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

Minutes of the meeting held on **Thursday 19th January 2023** at **13:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Mr VI G Fenton-May
Ms S Hunneyball
Professor K Hyrich
Professor H J Lachmann
Professor P J Lehner
Dr S Misbah
Professor S Price
Dr A Riordan
Professor K M G Taylor
Dr R Thorpe
Mrs M Wang[1]
Professor C Weir

Apologies

Professor G Dougan
Professor N French
Professor D Goldblatt
Mr R Lowe
Professor Y Perrie
Professor C Robertson
Professor M Turner
Professor S Walsh

Invited Experts

[redacted][2]
[redacted][3]
[redacted][2]
[redacted][3]

Observers[4]

[redacted]
Professor W S Lim
[redacted]

Professional Staff of MHRA Present

Principal Assessors

[redacted] - HQA
[redacted] - S&S

Presenters supporting specific items

[redacted] - S&S
[redacted] - HQA
[redacted] - HQA
[redacted] - S&S
[redacted] - HQA
[redacted] - HQA

MHRA Observers

[redacted] - S&S
[redacted] - S&S
[redacted] - HQA
[redacted] - HQA
[redacted] - S&S
[redacted] - S&S
[redacted] - Comms

Government Legal Team

[redacted]

Secretariat

[redacted]

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

[1] left during item 4
[2] presented item 2 and left after this item
[3] presented item 3 and left after this item
[4] all left after item 3

[redacted]

5th May 2023

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 Dougan, French, Goldblatt, Perrie, Robertson, Turner, Walsh and Mr Lowe for this meeting.

1.5 The Chair welcomed the following presenters to the meeting:

Item 2: Risk of Death with young people after COVID-19 vaccine
[redacted] Office of National Statistics
[redacted] Office for National Statistics

Item 3: Vaccination Errors
[redacted] Public Health Scotland (PHS)
[redacted] Health and Social Care Northern Ireland (HSCNI)

1.6 The Chair welcomed the following observers to the meeting:

[redacted] UK Health Security Agency (UKHSA)

[redacted] Public Health Scotland

[redacted] Public Health Scotland

[redacted] Public Health Wales

Professor Wei Shen Lim
Chair of the Joint Committee on Vaccination and Immunisation (JCVI)

[redacted]
NHS England and NHS Improvement (National)

2. Risk of death following COVID-19 vaccination or positive SARS-CoV-2 test in young people in England – presentation from ONS

2.1 The EWG were presented with the results of a self-controlled case study by the Office for National Statistics (ONS) exploring the relative incidence of all-cause and cardiac-related deaths in 12–29 year-olds in a period following vaccination or SARS-CoV-2 infection compared to a baseline time period. These data are further analyses following a previous presentation to the EWG in March 2022.

2.2 The EWG were shown the primary results of the study which showed no significant increases in the risk of cardiac-related deaths, or deaths due to any cause, in the twelve weeks following vaccination with a COVID-19 vaccine.

2.3 The EWG noted the study estimated a statistically increased risk of cardiac related deaths in females within 12 weeks of a first dose of a non-mRNA vaccine and a borderline increased risk of cardiac related deaths in males within 12 weeks of a second dose of an mRNA vaccine. The study also showed that there were substantially increased risks of all-cause and cardiac related deaths, including in hospital deaths, following SARS-CoV-2 infection but that vaccination reduced the risk of death.

2.4 The EWG noted the very small number of deaths identified in the weeks following vaccination particularly given the scale of the vaccine exposure. The EWG discussed the likelihood of a chance finding given the multiple analyses conducted and that, given the very small number of cardiac deaths leading to the signal of an increased risk in females following a non-mRNA vaccine, that the analysis could have shown a different result with only one or two fewer deaths.

2.5 The EWG discussed the restrictions to the use of the AstraZeneca vaccine and that this meant that young people vaccinated with a non-mRNA vaccine in this study were likely to be predominantly those considered clinically vulnerable who had received their vaccine prior to April 2021. They agreed that an analysis restricted to this time period would be helpful.

2.6 The EWG also agreed that it would be important to look further at the deaths identified to determine if there were any patterns in the cause of death, if the patients had pre-existing conditions or comorbidities, and given the risk of thrombosis with thrombocytopenia with the AstraZeneca vaccine if there was any evidence of thrombocytopenia in these patients. They advised that very careful consideration of any coroner records was needed in order to interpret the signal seen.

2.7 The EWG concluded that there were limitations to the study but that it supported a positive benefit risk balance for the COVID-19 vaccines particularly given the risk of cardiac-related death following SARS-CoV-2 infection.

3. Vaccination errors with COVID-19 Vaccines – Northern Ireland & Scotland

3.1 The EWG heard presentations from Public Health Scotland and the Health and Social Care (HSC) Public Health Agency in Northern Ireland on their experiences regarding COVID-19 vaccination errors throughout the COVID-19 vaccination campaign.

3.2 The EWG noted that numerous types of vaccination errors had been reported in association with COVID-19 vaccines in Scotland and Northern Ireland and that the nature of the errors reported had changed as the vaccination programme had evolved over time. The EWG also noted that there was likely to be underreporting of COVID-19 vaccination errors although it was not possible to ascertain the extent of underreporting in Scotland and Northern Ireland.

3.3 The EWG acknowledged the increased complexity of the COVID-19 vaccination campaign as it had progressed, for example, different COVID-19 vaccines for different age groups and different volumes of vaccine administered for different doses. The EWG heard that the Public Health Agencies in Scotland and Northern Ireland had worked closely with immunisation coordinators and leads to raise awareness of the types of vaccination errors being reported during the campaign and had continually updated their healthcare professional training materials to reduce the risk of vaccination errors occurring.

3.4 The EWG agreed on the importance of learning from the vaccination errors reported in association with COVID-19 vaccines for future vaccination programmes.

4. Spikevax bivalent Original/Omicron BA.4-5 (50 micrograms/50 micrograms)/mL dispersion for injection - PLGB 53720/0006-0007

4.1 This bivalent vaccine targeting the original strain and the Omicron BA.4-5 variant was authorised by the EC on 20 October 2022 without any clinical data. It is indicated as a booster in individuals 12 years of age and older. A line extension has been applied for by the MAH using the EU reliance route.

4.2 [redacted]

4.3 Immunogenicity data are now available in about 500 adults and were presented. They meet the criteria for use of this vaccine as a booster. The reactogenicity profile is in line with those of the other Spikevax vaccines.

4.4 The updated Risk Management Plan (RMP) was summarised for the EWG. The EWG noted that no changes to the summary of safety concerns or risk minimisation measures in the RMP were proposed. The EWG heard that a phase 2/3 study protocol to evaluate the immunogenicity and safety of bivalent Spikevax boosters was included in the pharmacovigilance plan and that 3 other study protocols in the pharmacovigilance plan would be updated to include bivalent vaccines. The EWG agreed that the company should submit a 3-month Summary Safety Report for the BA. 4-5 bivalent product as part of routine pharmacovigilance.

4.5 The authorisation of the vaccine was endorsed by the EWG subject to minor changes to the product information, and satisfactory responses to the other concerns.

5. Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose concentrate for dispersion for injection (Tozinameran/ Famtozinameran) PLGB 53632/0014

5.1 The EWG heard that a line extension application for Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose concentrate for dispersion for injection has been submitted via the EC Decision Reliance procedure. [redacted] It is proposed for use as a booster dose in children aged 5-11 years.

5.2 The EWG heard an overview of the quality aspect of the application. The product is similar to the already approved bivalent BA. 4-5 vaccine [redacted] except for a different fill volume [redacted] which is the same as the currently approved fill volume for [redacted]

5.3 Therefore, no significant issues are identified with respect to quality. The proposed long-term shelf-life of 12 months is also acceptable. The need to review the specification limits for RNA ratio is recommended by the CHMP and also endorsed by the MHRA.

5.4 The EWG heard that there were no clinical data available yet with this vaccine in children aged 5 to 11 years from the ongoing clinical trial C4591048. This will be provided as a post-approval measure. 1-month post dose immunogenicity data in adults and safety data in subjects aged 12 years and above are now available from Cohort 2 of the ongoing clinical trial C4591044 and were presented. When compared with a historical control group that had received a [redacted] booster (4th) dose of the Original/Omicron BA.1 vaccine, subjects that received a [redacted] booster (4th) dose of the Original/Omicron BA.4-5 vaccine elicited higher Omicron BA.4/BA.5 geometric mean titres 1-month post dose in both age groups (18-55 years and >55 years). In cohort 2 subjects and the historical control group, overall similar boosting responses were observed to Omicron BA.1 and a good boosting response was observed to the reference strain. The reactogenicity profile of the Original/Omicron BA.4-5 vaccine was generally similar to that of the other Comirnaty vaccines, within the respective age groups and no new or concerning safety findings were identified.

5.5 Overall, the EWG considered that, given the total mRNA content of this vaccine is the same as that in the currently approved monovalent vaccine in 5–11-year-olds [redacted], the positive results seen from the Cohort 2 data in older subjects could be extrapolated to this age group. The EWG noted that this approach is further supported by the reassuring post-marketing safety data for this vaccine available from the United States. One member of the EWG expressed a preference to wait for the upcoming data in 100 subjects aged 5-11 years from study C4591048 before approval.

5.6 The EWG noted that the patient information leaflet was not as specific to the target population as it could be and that there are also some inconsistencies in the text whereby instead of referring to ‘your child’ it sometimes reverts back to ‘you’. The EWG heard that this issue has been raised with the company who are awaiting a timetable for the EMA procedure where this will be addressed in the EU leaflet and the GB leaflet will be aligned accordingly.

5.7 The EWG was presented with details of the updated Risk Management Plan (RMP) submitted to support the line extension application. The EWG was informed that there were no significant changes to the safety specification, pharmacovigilance plan or RMP made in relation to the application. In relation to the investigation of post-approval vaccine effectiveness, the EWG was informed that the company had notified MHRA of plans to initiate a new study of UK patients via the COVIDRIVE platform since the one ongoing UK study of vaccine effectiveness with Comirnaty is experiencing difficulties in recruitment.

5.8 In considering the available post-authorisation safety data with the Comirnaty Original/Omicron BA.4/5 bivalent vaccine, the Commission was presented with results from a Centers for Disease Control and Prevention (CDC) publication on post-authorisation safety in children aged 5 to 11 years who received this bivalent vaccine. While the data were overall reassuring, the high incidence of vaccination errors was noted.

5.9 The EWG was presented with details of a recent CDC publication highlighting a signal of ischaemic stroke in people aged over 65 years who received the Comirnaty Original/Omicron BA.4/5 bivalent vaccine in the US, detected via the Vaccine Safety Datalink. The EWG was informed that details of the methodology used are awaited, the CDC could not replicate the finding in other data sources and no other international regulator has raised it as a signal. The MHRA will present a paper on the signal to the EWG at its next meeting.

5.10 The EWG endorsed two GB-specific post-approval commitments for the RMP, requiring the company to submit a 3-month summary safety report, including a comprehensive review of medication errors, and a protocol synopsis for a UK study of post-approval vaccine effectiveness in children aged 5-11 years given the Comirnaty Original/Omicron BA.4/5 bivalent vaccine.

5.11 The EWG agreed with the post-marketing approval measures requested by the EMA and that this line extension application is approvable.

6. Minutes of the meetings held on:

- Monday 19th July 2021
- Tuesday 31 August 2021
- Friday 18th November 2022

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.

7. Any Other Business

7.1 None.

8. Date and time of next meeting

The next meeting is to be arranged.

The Meeting today started at 10:31 and ended at 15:23.

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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.

Annex II

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

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).

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.

Professor Lachmann - Other relevant interest as a volunteer participant in the Oxford vaccine study and no other involvement in the study.

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 - NPNS - Imperial College and Other relevant interest arising from his department collaborates with Imperial College on a number of clinical trials.

Observers

[redacted] - NPS – was part of an expert working group ([redacted] with [redacted] conducting the initiative on behalf of [redacted] to discuss strategies to improve 'vacceptance'. [redacted] has not received any form of payment or other remuneration as described above but a paper is expected to be published.

[redacted] - NPNS - arises from the institution (N[redacted]) where [redacted] works has received unrestricted investigator-initiated research funding from [redacted] for an unrelated prospective population-based cohort study of pneumococcal pneumonia in which [redacted] is the [redacted].