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

Minutes of the meeting held on **Tuesday 3rd August 2021** at **12:30** via videoconference

Participants Present

Members

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

Apologies

Professor N French
Professor D Goldblatt
Sir M Jacobs
Professor P J Lehner
Professor T Solomon

Observers (left after Item 5)

[redacted]

Secretariat

[redacted]

[1] left during item 6

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted] - VRMM

Presenters supporting specific items

[redacted] - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - LD

MHRA Observers

[redacted] - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted]-Rahi – MHRA Policy
[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
Ms N Rose - NIBSC
[redacted] - VRMM
[redacted] - VRMM
Mr P Tregunno - VRMM
[redacted] - LD
[redacted] - Comms

[redacted]

25th August 2022

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

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 French, Goldblatt, Lehner, Solomon and Sir Michael Jacobs for this meeting.

1.5 The Chair welcomed the following observers:

[redacted] JCVI

[redacted] Public Health Wales

[redacted]
NHS England Medical [redacted]

[redacted]
Public Health Scotland

[redacted]
Public Health England

[redacted]
NHS England and NHS Improvement (National)

2. Minutes of the meeting held on Friday 21st May 2021

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

3. Review of COVID-19 Vaccines and Herpes Zoster

3.1 The EWG commented on a paper titled 'COVID-19 vaccines and risk of herpes zoster' and a slide presentation summarizing the data assessed, and the conclusions of the paper and advice sought.

3.2 Overall, the EWG agreed that the data were reassuring in showing no signal for herpes zoster (shingles) in association with the three COVID-19 vaccines deployed in the UK (Pfizer-BioNTech, AstraZeneca and Moderna COVID-19 vaccines). The Group considered that this could be an important negative finding of interest to the general public.

3.3 The EWG did not consider there to be any biological plausibility underpinning a theoretical association between COVID-19 vaccines and herpes zoster.

3.4 The Group commented that the background incidence of shingles may be different during the pandemic than pre-pandemic due to reduced social mixing and reduced uptake of the shingles vaccine. Quantifying the levels of antiviral drug prescribing pre- and post-COVID-19 vaccination periods was suggested as a possible means of measuring changes in herpes zoster incidence.

3.5 The EWG noted that the reporting rates of herpes zoster post-COVID-19 vaccination did not appear to exceed the background incidence of shingles. The Group also noted the approximately linear increase in the reporting rates of herpes zoster with increasing age following COVID-19 vaccination, which was peaking in the 60-69 year-old age group and then declining in those aged over 70 years. The age-related trends were considered to reflect the typical patterns of naturally-occurring herpes zoster, incorporating vaccination for shingles in the over 70 year-old age group. The higher reporting rates observed in females than males were also considered to be consistent with background patterns.

3.6 The EWG noted that the herpes zoster reports were largely non-serious in nature, and this was considered to be reassuring.

3.7 Concerning the pharmacoepidemiological study proposed in the paper to further explore a possible association between COVID-19 vaccines and herpes zoster, the EWG endorsed taking this forward but regarded it as a lower priority project in the context of other more serious signals being investigated.

4. Vasculitis and COVID-19 vaccines

4.1 The EWG considered an assessment of spontaneous reports of vasculitis disorders received via the UK Yellow Card Scheme for the AstraZeneca, Pfizer-BioNTech and Moderna COVID-19 vaccines with a data lock point of 14th July 2021. This assessment included new events of vasculitis and flare-ups of pre-existing vasculitis.

4.2 The EWG noted that vasculitis is a heterogenous group of conditions with a wide range of pathophysiological and immunological aetiologies. The EWG noted that the cause of cutaneous vasculitides is sometimes never found. The EWG discussed the Yellow Card data reporting vasculitis disorders with the highest background prevalence, including Giant Cell Arteritis and Polymyalgia Rheumatica and noted that these conditions have complicated diagnoses. The EWG commented that the majority of cases reporting Giant Cell Arteritis were not likely to be Giant Cell Arteritis, and that ideally a biopsy or ultrasound are required to confirm the diagnosis. The EWG commented that a flare-up of polymyalgia rheumatica would appear similar in presentation to post-vaccination reactogenicity reactions, and cases reporting events following

both doses may be due to tapering off steroids if polymyalgia rheumatica had been diagnosed following the first dose of vaccine.

4.3 The EWG were informed that data from the clinical trials for all vaccines, and data analysed within the monthly safety reports submitted by the vaccine manufacturers have not identified a signal for vasculitis.

4.4 The EWG advised that the currently available evidence does not appear to support an association between AstraZeneca, Pfizer-BioNTech and Moderna COVID-19 vaccines and vasculitis disorders. The EWG advised that no regulatory action was required currently. The MHRA was advised to continue to closely monitor reports of vasculitis disorders with COVID-19 vaccines.

4.5 The EWG noted the possible link between vasculitis and the vaccines raised by Coroners and suggested that the MHRA could consider communicating in the weekly ADR report to highlight the assessment done, but that any inclusion should be brief, highlighting the fact that no signal was identified, without detailing specific events or numbers.

5. Update on myocarditis/pericarditis with COVID-19 vaccines

5.1 The EWG were presented with an update on reports of myocarditis and pericarditis following administration of the Pfizer/BioNTech, Moderna and AstraZeneca COVID-19 vaccines as well as new international data.

5.2 The EWG were informed that for the Pfizer/BioNTech vaccine, there had been an increase in reporting rates after the first dose in the under 50 years age groups. For the second dose, reporting rates have decreased but remain higher than the first dose reporting rates. For the Moderna vaccine, most reports are now myocarditis rather than pericarditis and the majority have occurred after the first dose, in line with the current usage of the Moderna vaccine. Reporting rates are higher than those for the Pfizer/BioNTech vaccine, however these continue to fluctuate as exposure increases. For the AstraZeneca vaccine, the reporting rates have remained lower than for the mRNA vaccines.

5.3 The EWG were presented with data from the US CDC. The EWG were informed that the majority of reports were in younger males with onset within 7 days of vaccination. The majority of patients had an outcome of recovered following myocarditis. Analysis in the Vaccine Safety Datalink (VSD) showed a significant risk after second dose for both the Pfizer/BioNTech and Moderna vaccines. The EWG were also presented data from Israel, where a signal for myocarditis has been seen following second dose of the Pfizer/BioNTech vaccine. It was noted that events had a mild clinical course and occurred within 7 days of vaccination.

5.4 The EWG were presented with two pre-print literature articles which investigated the risk of myocarditis following COVID-19 infection. The EWG endorsed the authors' conclusions that there was higher risk and increase mortality associated with myocarditis following COVID-19 infection, compared to myocarditis associated with the COVID-19 vaccines.

5.5 The EWG discussed the difference in reporting rates for second dose between the UK and Israel, noting the higher rate seen in Israel. The EWG noted the shorter dose interval being used in Israel while the UK was still gaining experience with the second dose due to the 8-12 week interval. The EWG concluded that no further regulatory action was required at this time, however the signal of myocarditis and pericarditis following COVID 19 vaccines should continue to be closely monitored.

6. The regulatory approach to booster indications for COVID-19 vaccines

6.1 The EWG was presented with an update on that trials that include booster vaccines and are on-going or planned in the UK. The first-in-human trial of AZ was amended to add late (after 45 weeks) 2nd or 3rd dose—data available in a Lancet preprint showed immunity was improved. Long term safety and immunogenicity follow-up will be included within COV009 trial.

6.2 Trial COV-Boost aims to determine reactogenicity and immunogenicity of booster vaccination against ancestral and novel variants of SARS-CoV-2. The trial is on track to report to JCVI by Autumn, and the Sponsor plans to revise stage 2 to use variant vaccines (amendment due end August). The trial includes AZ, Pfizer, Moderna, Novavax, Valneva, and Curevac vaccines.

6.3 OCTAVE-DUO, a Phase III, Multicentre, Randomised Trial Comparing SARS-CoV-2 re-boost vaccine strategies in immunocompromised patients was approved on 19 h July 2021 by MHRA-CTU and is supported by DHSC. The trial includes Pfizer, Moderna, and Novavax vaccines.

6.4 VAT00002 (Sanofi)- Immunogenicity and Safety of SARS-CoV-2 Recombinant Protein Vaccines with AS03 Adjuvant in Adults 18 Years of Age and Older as a Primary Series and Immunogenicity and Safety of a Booster Dose of SARS-CoV-2 Adjuvanted Recombinant Protein Vaccines (two Monovalent and one Bivalent). VAT00002 is ongoing with initial phase 2 cohorts (prime-boost), and 3 new cohorts to address variants. The trial includes Sanofi vaccines.

6.5 VLA2001-301 has commenced, but addition of booster doses is still in the planning stage. The booster extension to this phase III trial of a vaccine from Valneva will only be with the original vaccine and does not include a vaccine for variant strains.

6.6 The EWG noted that of the booster trials running in the UK only the Sanofi trial uses a variant vaccine booster, the other trials boost with the originator/s.

6.7 The EWG was presented with regulatory options for authorisation of homologous and heterologous booster indications. An update of the regulatory activities of the 8 vaccines currently undergoing assessment was also presented as well as the development plan of these companies regarding boosters.

6.8 The EWG discussed whether as an exploratory exercise a series of questions could be developed to be addressed by the pharmaceutical industry the aim of which would be to aid regulatory benchmarking of requirements for booster vaccine applications. The EWG discussed that one such question could request the immunological rationale that specifically supports a given company's combination of prime and booster vaccines.

6.9 The EWG heard there are discussions internationally about possible regulatory approaches to booster dosing, however, the applications are likely to be submitted before conclusions on harmonisation are reached. Therefore, the pragmatic option may be to assess each application on the merits and limitations of the data provided and steer away from a comparative analysis of different vaccines, because the need for boosters is time sensitive.

6.10 The EWG discussed the need for standardisation in order to be able to assess efficacy across vaccines and vaccine platforms and noted that neutralisation assays may currently represent the best option to achieve this. The EWG heard that because the correlates of protection are not yet known, data from neutralisation assays is being accepted to support comparable efficacy between products. The MHRA are advising companies to use WHO reference standards in their assays, but in some cases variability in the assay method will still occur.

6.11 The EWG discussed whether a model similar to that employed by REMAP-CAP, which compared multiple therapeutic agents in classes grouped together for analysis, would be appropriate to apply for comparisons of the COVID-19 vaccines and boosters. The EWG made a comment that this would depend on data sharing and may not be feasible given the timeframe. The EWG noted that further data will also arise from real-world effectiveness studies.

6.12 The EWG discussed that some applications may use historical control data. The EWG confirmed that a decision on the level of influence, or weight, to ascribe to historical control data is possible. However, in addition to confounders that are better understood, data on vaccines will also carry risks of confounding related to the evolving nature of the pandemic and the related adjustments will likely be complex.

6.13 The EWG noted that human challenge studies might be able to support data on effectiveness.

7. Any Other Business

None.

8. Date and time of next meeting

The next scheduled meeting is to take place on **Thursday 19th August** at **10:30**.

The Meeting today started at 12:31 and ended at 14:54.

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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.

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.

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

Professor Perrie - NPNS 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 - 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] - Lapsed and NPNS - Regarding companies to declare interests for, prior to joining Public Health Scotland, [redacted] worked for a company that provided epidemiological services to the pharmaceutical industry. Whilst working there, [redacted] supported respiratory vaccine development activities at [redacted] has now left that role.

[redacted] - Other relevant interests 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.