COMMISSION ON HUMAN MEDICINES (CHM)

COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Tuesday 25th August 2020** at **11:00** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan
Professor N French
Professor D Goldblatt
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[1]
Professor T Solomon
Dr R Thorpe
Professor C Weir

Invited Experts

Professor I J Douglas
[redacted]

Secretariat

[redacted]

Professional Staff of MHRA Present

Supporting Specific Items

[redacted]
Dr J Bonnerjea
Dr P Bryan
Dr K Wydenbach

MHRA Observers

[redacted]
Dr S P Lam
[redacted]

[redacted]

29th September 2020

1 – Joined during item 3

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 prior to the first meeting:

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.

Professor Lachman – 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.

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).

[redacted] **-** Other relevant interests – [redacted] provides clinical care for patients with Covid-19; [redacted]

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:

Professor Douglas - Personal non-specific in Oxford University, lecturing fees in the last 12 months. Personal interest in GlaxoSmithKline – Shares, current holding Bayer – October 2019 fee for delivering investigator training related to Aflibercept. Non-personal in GlaxoSmithKline - current research grant
At the chair's discretion, Professor Douglas was permitted to remain for the discussion and to answer, but not ask, direct questions from the chair and other members.

[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, but not ask, direct questions from the chair and other members.

[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 2016-2021. The grant partially contributes to funding [redacted] salary. [redacted] research and employment is not dependent on this funding and Astra Zeneca have no influence on the nature of [redacted] research, or on reporting or dissemination of results.

The register of interests declared by participants had not been deemed to debar any participation. No further interests were declared.

2. Establishment of the Expert Working Group – procedural aspects

2.1 The Expert Working Group (EWG) reviewed the suggested Terms of Reference, the proposed membership and confidentiality requirements. It was noted that the group will advise on the quality, safety and efficacy of Covid-19 vaccines prior to their authorisation, and on emerging evidence on risks and benefits during the course of any Covid-19 immunisation campaign. It was agreed that meeting of the Expert Working Group will be virtual meeting for the foreseeable future. The likely life-time

of the Group was discussed, and it was suggested that the Group will be required for at least 12 months. It was suggested that it may be useful to have a patient representative on the group.

3. Information received from AstraZeneca on their rolling submission

3.1 The EWG heard about the timelines currently planned by Astra Zeneca for their EMA submission:

- End of September: Non-clinical dossier
- Mid-October: CMC dossier
- Beginning of November: Clinical dossier (interim analysis of efficacy - safety)
- Beginning of December: Clinical dossier (primary analysis of efficacy - safety)
- End of December: Formal Marketing Authorisation Application submission

3.2 The EWG heard a summary of the AZD1222 vaccine clinical development plan designed by Oxford University (OU), which includes a Phase I/II study and a Phase II/III study conducted in the UK and two foreign studies initiated in Brazil and South Africa, respectively. Overall, the four studies should enrol approximately 20,000 subjects. Preliminary safety and immunogenicity results of the Phase I/II recently published in The Lancet were presented. Based on these data, OU decided to amend the study protocols to vaccinate a maximum of subjects with a 2-dose regimen.

3.3 The EWG heard about Astra Zeneca's statistical analysis plan for vaccine efficacy, which will be based on a pooled analysis of the four trials and will include an interim and a primary analyses, both triggered by 40 cases of PCR-positive symptomatic COVID-19 disease but in a different population in terms of number of doses received. A statistically significant result would be achieved if the 95% confidence interval (CI) around vaccine efficacy (VE) were > 0%, i.e., the vaccine is demonstrated to be more effective than a placebo.

3.4 The EWG heard that both WHO and FDA guidance recommend as success criteria for vaccine pivotal trials a 95% lower bound of CI that exceeds 30% and a point estimate for VE of at least 50%.

3.5 The EWG expressed significant concerns about approving a vaccine with a 95% CI lower bound between 0 and 30%. It was noted that even though achieving a CI lower bound > 0% was the target for the primary analysis, the trial would not be stopped at this point so there would be continued follow-up and therefore the possibility for further analyses which could generate a higher CI lower bound. Consideration could be given to a vaccine with a 95% CI lower bound > 20% depending on VE point-estimate and robustness of immunogenicity and safety data. A similar approach has been communicated to Astra Zeneca by the EMA Rapporteurs.

3.6 The need to evaluate if the vaccine was 'sterilizing' (i.e., able to prevent any infection, including asymptomatic) was also emphasised; it was confirmed that this was a secondary endpoint.

3.7 The EWG raised issues about the likely heterogeneity of the populations and virus circulation rates across the different countries with potential difficulties in interpreting the pooled analysis results, particularly in the 40 cases planned for the primary efficacy analysis. It seemed possible that all 40 cases could be predominantly clustered in one region or population. The EWG noted that subgroup analyses would be useful to aid understanding of consistency of efficacy and safety in different populations, however it was noted that with only 40 cases to be observed for the primary analysis the possibilities for efficacy sub-group analyses would be limited at that stage.

3.8 [redacted]

3.9 The EWG commented about comparisons between vaccines when several vaccines would be proposed for approval and it was confirmed that each vaccine would be approved on its own based on its quality, safety and efficacy results.

3.10 The EWG also highlighted the possible [redacted] and its potential impact on the immune response, especially with a 2-dose vaccine regimen.

4. Future work / other vaccines

4.1 The EWG had the opportunity to review a paper on some of the potential future vaccines that may be used in clinical trials in the UK or be included in a marketing authorisation application involving the UK. It was clarified that the overview did not include any indication of considerations for each vaccine from the Government Vaccine Taskforce but focused on the scientific aspects for each vaccine. The list of vaccines was not exhaustive and included vaccines at various stages of development, including three which have the potential to deliver phase III data in the next 6 months.

5. Any Other Business

5.1 According to GDPR guidelines, the Group was asked for their permission to share their email address with other members of this group to enable everyone to be included in the 'To' line for all emails and not in the 'BCC' line.

5.2 The members of CHM, Expert Advisory Groups (EAG) and Expert Working Groups (EWG) are usually published on the Government website as well as through summary minutes. The full list of membership may be published externally. The group was asked to inform the ECS secretariat as to whether they had any objections for their name to be published on the website.

5.3 The EWG was informed that with regards to the 'sharing of documentation', there is a secure portal system used by the ECS Secretariat for sharing information. They were informed that the Secretariat will register them onto the portal.

6. Date and time of future meetings

6.1

- **Tuesday 29th September (2.30pm – 5pm)**
- **Wednesday 14th October (10.30am - 1pm)**

- **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 11:04 and ended at 12:56.

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.