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

Minutes of the meeting held on **Friday 29th October 2021** at **14:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan[1]
Professor N French
Ms S Hunneyball
Sir M Jacobs
Professor H J Lachmann[2]
Professor P J Lehner
Mr R Lowe
Dr S Misbah
Professor Y Perrie
Professor S Price
Professor C Robertson[3]
Professor T Solomon[4]
Professor K M G Taylor
Dr R Thorpe[1]
Professor M Turner
Professor S Walsh
Mrs M Wang
Professor C Weir

Apologies

Mr VI G Fenton-May
Professor D Goldblatt
Professor K Hyrich
Dr A Riordan

Invited Experts

[redacted][4]
[redacted][5]

Observers

[redacted]

Professional Staff of MHRA Present

Principal Assessors

[redacted] - VRMM

Presenters supporting specific items

[redacted] – VRMM
[redacted] – VRMM
[redacted] - VRMM

MHRA Observers

[redacted]- VRMM
[redacted] - VRMM
Dr S Branch – VRMM
Dr A Cave – Chief Scientific Officer
[redacted] – MHRA Policy
[redacted] - Comms
[redacted] – VRMM
[redacted] - VRMM
Mr P Tregunno - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - VRMM

Secretariats

[redacted]

[redacted]
13th April 2022

[1] left during item 4
[2] joined during item 2
[3] pjoined during item 5
[4] participated for items 3 & 4
[5] participated for item 2 only

Key
LD = Licensing Division
VRMM = Vigilance & Risk Management of Medicines
NIBSC = National Institute for Biological Standards & Control
Directorate = Director of Operational Transformation

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, Dr Riordan and Mr Fenton-May for this meeting.

1.5 The Chair welcomed the following invited experts:

[redacted] Kings College Hospital

[redacted] University of Edinburgh

[redacted] University of Liverpool and Liverpool University Hospitals

1.6 The Chair welcomed the following observers:

[redacted]
Public Health Scotland

[redacted]
UK Health Security Agency

[redacted]
NHS England and NHS Improvement (National)

2. COVID-19 Vaccines and the risk of Immune Thrombocytopenia

2.1 The EWG were presented with an assessment of the available evidence pertaining to immune thrombocytopenia (ITP) following COVID-19 vaccination.

2.2 There had been two previous presentations on ITP to the EWG, most recently in April 2021, following the reporting to MHRA of a number of spontaneous adverse event reports of ITP following COVID-19 vaccination. At that time, the EWG concluded that no further action was warranted with respect to ITP, based on the data available. ITP had also been considered by the Commission on Human Medicines (CHM) in May 2021, with the CHM noting the lack of confirmatory diagnosis in the ITP spontaneous cases and proposing that expert advice should be sought to review the cases and identify how many could be confirmed. At the time of this latest review presented to the EWG, ITP was not listed in the product information for any COVID-19 vaccine.

2.3 The EWG was now presented with an analysis of the available spontaneous reports of ITP following medical adjudication, as previously requested. For the adjudications the MHRA had sought advice from a consultant haematologist to develop case classification criteria and derive a cohort of cases classified as 'confirmed', 'possible' or 'insufficient information' with respect to the diagnosis of ITP. In addition to spontaneous reports, the other data considered in the latest assessment comprised: 1) clinical trial data, 2) Public Health England (PHE) Snap Survey data, 3), epidemiological data for observed vs expected (O-E) analysis and 4) published literature.

2.4 The EWG was informed of the following assessment findings. Clinical trial data did not show a signal for ITP. Following medical adjudication of the Yellow Card reports of ITP, there were 76 confirmed cases for the AZ vaccine, 40 for Pfizer, 2 for Moderna and 12 for Janssen, with 2 fatal cases reported, both with the AZ vaccine. Approximately 10-20% of Yellow Card reports involved patients with prior primary ITP or medical conditions associated with secondary ITP. The PHE Snap Survey Data comprised 51 cases of ITP in total, 36 for AZ, 12 for Pfizer, one for Moderna and 2 unspecified; similar proportions to the Yellow Card cohort involved prior primary ITP or conditions associated with secondary ITP. O-E analyses of the Yellow Card reports did not provide strong evidence of a signal for ITP without thrombosis with any dose of a COVID vaccine, however, in the sensitivity analyses, there was strengthening of the signal raised previously with the AZ vaccine in O-E analyses, but no signal assuming a greater than 25% reporting rate. The literature review identified 33 publications pertaining to ITP in association with COVID-19 vaccines, the great majority being case reports; an observational study of ITP and COVID-19 vaccines in Scotland provided some evidence that the risk of ITP may be increased after the first dose of AZ vaccine with no increased risk observed with the Pfizer vaccine. Three studies suggested that an exacerbation of pre-existing ITP may occur after vaccination against COVID-19 (reported in 3-12% of patients in the studies).

2.5 The EWG considered that, while the statistical evidence for a signal of ITP with the AZ vaccine remained fairly weak in O-E analyses, the new data did indicate some strengthening of the trend identified previously. The EWG agreed that advice on monitoring platelet levels should be incorporated into the product information for the AZ vaccine while allowing flexibility for healthcare professionals in how often this is done.

2.6 The EWG concluded that the available evidence warrants the addition of ITP to the product information for the AZ vaccine but not for the other COVID-19 vaccines. It was noted that the AZ vaccine product information should include risk minimisation advice for patients with a history of primary ITP or risk factors for secondary ITP because these patients may be at particular risk of this reaction. The EWG agreed that, following review, the wording on ITP

recently adopted for the EU product information for the AZ vaccine was considered appropriate for the UK product information. The EWG advised that the UK product information update should be communicated in the MHRA's weekly online ADR report for the COVID-19 vaccines with no other communications considered necessary. Finally, it was advised that ITP should continue to be closely monitored for all COVID-19 vaccines.

3. Transverse Myelitis and COVID-19 vaccines

3.1 The EWG was presented with a review of the currently available evidence from clinical trials, literature and spontaneous sources (including Yellow Card data with a data lock point of 12th October 2021) regarding transverse myelitis (TM) following vaccination against COVID-19 with the AstraZeneca, Pfizer-BioNTech, Moderna and Janssen COVID-19 vaccines. Company reviews of this issue were also presented.

3.2 The EWG was generally reassured by the low level of reporting of TM with the COVID-19 vaccines and advised that the number of vaccine related events may be overestimated due to a high background rate of TM in MS patients (estimated to be up to 5000 new cases/year in the UK). It was anticipated that many patients presenting with TM may subsequently be diagnosed with MS, with TM being secondary to MS. It was also suggested that based on identification of cold MS lesions, TM may pre-date COVID-19 vaccination.

3.3 To improve the identification of cases, it was recommended that information should be obtained as part of case follow up on whether longitudinally extensive lesions had been identified on MRI scanning and if aquaporin-4 and myelin oligodendrocyte glycoprotein (MOG) antibodies had been detected in patients presenting with TM post vaccination.

3.4 The EWG heard that the evidence for the AstraZeneca vaccine included a report of TM in the treatment arm of the clinical trials, as well as a limited number of Yellow Card reports in the context of usage (an estimated 4 reports per million vaccine recipients). However, the EWG also heard that a signal for TM had been detected in the observed/expected (O/E) analysis of the Yellow Card data in all age groups, with the exception of the under 18 year age group in which use of the AstraZeneca vaccine was very limited. It was noted that a conservative approach had been taken in the O/E analysis to include all reported cases, which may overestimate the signal if cases were not meeting a case definition criterion. The EWG agreed that the O/E analysis of TM was associated with a number of limitations but was reassured that this event was being studied as part of the ongoing OpenSafely epidemiological study which may provide further information on reporting rates of TM.

3.5 The EWG recommended that the overall evidence presented for the AstraZeneca vaccine was sufficient to warrant an update to the product information to include TM. It was also advised that a second dose of the AstraZeneca vaccine should not be given to those who experience TM after receiving a first dose of this vaccine. The EWG also recommended that this information should be communicated via the MHRA Coronavirus vaccine weekly summary of Yellow Card reporting. The EWG however advised that it was not necessary at the current time to recommend that patients with MS should avoid the AstraZeneca vaccine.

3.6 The EWG was informed of an ongoing EU review of TM by the PRAC for all COVID-19 vaccines with a proposal to include TM in the EU product information for the Janssen vaccine. In light of this review, the EWG recommended that the MHRA should consider aligning with the actions taken by the EU for the Janssen vaccine once this review has concluded.

3.7 The EWG agreed, based on the evidence presented, that no action was needed at the current time in relation to TM with the Pfizer and Moderna vaccines, but TM should continue to be closely monitored with these vaccines.

4. Optic neuritis and COVID-19 vaccines

4.1 The EWG was presented with a review of the currently available evidence from clinical trials, literature and spontaneous sources (including Yellow Card data with a data lock point of 12th October 2021) regarding optic neuritis (ON) following vaccination against COVID-19 with the AstraZeneca, Pfizer-BioNTech, and Moderna COVID-19 vaccines. Company reviews of this issue were also presented.

4.2 The EWG was also informed that the EMA were keeping optic neuritis under review as an adverse event of special interest (AESI) in the monthly safety update reports for each of the COVID-19 vaccines (including the Janssen vaccine) and that based on the available evidence, no regulatory action had been proposed by the EMA at the current time.

4.3 The EWG agreed that there was currently no strong evidence for a risk of ON following vaccination with any of the COVID-19 vaccines reviewed up to the data lock point, although based on the observed/expected (O/E) analysis of the available Yellow Card data, there was potentially weak evidence for an increased risk of ON with the AstraZeneca vaccine.

4.4 The EWG recommended that the data for ON should continue to be closely monitored especially for the AstraZeneca vaccine. It was also noted that global cases of ON post COVID-19 vaccination collected by a group of ophthalmologists had identified only 73 patients and, in line with the evidence considered by the EWG, the limited number of patients globally may fall within natural background rate for this event.

4.5 It was noted that there were also a limited number of reports of neuromyelitis optica (NMO) spectrum disorder received for the AstraZeneca and the Pfizer vaccines; the EWG recommended that due to the overlap with ON and TM that reports of NMO should also be closely monitored.

4.6 The EWG recommended that as part of clinical follow up of cases, information should be requested on whether aquaporin-4- and MOG-antibodies had been detected.

4.7 The EWG concluded that no regulatory action was warranted at this time.

5. Safety Update on COVID-19 Vaccine Janssen

5.1 The EWG were presented with an update on safety topics being reviewed for the Janssen vaccine and an update on the approval of booster vaccines in the US.

5.2 The EWG were presented with the latest MHRA assessment of non-UK Thrombotic Thrombocytopenia Syndrome (TTS) reports against the MHRA case definition. The EWG were informed that there was a total of 90 non-UK TTS reports that met the case definition (20 confirmed, 6 probable, 64 possible) as of the data lock point of 20 October 2021. The EWG noted that there had only been a small increase in the number of TTS cases since the EWG were last presented the data, however the updated data did not raise any new concerns.

5.3 The EWG were informed that the previously agreed product information updates for capillary leak syndrome and Guillain-Barre syndrome had now been submitted, with the approval of the updates expected soon.

5.4 The EWG were informed that the EU product information had been updated to include venous thromboembolism and immune thrombocytopenia as adverse events. A variation to update the GB CMA product information in line with these changes is expected to be submitted via the reliance procedure. The EWG were informed that the EMA planned a Direct Healthcare

Professional Communication (DHPC) letter to communicate the risk of immune thrombocytopenia. However, the EWG considered a DHPC letter would not be required for the UK at this time due to the Janssen vaccine not yet being deployed.

5.5 The EWG were informed that the EMA have requested that Janssen update the product information to include transverse myelitis as an adverse event. The EWG noted that the updates were yet to be finalised but would be expected to be submitted via the reliance procedure once approved by the EMA.

5.6 The EWG were informed that the US FDA had updated their healthcare professional factsheet to include myocarditis and pericarditis as post-marketing events that had been reported following administration of the Janssen vaccine. The EWG were informed that this appeared to be a precautionary update as the warnings included for the mRNA vaccines were not included for the Janssen vaccine. The signal for myocarditis and pericarditis will continue to be closely monitored.

5.7 The EWG were informed that the US FDA have authorised a booster dose of Janssen vaccine to be administered at least 2 months after the primary vaccination in individuals aged 18 years and older. The FDA also approved the use of heterologous booster vaccinations. The EWG were also informed that public health bodies in France had recommended that individuals who had received the Janssen COVID-19 vaccine should receive an mRNA COVID-19 booster vaccine 4 weeks after the primary vaccination due to reports of breakthrough infections. The EWG noted that the 2-month timeframe authorised for a booster in the US would be the same interval between the first and second primary doses for other COVID-19 vaccines. The EWG noted that if the Janssen vaccine is to be considered for deployment in the UK, there should be consideration as to whether a second dose should be administered 2 months after the primary dose.

6. Any Other Business

None.

7. Date and time of next meeting

The next scheduled meeting is to take place on **Tuesday 9th November** at **14:30**.

The Meeting today started at 14:32 and ended at 16:12.

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.

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).

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.

Sir Michael Jacobs - Other relevant interest - 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 – 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. Other relevant interest in AstraZeneca arising from being part of a collaboration in which the epidemiology and therapeutic approaches to Vaccine associated Thrombosis-Thrombocytopenia (VITT).

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).

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 - 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 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.