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

Minutes of the meeting held on Wednesday 13th April 2022 at 10:30 via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)

NOT FOR PUBLICATION

Professor J Breuer

Professor G Dougan

Mr VI G Fenton-May1

Professor N French

Ms S Hunneyball

Professor K Hyrich

Professor H J Lachmann

Professor P J Lehner

Mr R Lowe

Dr S Misbah

Professor Y Perrie

Professor S Price

Professor C Robertson¹

Professor T Solomon

Professor K M G Taylor

Dr R Thorpe

Professor S Walsh

Mrs M Wang

Professor C Weir

Apologies

Professor D Goldblatt

Sir M Jacobs

Dr A Riordan

Professor M Turner

Invited Expert²



Observers



<u>Secretariat</u>

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD

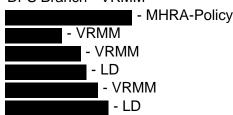


Presenters supporting specific items

- VRMM - LD

MHRA Observers

- LD - VRMM - LD Dr S Branch - VRMM



Government Legal



23rd June 2022

Key LD = Licensing Division

VRMM = Vigilance & Risk Management of Medicines

NIBSC = National Institute for Biological Standards & Control

Comms = MHRA Communications

¹ joined during item 2

² participated for item 2 only

CHM/COVID19VBREWG/2022/9th MEETING

1. Introduction and Announcement

1.6

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, Turner, Dr Riordan, and Sir Jacobs for this meeting.
- **1.5** The Chair welcomed the following invited experts who joined for item 2 Monthly Myo/Pericarditis update:

of Cambridge;	
Bristol Heart Institute	
Distorrical institute	
The Chair welcomed the following observers to the me	eeting:
-	-
UKHSA	
Public F	lealth Scotland
Public Health Agency	
	Public Health Wales
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University

UKHSA

NHS England and NHS Improvement (National)

2. Monthly Myo/Pericarditis update

- The EWG was presented with an update on the Yellow Card reports of suspected myocarditis and pericarditis with AstraZeneca, Moderna and Pfizer COVID-19 vaccines up to 06 April 2022. The update to EWG also included an updated Yellow Card observed vs expected analysis and new literature and international data which had become available since the last update on this topic on 18 March 2022.
- The EWG noted that reports of suspected myocarditis/pericarditis remain very rare with all vaccines, although more frequently reported with the mRNA vaccines. The EWG heard that reporting rates were stabilising, and the rates are similar between first and second doses with consistently lower rates seen after the third/booster dose. There is a higher frequency in younger ages and males and with a typically short time to onset of less than 7 days. The EWG was reassured that the suspected myocarditis reports showed acute presentation with the outcome reported as recovered or recovering in the majority of cases for all vaccines and symptoms mainly described as mild and only required standard treatment. The EWG noted that the available data on long-term outcomes in the Yellow Card reports have not indicated any long-term consequences, however further information is required to confirm the long term effects.
- 2.3 The EWG noted new international data from Japan and Singapore demonstrating a similar pattern of reporting of myo/pericarditis following mRNA COVID-19 vaccines as observed in the UK, including reduced rates of reporting after the third/booster dose compared with the primary vaccination series. The EWG discussed that reasons for this are not currently understood but could be due to dosing intervals.
- The EWG were reassured by the accruing data from the literature demonstrating that the risks of myo/pericarditis following COVID-19 infections are higher than those seen following vaccination, even in groups seeing the highest rates after vaccination. The EWG considered that these data further strengthened the positive risk-benefit balance of the vaccines.
- 2.5 The EWG discussed a meta-analysis of myopericarditis following COVID-19 vaccination and non-COVID-19 vaccination that had just been published in The Lancet Respiratory Medicine. This metanalysis reported that the incidence of myopericarditis was significantly higher following smallpox vaccinations compared COVID-19 vaccination. The EWG discussed that the long-term outcomes of people who developed myo/pericarditis following smallpox vaccinations had not been studied and therefore any impact of long-term cardiac health was not known in these patients.
- The EWG considered data from a small US study of the long-term outcomes in 16 patients under 18 years who had experienced myocarditis following receipt of an mRNA COVID-19 vaccine. All patients had been followed up for between 3-8 months and 15 had full resolution of symptoms; however, 11 of these patients still showed late gadolinium enhancement (LGE), although amongst the 8 patients tested, there was no effect on the ability to exercise. The EWG advised that although this was a small study, the continued

LGE was still a concern and further data are needed to improve our understanding on potential long-term effects in these patients.

- 2.7 The EWG agreed that there remains limited evidence that exercise can induce vaccine associated myo/pericarditis and agreed with the recently updated UKHSA guidance that also does not adverse restricting physical activity after vaccination unless typical symptoms of myo/pericarditis are experienced.
- 2.8 The EWG concluded that the benefit/risk ratio of AstraZeneca, Pfizer and Moderna vaccines remained positive and that no regulatory action was required based on the data presented.

3. mRNA Covid-19 vaccines - risks of reverse transcription

The EWG were informed that the MHRA had received an expression of concern from a member of the public to the effect that mRNA present in some vaccines for COVID could be subject to reverse transcription into DNA which could integrate into the human genome and pose a safety concern, including to future generations.

The EWG were informed that this issue had been discussed within the MHRA prior to approval of any vaccine with the conclusion then that as the mRNA in the vaccines is novel and as reverse transcriptase's are specific, no such reverse transcription would be expected.

- The concern expressed to the MHRA related to a publication (Alden et al 2022, https://www.mdpi.com/1467-3045/44/3/73 Intracellular Reverse Transcription of Pfizer-BioNTech COVID-19 mRNA Vaccine BNT162b2 In Vitro in Human Liver Cell Line). The Committee considered a second paper which made the claim that RNA from the SARS-CoV-2 virus can be transcribed into DNA that can integrate and be later expressed (Zhang et al 2021 https://www.pnas.org/doi/full/10.1073/pnas.2105968118 Reverse-transcribed SARS-CoV-2 RNA can integrate into the genome of cultured human cells and can be expressed in patient-derived tissues).
- 3.3 The EWG considered this information in detail and gave advice that the paper by Alden did not represent evidence of concern. Its conclusions were not supported by the data shown and the paper showed no evidence of genomic integration; there were multiple methodological limitations that undermined credibility of the claims made. In relation to the paper by Zhang et al, this did not relate to vaccines but to the virus; the Committee noted it was a controversial publication with virologists disputing it.

Overall, the EWG advised the MHRA that there was, at present, no credible evidence of risk arising from integration into the genome after reverse transcription of RNA from vaccines for Covid. The germline is not affected, and future generations are not at risk.

Nevertheless, the EWG advised that it may be prudent for the MHRA to develop a statement to summarise its view and the reasons for this and to update it with any further relevant developments, to provide reassurance to the public that the topic is given due consideration.

4. Minutes of the C19VBR EWG meetings for review

- **4.1** The minutes of the meetings listed below were approved as a true and accurate record of the proceedings.
 - Tuesday 9th March 2021
 - Tuesday 19th October 2021
 - Friday 29th October 2021
 - Friday 19th November 2021
 - Thursday 6th January 2022
 - Friday 18th February 2022

5. Any Other Business

None.

6. <u>Date and time of next meeting</u>

The next meeting has been scheduled for Friday 29th April 2022 at 11:30.

The Meeting today started at 10:31 and ended at 11:44.

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.

CHM/COVID19VBREWG/2022/9th MEETING

OFFICIAL – SENSITIVE COMMERCIAL NOT FOR PUBLICATION

Annex II

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.

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).

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 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.

Professor Lachmann – Other relevant interest 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).

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 - <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).

Professor Solomon - Other relevant interests – 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 - 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.

Observer

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.