - 2pm)**

The Meeting started at 14:30 and ended at 16:39.

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.