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COMMISSION ON HUMAN MEDICINES (CHM) COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on Monday 12th April 2021 at 11:00 via videoconference

Participants Present

<u>Members</u>

Professor Sir M Pirmohamed (Chair) Professor G Dougan Mr VI G Fenton-May **Professor N French** Professor D Goldblatt Ms S Hunneyball¹ Professor K Hyrich Sir M Jacobs Professor H J Lachmann Professor P J Lehner Mr R Lowe Dr S Misbah Professor Y Perrie Professor S Price Dr A Riordan Professor C Robertson² Professor T Solomon Professor K M G Tavlor Dr R Thorpe **Professor M Turner** Dr S Walsh Mrs M Wang Professor C Weir

Apologies

Professor J Breuer

Observers



Secretariat



- ¹ Left for 30 mins and returned during item 2
- ² Joined during item 2

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD

Presenter supporting specific item

- VRMM
- VRMM
- VRMM

MHRA Observers - VRMM - LD - VRMM - LD Dr S Branch - VRMM - LD - MHRA-Policy - VRMM - Comms - VRMM - LD - VRMM - VRMM - LD - VRMM - LD Mr P Tregunno - VRMM - LD



22nd July 2022

Key

LD = Licensing Division **VRMM** = Vigilance & Risk Management of Medicines **Comms** = MHRA Communications

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1. Introduction and Announcement

1.1 The Chair reminded Members, invited Experts and observers 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 Breuer for this meeting.
- **1.5** The Chair welcomed the following observers:

Professor
Dr
Dr Bublic Health Scotland
Dr Bublic Health England
Dr Public Health Wales
Dr MB ChB, FRCGP, FIMC (RCSEd), DUMC Clinical Workstream – National COVID-19 Vaccination Programme

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2. Update on COVID-19 Vaccines and risk of thromboembolic events with concurrent thrombocytopenia

- 2.1 The VBR EWG was presented with the latest data on thromboembolic events with thrombocytopenia associated with the COVID-19 Vaccines up to a data lock point of 5 April 2021. A summary of regulatory actions taken by the MHRA and EMA since the last VBR EWG meeting on 6 April 2021 was also presented.
- 2.2 A summary of the case reports associated with the AstraZeneca COVID-19 Vaccine was presented along with summary tables of co-morbidities and concomitant medication for the 19 confirmed cases with thrombocytopenia associated with CVST or non-CVST events. It was noted that 5 were obese, 4 cases had no reported co-morbidities or concomitant medication, 1 had been treated for hypothyroidism and the majority were Caucasian. No apparent risk factors were identified. The overall fatality rate has decreased to 22% but it was not clear if this reduction reflected reporting of less serious cases or improved patient management. The EWG also noted that a possible pregnancy case has been reported along with a single case following a second dose of the vaccine. Approximately 1 million second doses of the AstraZeneca COVID-19 Vaccine have been administered mainly to older people in the UK to date.
- 2.3 The UK and foreign cases associated with the Pfizer, Moderna and Janssen COVID-19 vaccines were summarised using the same case definition. It was noted that the Janssen paediatric trial has been suspended because of issues related to reactogenicity and that the initial marketing authorisation for this product is currently under MHRA evaluation via an EE reliance procedure.
- 2.4 For the AstraZeneca COVID-19 Vaccine, the EWG heard that there had been no significant change to the overall incidence or fatality rates of CVST with thrombocytopenia since the last meeting. An increase in the estimated incidence of CVST+ other site thromboembolic events with thrombocytopenia had been seen since the last data lock point, although the confidence intervals were overlapping. The difference was driven by events in vaccinees aged between 50 and 70, which corresponds with the ages currently being targeted for vaccination. No change was seen in the fatality rate for CVST+ other site thromboembolic events.
- 2.5 The EWG was presented with an updated evaluation of events of interest after COVID-19 vaccines using first episodes in the SUS database linked to National Immunisation Management System by NHS number. The adjusted risk of CVST in the 15-39 age group was increased, particularly in the defined risk window of 4 to 13 days after immunisation with the AstraZeneca COVID-19 Vaccine. Two cases of disseminated intravascular coagulation have also occurred in the same age group following vaccination with the Pfizer vaccine but this only provides weak evidence of an association. Cases of thrombocytopenia are not reliably identified using this data.
- 2.6 Three cases of capillary leak syndrome (CLS) associated with the AstraZeneca COVID-19 vaccine were also presented. It was noted that CLS is a very rare, relapsing-remitting disorder of unknown aetiology and that 2 cases had such a prior history, making any causality assessment difficult. The EWG concluded that this signal should be closely monitored.
- 2.7 The EWG concluded that it was not possible to evaluate individual risk-benefit profiles for sub-populations of healthy people and patients with comorbidities in the age-stratified data presented but the overall benefit-risk balance for the AstraZeneca COVID-19 Vaccine

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remained positive. It also advised the MHRA to continue closely monitoring these events associated with COVID-19 vaccines, particularly following second doses.

3. Third update on the Safety Data for the Pfizer/BioNTech COVID-19 Vaccine

3.1 The EWG was provided with a verbal update on the cumulative safety data for the Pfizer/BioNTech COVID-19 Vaccine, up to a data lock point of 6 April 2021. The EWG was informed of the current usage data for first and second doses of the Pfizer/BioNTech COVID-19 vaccine in the UK, up to the 4 April 2021.

The EWG heard that the nature of the Yellow Card reports was similar to that previously presented for the Pfizer/BioNTech vaccine. A slight decrease in the reporting rate was noted which may suggest increased awareness of common side effects experienced after receiving the Pfizer/BioNTech vaccine as the vaccination campaign progresses. The EWG heard that the most frequently reported events were consistent with previous safety updates and those observed in clinical trials, and that the reporting was noted to be largely related to typical reactogenicity events, and that this was true for both first and second doses.

Higher proportions of reports in females and in those under the age of 55 years was noted for both first and second doses; higher reporting in females has previously been discussed at the EWG as potentially caused by underlying reporting biases in spontaneous reporting systems, in combination with a higher proportion of female vaccinees in the health and social care work force population prioritised by the vaccine campaign.

3.2 The EWG heard that caution should be used in interpretation of the UK Yellow Card dose data, as dose number is not a mandatory reporting field and routine collection of these data was introduced from February 2021.

The EWG were also informed of data from international regulators, which included similar reactogenic events after the second vaccine dose, and an increased frequency of events after the second vaccine dose compared to the first dose which is similar to that seen in clinical trials.

3.3 The EWG were also provided with an update of the adverse events of special interest which are currently under review for the Pfizer/BioNTech vaccine. These included fatal cases, anaphylaxis, Bell's palsy, Guillain-Barré syndrome and cardiac adverse event reports including myocarditis and pericarditis.

The EWG were informed of trends in the data from the UK vaccination programme and new data from international regulators. The EWG heard of potential confounding factors were described in the data, such as age, plausibility of time to onset, variable reporting terms, reporter's opinion of causality and significant comorbidities.

The EWG was informed of ongoing epidemiological studies and analysis, including rapid cycle analysis and mortality stratified by frailty index, that seeks to identify any emerging signals and trends in reporting data for the Pfizer/BioNTech vaccine.

3.4 The EWG discussed the data available regarding fatal anaphylactic reactions, Guillain-Barre and Bell's palsy.

The EWG commented that tryptase laboratory test values should be interpreted with caution and requested that further details on the anaphylaxis reports be provided when available.

The EWG discussed the cases of Guillain-Barré and Bell's palsy, including epidemiological evidence that the background population rate of Guillain-Barré during the pandemic has

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reduced and that Guillain-Barré has been associated with COVID-19 infection. The EWG recommended that safety data for Bell's palsy in relation to the Pfizer/BioNTech vaccine and Moderna vaccine should continue to be monitored, and suggested sources of safety data from epidemiological studies and the NHS.

The EWG also requested that cases of exposure during breast-feeding be presented in future updates on reproduction issues.

3.5 The EWG concluded that no new safety concerns had been identified and therefore no further regulatory action was required based on the data presented.

4. <u>Any Other Business</u>

None.

5. Date and time of next meeting

The next meeting is scheduled to take place on Friday 23rd April at 14:00.

The Meeting today started at 11:01 and ended at 12:24.

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.

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The following participants declared interests and other relevant interests at the meeting today:

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

<u>Other relevant interests</u> 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 - <u>Other relevant interest</u> - Provides clinical care when in covering the acute medical wards where patients with COVID-19 are cared. <u>NPNS</u> 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 - <u>Other relevant interest</u> – 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 – <u>NPNS</u> - Professor Hyrich was co-I on an investigator-initiated research grant exploring predictors of outcome in rheumatoid arthritis. <u>NPNS</u> Pfizer- she is a Co-I on a grant exploring adherence to JAK inhibitors in rheumatoid arthritis. <u>NPNS</u> in Abbvie, Professor Hyrich gave some lectures at an education conference on effectiveness of treatment for rheumatoid arthritis.

Sir Michael Jacobs - <u>Other relevant interest</u> - 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 – <u>Other relevant interest</u> as a volunteer participant in the Oxford vaccine study and no other involvement in the study.

Professor Lehner - <u>Other relevant interest</u> – 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).

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Dr Misbah - <u>NPNS</u> - Holds honorary Senior Lectureship with University of Oxford & Oxford University Hospitals NHS Foundation Trust.

Professor Perrie - <u>NPNS</u> 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 Price - <u>NPNS</u> 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 - <u>Other relevant interests</u> - Participant in Oxford University's ChAdOx1 nCoV-19 clinical trial –received immunisation 27/8/2020. <u>NPNS</u> - Postgraduate External Examiner for Oxford University (Postgraduate Diploma in Paediatric Infectious Diseases).

Professor Solomon - <u>Other relevant interests</u> – 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 – <u>Other relevant interests</u> arising from being highly sensitive to insect stings, and plant products such as Hyacinth bulbs, as recorded on Mrs Wang's medical records. The family of Mrs Wang lives with several rare diseases and conditions, some of which result in epileptic fits.

Professor Weir - <u>NPNS</u> - Imperial College and <u>Other relevant interest</u> arising from his department collaborates with Imperial College on a number of clinical trials.

Observers

Professor - <u>NPNS</u> - University of Oxford employee (with no involvement in research or clinical trials related to Oxford AZ vaccine)

Dr - Lapsed and <u>NPNS</u> - Regarding companies to declare interests for, prior to joining Public Health Scotland, worked for a company that provided epidemiological services to the pharmaceutical industry. Whilst working there, supported respiratory vaccine development activities at Janssen (Johnson & Johnson).

Dr Other relevant interest in Pfizer & GSK- The Immunisation and Countermeasures Division has provided vaccine manufacturers (including Pfizer and GSK) with post-marketing surveillance reports on pneumococcal and meningococcal infection which the companies are required to submit to the UK Licensing authority in compliance with their Risk Management Strategy. A cost recovery charge is made for these reports.