OFFICIAL – SENSITIVE COMMERCIAL NOT FOR PUBLICATION

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

Minutes of the meeting held on Thursday 16th February 2023 at 09:30 via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)

Professor J Breuer¹

Professor G Dougan²

Mr VI G Fenton-May

Professor N French

Ms S Hunneyball

Professor P J Lehner

Mr R Lowe

Dr S Misbah

Professor S Price

Dr A Riordan

Professor C Robertson²

Professor K M G Taylor

Dr R Thorpe

Mrs M Wang

Professor C Weir

Apologies

Professor D Goldblatt

Professor K Hyrich

Professor H J Lachmann

Professor Y Perrie

Professor M Turner

Professor S Walsh

Invited Expert



Observers⁴



Professional Staff of MHRA Present

Principal Assessor

- HQA - S&S

Presenters supporting specific items

- S&S - HQA - S&S

MHRA Observers

- S&S
- S&S
- S&S
- HQA
- HQA
- S&S
- Comms
- S&S

Government Legal Team



5th May 2023

<u>Key</u>

HQA = Health Quality & Access Group S&S = Safety & Surveillance Group Comms = MHRA Communications & Engagement

¹ joined during item 3

² stepped out during item 2 & returned during item 3

³ data presentation for item 2 and left after this item

⁴ left after item 2

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 Professors Goldblatt, Hyrich, Lachmann, Perrie, Turner and Walsh for this meeting.
- **1.5** The Chair welcomed the following presenter to the meeting:

Item 2: Data Presentation

UK Health Security Agency (UKHSA)

1.6 The Chair welcomed the following observer to the meeting:

NHS England and NHS Improvement (National)

- Data presentation from UKHSA and CDC preliminary signal of ischaemic stroke in people aged 65 and older with the Pfizer-BioNTech Original/Omicron BA.4/5 bivalent COVID-19 vaccine
- 2.1 The EWG heard a presentation from the UK Health Security Agency (UKHSA) on their analysis of ischaemic stroke in individuals aged 50 years and older after COVID-19 Original/Omicron BA.1 bivalent booster vaccine using Secondary User Service (SUS) inpatient discharge data for admissions from 05 September 2022 to 04 December 2022. The EWG heard that the cases of ischaemic stroke identified in people aged 50 and over were mostly in people over the age of 65 years and just over half of the cases were in females. The EWG noted that while most case were following Moderna Original/Omicron BA.1 bivalent COVID-19 vaccine, this was in line with the earlier roll out of Moderna bivalent vaccine in the 2022 autumn booster campaign compared to the Pfizer bivalent vaccine.

- The EWG heard that the results from the SUS analysis showed no evidence of an increased risk of ischaemic stroke in the 3 weeks post vaccination in either people aged 50 years and above or 65 years and above with either Moderna or Pfizer bivalent COVID-19 vaccines compared with vaccinated people from day 22 onwards.
- 2.3 The EWG noted that a further analysis of the SUS data of the risk of ischaemic stroke in relation to co-administration of influenza vaccine with COVID-19 bivalent vaccine may be possible and the feasibility of doing this would be investigated further by UKHSA.
- 2.4 Following the presentation from UKHSA, the MHRA delivered a summary of its assessment of the evidence for an association between the Pfizer-BioNTech Original/Omicron BA.4/5 vaccine and ischaemic stroke. It was noted that, while mRNA Original/Omicron BA.1 vaccines were deployed in the UK's Autumn 2022 booster campaign, an Omicron BA.4/5-adapted bivalent vaccine has never been deployed in the UK.
- 2.5 The evidence included the CDC analysis which first identified the signal, the UKHSA analysis described above, a review of Yellow Card data focusing on the mRNA Original/Omicron BA.1 bivalent vaccines, two literature articles from Denmark and Israel and an observed vs expected analysis using Yellow Card reports for the Original/Omicron BA.1 bivalent vaccines.
- 2.6 The EWG was informed that the CDC analysis, comprising a Rapid Cycle Analysis in the Vaccine Safety Datalink (VSD), had identified an increased risk of ischaemic stroke in people aged 65 years and over within 1-21 days of receiving the Pfizer-BioNTech Original/Omicron BA.4/5 vaccine, compared with those receiving the vaccine between days 22-42 prior. No signal was detected with the Moderna Original/Omicron BA.4/5 vaccine. Post hoc analyses found a clustering of cases between days 11-22 post-vaccination, with most of the patients occurring in this period, at one VSD site, having received same-day administration of a high dose or adjuvanted influenza vaccine. There was a statistically significantly increased risk of ischaemic stroke in those receiving a high dose or adjuvanted influenza vaccine with the Pfizer-BioNTech Original/Omicron BA.4/5 vaccine in days 1-21 post-vaccination compared with days 22-42. The EWG was informed that the CDC has not recommended any change in US vaccination policy due to this finding and it plans to investigate the signal further in a formal epidemiological study, including an analysis of the effect of coadministration of COVID-19 and influenza vaccines on ischaemic stroke risk.
- 2.7 The EWG was presented with an overview of the available Yellow Card data which comprised very few reports of ischaemic stroke with the mRNA Original/Omicron BA.1 bivalent vaccines and did not support a signal. A nationwide cohort study from Denmark and a self-controlled case series from Israel examining the risk of cerebrovascular infarction and ischaemic stroke, respectively, following the Pfizer-BioNTech Original/Omicron BA.4/5 vaccine, did not identify a signal. An observed vs expected analysis conducted using Yellow Card data did not identify any signals for the monovalent or Omicron BA.1-adapted bivalent mRNA vaccines.
- 2.8 The EWG considered that the CDC signal, arising from one data source only and neither replicated in other US databases nor identified by international regulators, did not present strong evidence for an association between the Pfizer-BioNTech Original/Omicron BA.4/5 vaccine and ischaemic stroke. While cardiac events occurring post-influenza infection are well-recognized, the EWG recommended that MHRA review the evidence for an increased risk of stroke following influenza infection and consider the possible impact of this on analyses of COVID-19 vaccination and stroke.

2.9 The EWG concluded that there was no need for regulatory action based on the evidence presented and requested that MHRA collaborate with UKHSA to explore any effect of concomitant administration of mRNA COVID-19 vaccines with influenza vaccines on ischaemic stroke risk. The MHRA was also advised to closely monitor Yellow Card data and any other emerging data on ischaemic stroke risk including results from the pending FDA epidemiological study.

3. Spikevax booster indication in children 6-11 years old – ECDRP

- 3.1 This variation concerns the use of Spikevax original and Spikevax bivalent original/BA.1 as a booster in children 6-11 years old at the dose of 25µg. It was authorised by the EC on 16 December 2022.
- 3.2 The data supporting this age extension are based on an immunogenicity and safety study, which was conducted with the original monovalent vaccine and enrolled about 1,300 children. Neutralising antibodies were significantly boosted and the reactogenicity of the booster appeared somewhat lower after the booster (25µg) than after primary immunisation (2 x 50µg).
- 3.3 The EWG noted that the same Risk Management Plan (RMP) had been submitted for the Spikevax and Spikevax bivalent BA.1 booster in children aged 6 to 11 years as had been submitted for the Spikevax bivalent BA. 4/5 vaccine in over 12s considered by the EWG at their previous meeting. The EWG discussed the particular importance of post marketing surveillance of the Spikevax bivalent BA.1 booster in 6 to 11 years given that the indication is based on data extrapolated from the immunogenicity and safety of the BA.1 vaccine booster in adults. The EWG agreed that the company should submit a Summary Safety Report for Spikevax and Spikevax BA.1 boosters in children aged 6 to 11 years, including a comprehensive review of medication errors, covering the first 3 months since approval in the EU.

4. Minutes of the meetings held on:

- Friday 23rd April 2021
- Friday 14th May 2021
- Wednesday 6th October 2021
- Tuesday 9th November 2021
- Wednesday 17th November 2021
- Tuesday 13 December 2022
- Friday 4th February 2022
- **4.1** All minutes listed above were approved as true and accurate record of the proceedings, subject to some minor amendments, typos and grammatical errors, which have been resolved.

5. Any Other Business

5.1 Verbal update on COVID-19 vaccine ADR data publication

5.1.1 The EWG were presented with an update on the plans for transition to routine data publication and communication of safety concerns for COVID-19 vaccines after March 2023. The Group were reminded that in June 2022 they endorsed the proposal to reduce the frequency of the weekly publication on COVID-19 vaccine ADR data in a phased approach,

starting with a monthly publication from August 2022 reducing to quarterly from the end of 2022.

- 5.1.2 The EWG noted that monthly reports had continued throughout the duration of the Autumn 2022 COVID-19 vaccine booster programme, during which over 20 million doses of bivalent mRNA vaccines had been administered in the UK. The EWG heard that the Autumn 2022 booster programme had now concluded, and the MHRA's ongoing surveillance of the Moderna and Pfizer (Original/BA.1) bivalent vaccines had not revealed any new safety concerns, with the nature of the suspected adverse events being in line with that seen with the monovalent mRNA vaccines.
- 5.1.3 The EWG noted that the departure from the June 2022 proposal to move to a quarterly narrative publication from the end of 2022 to stopping regular narrative publication after March 2023 was proportionate to the established safety profile of the main COVID-19 vaccines used in the UK immunisation programme to date and the lack of any new safety signals concerning bivalent COVID-19 vaccines. Moreover, the proposal is in alignment with other major regulators who no longer publish regular narrative information concerning COVID-19 vaccines.
- 5.1.4 The EWG noted that regular publication of Adverse Drug Reaction (ADR) data will continue, including the new interactive analysis prints, in line with approaches for other medicinal products. The EWG also noted that robust safety monitoring and surveillance of COVID-19 vaccines will continue along with prompt communication on any updated safety advice.
- 5.1.5 The EWG endorsed the approach and suggested that it would be important to provide signposting for patients to previous versions of the narrative publication on COVID-19 vaccine Yellow Card data.

5.2 Future Steps

5.2.1 It was suggested that the final meeting of the group be held in-person at 10SC. MHRA and the Committee Services Team will look into the logistics as to whether this will be possible.

6. Date and time of next meeting

The next meeting is to be arranged.

The Meeting today started at 09:31 and ended at 10:54.

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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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Annex II

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

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Professor Sir Munir Pirmohamed - <u>NPNS</u> 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 - <u>NPNS</u> – 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 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). Member of the independent Data Safety Monitoring Board for COV-BOOST trial.

Mrs Wang - Other relevant interests 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.