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

Minutes of the meeting held on **Friday 29th January 2021** at **13:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer[1]
Professor G Dougan
Professor N French
Professor D Goldblatt
Ms S Hunneyball
Professor K Hyrich
Sir M Jacobs
Professor H J Lachmann[2]
Professor P J Lehner
Dr S Misbah[3]
Professor S Price
Dr A Riordan
Professor C Robertson
Professor T Solomon
Dr R Thorpe
Mrs M Wang
Professor C Weir

Apologies

Professor P Shah

Members of the CTBV Expert Advisory Group

Professor B K Park
Professor M Turner

Members of the CPS Expert Advisory Group

Mr VI G Fenton-May
Mr R Lowe
Professor Y Perrie
Professor K M G Taylor (Chair of CPS)
Dr S Walsh

Observers

[redacted] (Imperial)
Professor S Ralston (Chair of CHM)

Invited Experts

[redacted]

Professional Staff of MHRA Present

Principal Assessors[4]

Dr J Bonnerjea - LD
Dr P Bryan - VRMM

MHRA Presenters supporting specific items[4]

[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - VRMM
[redacted] - LD
[redacted] - Government Legal Team
[redacted] - VRMM

MHRA Observers

[redacted] - LD - Medical Writer
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
Dr S Branch - VRMM
[redacted] - MHRA-NIBSC
[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - LD - Medical Writer
[redacted] - VRMM
Dr SP Lam - LD
Mr K McDonald - LD
[redacted] – VRMM
[redacted] - VRMM
[redacted] - LD
[redacted] - LD
[redacted] - MHRA-NIBSC
Ms N Rose - MHRA-NIBSC
[redacted] - MHRA-NIBSC
[redacted] - LD
[redacted] - LD
[redacted] - VRMM
Mr P Tregunno - VRMM
[redacted] - Government Legal Team
[redacted] - MHRA-NIBSC
[redacted] - LD
[redacted] - LD

[redacted] - VRMM
Dr K Wydenbach - LD

Secretariat

[redacted]

[redacted]

19th July 2021

[1] Joined during item 3
[2] left during item 9
[3] left during item 6
[4] supporting specific items

Key
LD = Licensing Division
NIBSC = National Institute for Biological Standards & Control
VRMM = Vigilance & Risk Management of Medicines
CTBV = Clinical Trials, Biologicals & Vaccines EAG
CPS = Chemistry, Pharmacy & Standards EAG
CHM = Commission on Human Medicines

1. Introduction and Announcement

1.1 The Chair reminded Members 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 The following members and invited experts declared interests and other relevant interests for this meeting:

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 Dougan – Personal interest specific to this meeting **–** Works with and is partially paid by the Wellcome Trust. Professor Dougan arranges the invite. At the chair's discretion, Professor Dougan was permitted to participate by answering specific questions from the chair, but not raise spontaneous comments or questions.

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 – 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.

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. Personal interest specific to this meeting – Sir Michael is a member of the Human Challenge Steering Committee. At the chair's discretion, Sir Michael was permitted to participate by answering specific questions from the chair, but not raise spontaneous comments or questions.

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)

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.

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

CTBV

Professor Park - NPNS in GSK Research & Development Ltd. and in Janssen as I received a research grant in the past two years. The grant has been handed over to a colleague in 2020 and the grant is due to finish in 2020. Professor Park received no direct payment. In addition, Professor Park have two active IMI grants for Transbioline and Quantitative Systems Toxicology, he is the PI on the TransBioline grant for the University of Liverpool. Both grants are paid directly to the University of Liverpool.

Professor Turner – Other relevant interest. Professor Turner is a Non Executive Director (non-remunerated) on the Board of the Cell and Gene Therapy Catapult (CGT). CGT have been tasked by UK Government with re-purposing a factory in Braintree to manufacture either a vaccine or a therapeutic mAb. No decision has been made as to whether or what product CGT Braintree may be asked to manufacture and that decision will be made by UK Government. Professor Turner does not believe that CGT Board will have any material input into the decision as to what product may be manufactured.

CPS

Mr V'lain Fenton-May – None
Mr Robert Lowe – None
Professor Yvonne 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 Kevin Taylor – None
Dr Susannah Walsh – None

CHM

Professor Ralston – NPNS – Sanofi, Pfizer, Janssen, AstraZeneca & Other relevant interests in NHS Lothian and Oxford University. Professor Ralston has an honorary consultant contract with NHS Lothian but has not been involved in any trials relating to COVID-19. He also has agreed to be an external examiner for Oxford University clinical trials MSc; however, this has not yet started.

1.4 The Chair welcomed the following invited experts for item 3:

[redacted] Human Challenge, Vaccines Taskforce
[redacted] Human Challenge, Vaccines Taskforce
[redacted] University of Southampton & Human Challenge Board Member
Read R.C.
[redacted] Imperial College (Study PI)

The Chair welcomed the following invited experts for item 4:

[redacted]

The Chair also welcomed [redacted] from Imperial who attended as an Observer.

2. Update on off-label prescribing of vaccines (for information)

2.1 The EWG was given an update regarding the previously raised questions about how the Regulation 174 approvals legally interact with the Specials Regime.

2.2 The EWG heard that a clause has now been introduced to the wording of conditions of all Regulation 174 vaccine approvals that covers off-label prescribing. This clause clarifies that an authorisation under Regulation 174 does not displace or preclude the reliance on the specials route of administration in the appropriate situations.

2.3 The EWG heard that the off-label use of vaccines cannot be further recommended or specified by MHRA and that the added clause merely states that the Regulation 174 approval does not displace or preclude the use of specials route of administration where these may appropriate in the judgement of individual prescribers or subject to the recommendations and priorities specified by the JCVI or other similar bodies.

2.4 The EWG were reminded that the added clause does not affect the liabilities of the prescriber as explained under Regulations 345 of the Human Medicines Regulations 2012. The added clause does not amount to a recommendation of use under Regulation 174. A healthcare professional prescribing this product off-label would not be considered to be doing it pursuant to the recommendation made under Regulation 174.

3. Presentation from Imperial/VTF – Human Challenge Study

3.1 The EWG viewed slides and heard a presentation from the Imperial/VTF on the general principles of human challenge studies, their strengths and requirements and how they are expected to accelerate the development of new vaccines. This type of study aims to answer questions such as the effect of vaccines and other treatments on viral shedding, and the effect of previous infections and any protection generated from this on viral shedding.

3.2 The EWG heard that these studies can look at critical challenges that may present themselves such as decisions regarding dosing or interval schedules, reduction of transmission and when to re-vaccinate.

3.3 The EWG heard that this type of study can also include non-vaccine therapies, such as therapeutics used for prophylaxis, antivirals and monoclonal antibodies as the study uses a disease model rather than an infection model.

3.4 The EWG discussed the benefits and limitations of these studies following the presentation from Wellcome on the Human Challenge Study.

4. Presentation from Wellcome – Human Challenge Study

4.1 The EWG viewed slides and heard a presentation from the Wellcome Trust. The EWG heard about the Wellcome programme of human challenge studies, with a goal to establish these studies in a low resource endemic setting so that vaccines can be tailored towards a target population.

4.2 The EWG heard about the programme of human challenge studies for SARS-CoV-2, which include characterisation studies and how they can be conducted ethically and safely. Current risk mitigation strategies in terms of treatment include pre-emptive remdesevir, monoclonal antibody cocktails, and dexamethasone.

4.3 The EWG discussed that there is a need to bridge clinical challenge data from young healthy adult individuals to target populations such as the elderly.

4.4 The EWG noted that the study will need to ensure a duty of care towards the volunteers especially in regard to persistent infections. The EWG noted that the presence of counselling young adult volunteers was reassuring and was the step in the right direction to ensure viral shedding was not taking place in the community.

4.5 The EWG heard that the study will carefully clinically screen individuals to ensure no prior history of recurrent infectious disease was present to exclude subjects with immune defects. The EWG raised concerns about the long-term effects of COVID infection in some individuals (long-COVID).

4.6 The EWG questioned the trigger points for the interventions and rescue therapies for the characterisation study, when a young adult patient is presenting symptoms of severe disease. The EWG heard that the trigger points were based around the physiological responses in those volunteers, such as gas exchange in the individual and untoward pro-inflammatory responses, with the potential use of remdesivir, monoclonal antibodies and dexamethasone in severe manifestations of the disease. Such subjects would be treated in a NHS unit independent from the study.

4.7 The EWG were reassured to hear the steps taken by the team to ensure the involvement of public in terms of public engagement studies which showed immense public support for the human challenge studies. The task force clarified that the work around spreading a clear message to the public is ongoing and continually monitored.

4.8 The EWG discussed the limitations to the challenge study such as the use of viral shedding rather than a disease model, as this does not allow for a clinical readout. The EWG questioned how efficacy will be inferred from viral replication in the upper respiratory tracts and whether this was sufficient for correlation with the efficacy of the vaccines. It was noted that this was the preferred model of choice in order to ensure the safety of the volunteers. To overcome the limitations of the disease model, the invited experts suggested alternative surrogate measures of efficacy, such as pathology seen on radiological imaging to serve as a form of a clinical readout.

4.9 The EWG agreed that challenge models will be critical going forward in understanding the different variants of SARS-CoV-2. The models will also provide an opportunity to determine whether the virus being detected is infectious.

4.10 The EWG noted the need for future discussions regarding the benefits if any of improvements to the approval pathway in terms of the nature and speed of the data these studies can produce for the current pandemic and future diseases.

4.11 The EWG expressed concern that preventing viral replication/load in the model would be a very high bar to set for any vaccine. It was raised that a model based on preventing symptoms of viral infection, especially for the accelerated vaccine development and testing, would be better.

4.12 The EWG felt that we are now moving from a previous situation of a fairly homogenous virus in a naïve population to a population who have had either had virus exposure or vaccination, and a virus that has variants. The human challenge models won't replace current research work but will add value in the nature of the data that it can produce.

5. Janssen non-clinical review

5.1 The EWG viewed slides and heard a presentation on the non-clinical aspects and the rolling review of the Janssen COVID-19 vaccine. The vaccine is an adenovirus type 26 vector.

5.2 The EWG were informed that the European Medicines Agency are reviewing the same dataset and it has been agreed that MHRA will consider what questions MHRA needs to put to the company after reviewing interactions between the European Medicines Agency and the company.

5.3 The EWG heard that the data presented on pharmacodynamics in terms of immunogenicity was reassuring. However, some discordance was noted with regards to the intracellular cytokine studies in mice and Rhesus monkeys. In mice, the intracellular cytokine response is predominantly confined to CD8 rather than CD4 cells. In Rhesus monkeys, the cytokine response is concordant between CD4 and CD8 cells. This may need to be explained by the company, as it is an unexpected finding, although it does not seem to affect the level of protection.

5.4 The EWG noted that the MHRA is awaiting toxicology data to be submitted. The EWG is keen to understand the reproductive toxicity, and whether the difference in lung pathology induced by SARS CoV-2 virus in the challenge study in rhesus monkeys between males and females could be due to lack of age matching between males and females).

5.5 The EWG discussed the possible requirements for future 1-dose and 2-dose studies (e.g. persistence of infection and persistence of antibodies in 1-dose studies). The EWG enquired as to what animal studies could be done to investigate this. The EWG considered whether 1-dose human studies would require longer-term follow-up on immunogenicity.

5.6 The MHRA confirmed that based on the rolling review data submitted in this sequence, there is no indication of whether the company will come to MHRA with a proposal for a 1-dose or 2-dose vaccine.

5.7 The EWG heard that data regarding the effects of SARS CoV2 challenge in vaccinated hamsters will be provided in sequence 2, due by the end of January. The EWG agreed that this data would provide a better understanding of immunogenicity.

The EWG concluded that the non-clinical package submitted so far was promising, but more data would be required, as outlined above.

6. Clinical AR – Update on AZD1222 efficacy and immunogenicity

6.1 The EWG viewed slides and heard a presentation on updated AZD1222 efficacy and additional immunogenicity data.

6.2 The EWG noted that efficacy was approximately 78% at dosing interval of 12 weeks or more and approximately 55% at dosing intervals of 4 to 8 weeks. However, not enough data is available to amend the dosing intervals at this stage. The EWG was concerned that early homologous boosting was confusing the data that were being presented.

6.3 The EWG discussed the available information on the clinical trial participants from South Africa and Brazil with regards to reinfection following vaccination, especially in terms of the new variants in those countries. The EWG noted that current data which depicts this sort of information is not available, however, will be requested from the company.

6.4 The EWG requested long-term data to be made available on the time of events in terms of infection to the time of vaccination in order to analyse the trends in infection rates. The EWG asked if more data would be made available on asymptomatic carriers.

6.5 The EWG noted that PHE are performing weekly analysis and will provide Pillar testing data versus vaccine records by mid-February.

6.6 The EWG concluded that the efficacy results were reassuring. The EWG advised that the product information (Information for Healthcare Professionals, Information for Recipients of the Vaccine and UK Public Assessment Report) should be amended to include updates on the age and dosage interval efficacy data based on the study data submitted; however, it was advised to wait for further data from the US (due in March) before considering a change in the dose interval recommendation in section 4.2 of the HCP information.

7. Verbal update on trends in reactogenic adverse reactions with the Pfizer and AZ vaccines

7.1 The EWG heard an update on the reactogenic adverse reactions in participants who received the Pfizer/BioNTech and the AZ COVID-19 vaccines. The EWG heard that a higher proportion of reactogenicity events had been reported in younger recipients of the vaccine.

7.2 The EWG heard that a comparison of the data collected from the Yellow Cards for the flu vaccine from 2011 up to the present day was compared against the data collected and reported for the Pfizer/BioNTech and the AZ COVID-19 vaccines. Analysis of the data was made using reports which were flagged as serious. Serious events were defined as causing disability and incapacitation, being life-threatening, causing hospitalisation, death or other (which includes definitions such as the inability to carry out daily activities).

7.3 The EWG heard that from the data collected, the cases flagged as serious (serious as defined within the categories mentioned above) were 42% for AZ vaccine and 34% from the Pfizer/BioNTech data and 48% for the flu vaccine. Within those figures, the proportion of each type of event was similar between the AZ and Pfizer/BioNTech, and slightly higher for the flu vaccines. For example, disability and incapacitation was observed in 6.5%, 6% and 9% of AZ, Pfizer and flu vaccine recipients, respectively.

7.4 The EWG heard that the frequency of serious reports flagged for the AZ vaccine was slightly higher than that for the Pfizer/BioNTech vaccine; however this figure was similar to the figure reported for the flu vaccine. The types of serious events observed with the vaccine were also comparable with those observed with the flu vaccine, typically reactogenicity (e.g. headache, myalgia, pyrexia).

7.5 It was also noted that the proportion reporting serious events was much higher amongst the under 65 age group versus over 65 age group. Similarly, for the type of serious event, the frequency of reporting was higher in the under 65 age group than the over 65 age group. For example, of the disability/incapacitation occurring in recipients of the Pfizer vaccine, 82% were under 65, and 84% for recipients of the AZ vaccine, and 55% for the flu vaccine. The potential for higher reporting was assumed to be in part due to more awareness in the younger age group regarding the yellow card scheme (particularly as a lot of these will be healthcare workers) and access to technology. However, further stratification of these events by age group is needed.

7.6 During the clinical trials, reactogenicity events were more frequently reported in the under 65 age group, although serious events in general were reported in the over 65 age group.

7.7 Preliminary information from the Zoe app shows a higher proportion of reactogenicity in those recipients of the Pfizer/BioNTech vaccine that have had previous COVID-19 infection (which was not reflected in the clinical trial data) and also in recipients after the second dose of vaccine. This data is also corroborated by the Yellow Card data. PHE does have a cohort of patients with prior COVID-19 infection confirmed by antibody testing, who could be useful in comparing with these data.

7.8 The increased reactogenicity observed in the under 65 age group is thought to correspond with a stronger immune response in this age group.

7.9 The EWG was informed that so far there has been no indication of a decrease of recipients under 65 refusing any of the vaccines because of the increased occurrence of reactogenicity events. However, it is something that will need careful monitoring and communication to ensure that it does not affect uptake of the vaccines in this age group.

7.10 The EWG noted that further data is being collected in terms of Yellow Card vaccine monitoring, and ongoing collaborations are present with PHE, and data from surveillance applications such as monitoring of the ZOE app. The EWG also noted the potential bias of reporting using Yellow Card towards more severe/serious events.

7.11 The EWG enquired about the current stage of the Yellow Card vaccine monitor, which recruits individuals who have been invited for vaccination. Invitations have been sent out to recipients and it is being considered whether to add questions concerning prior COVID-19 infection, but there is a concern as to how reliable that data will be. Apps have been launched in the US and Germany, which will also provide useful data.

7.12 The EWG raised concerns that there could be an under-reporting of events, especially from healthcare professionals, who may be more reluctant to report on themselves, even with increased familiarity of Yellow Card.

7.13 The EWG concluded that the data was on interest, as part of an ongoing monitoring of events experienced by recipients of the vaccines.

8. Verbal overview of safety data with AZ

8.1 The EWG heard that the AZ vaccine was authorised on 4 January 2021. To date, up to 1.6 million vaccines have been administered. It was noted that up to 25 January 2021, the MHRA has received 68069 ADR reports (~4 Yellow Card reports per 1000 doses). Reactogenicity reports were as expected, including ADRs such as headaches, chills, nausea, and injection site reactions. As had been mentioned previously, these were more prevalent in younger vaccine recipients, who were also predominantly healthcare professionals. A reduction in reactogenicity with the second dose has been observed with the AZ vaccine in clinical trials, but it is not possible to analyse this effect properly at this time. A small overall population of vaccinated recipients have reported reactogenicity symptoms (less than 0.5% of the population reporting as serious events).

8.2 The EWG heard that 36 fatal cases had been reported, most of which affected frail elderly care home residents with end stage diseases. As a result, it was noted that a number of reports were being submitted where an association with vaccination was not necessarily suspected but the reporter considered it good practice to report given the temporality of the fatality with vaccination.

8.3 The EWG heard events of special interest were also being reported; 10 cases reported facial paralysis but not all cases of facial paralysis were consistent with Bell's palsy with some describing facial numbness.

8.4 The EWG heard that one case of transverse myelitis had also been reported. This event was also reported in the clinical trials and is an adverse event of special interest.

8.5 The EWG confirmed further monitoring is taking place for all neurological adverse drug reactions via detailed follow up forms to help understand the exact nature of these adverse drug reactions.

8.6 The EWG noted that at the request of the FDA, AstraZeneca was requested to set up an independent panel to monitor the neurological adverse drug reactions of this vaccine. The panel considered that MHRA and the EWG should also be kept informed of its findings.

8.7 MHRA confirmed that a paper would be submitted to the EWG for next week's meeting.

9. Anaphylaxis data for AstraZeneca

9.1 The EWG heard a brief update on the anaphylaxis data for the AZ vaccine. They heard that although this vaccine does not contain the polyethylene glycol (PEG) component of the mRNA vaccines which can cause severe anaphylaxis, it does however contain a component known as polysorbate which is cross reactive with PEG.

9.2 The EWG heard that unlike PEG, polysorbate has been used as an excipient in other biological medicines as well vaccines used in the routine immunisation schedule (e.g. Fluad), Fluad has been part of the UK's annual influenza vaccination campaign for the past three years and millions of doses have been administered and no signal of anaphylaxis has been detected to date.

9.3 The EWG also heard that no signal for anaphylaxis was seen in clinical trials.

9.4 The EWG heard that a total of 14 cases reporting anaphylactic or anaphylactoid reactions were reported to the MHRA. Only a small proportion of cases reported immediate onset following vaccination (i.e. within 30 minutes of vaccination). Most cases did not appear to have the same level of severity as cases seen with the Pfizer vaccine and a specific waiting time after vaccination, as is in place for the Pfizer vaccine, was not deemed necessary at this point. In addition to this, current evidence on polysorbate as a vaccine excipient does not suggest that we would expect the rate of anaphylaxis to be increased with the AZ vaccine and clinical trial data did not identify any cases of anaphylaxis which were likely related to the vaccine.

9.5 The EWG heard that a number of hypersensitivity reactions were being reported post authorisation. It was noted that this reaction was also seen in the clinical trials.

9.6 The EWG noted that the frequency of anaphylaxis is more frequent in the Pfizer/BioNTech vaccine. The EWG considered that there was no strong basis for the inclusion of anaphylaxis in the product information and the 15 minute onset time noted with the Pfizer vaccine; however, it was agreed that the inclusion of any wording in the product information should be discussed with company. With regards to the inclusion of information for quantifying anaphylaxis in the Information for Healthcare Professionals, the EWG requested a proposal on appropriate wording that would not cause further alarm to the patient. The EWG was concerned to strike the right balance between informing patients and worrying them.

9.7 The EWG agreed a discussion with the company should take place to review cases indicative of hypersensitivity and/or angioedema that have been received in the post-authorisation setting and to determine if updates to the product information are needed.

10. Update on anaphylaxis data for mRNA COVID-19 vaccines

10.1 The EWG heard a brief update to the Yellow Card data reported for the Pfizer/BioNTech vaccine.

10.2 The EWG heard that up to 25 January 2021, the MHRA has received a total of 90 reports with the preferred term (PT) anaphylaxis, 6 with the PT anaphylactoid reaction, and 2 each for anaphylactic shock and anaphylactoid shock following the Pfizer/BioNTech vaccine. A reporting rate of 1.8 cases per 100,000 doses is estimated in the UK based on these cases. Overall, spontaneous reporting in the UK has maintained a similar pattern of events with an onset largely within 15 minutes of vaccine administration and with no particular history of allergic reactions in the cases.

10.3 The EWG heard that although Moderna's COVID-19 vaccine is not yet available in the UK, a review of post marketing data from the US by the CDC provided an estimate of 2.5 cases per million doses of the Moderna vaccine. The CDC has estimated approximately 0.5 cases per 1 million doses with the Pfizer/BioNTech vaccine.

10.4 The EWG heard that this is lower than the estimates of UK rates for the Pfizer/BioNTech vaccine, and agreed, that this was due to the differences in the criteria for determining the rates, with the US analysis excluding a high number of cases by using the Brighton Collaboration criteria, and so any comparison should be treated with caution.

10.5 The EWG noted that anaphylaxis is already listed as an identified risk in the Moderna risk management plan (RMP) and therefore do not propose new safety advice.

10.6 The EWG reiterated that the data presented on anaphylaxis following the Moderna and Pfizer COVID-19 Vaccine does not indicate any new safety concerns with these products and that the current advice on anaphylaxis and allergic reactions are still supported by the available data for both these vaccines.

10.7 The EWG heard that the UK RMP for the Pfizer/BioNTech vaccine does not currently include anaphylaxis as an important identified risk, however this is included in the EU RMP which was authorised after the UK's authorisation of this vaccine.

10.8 The EWG discussed that the UK RMP should be updated to include anaphylaxis as an important identified risk, bringing the information in line with the warnings depicted in the SmPC and further bringing the information in line with the EU RMP.

11. <u>Any Other Business</u>

None.

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

The next meeting is scheduled to take place on Thursday 4th February 2021 at 10:30.

The Meeting today started at 13:33 and ended at 17:32

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