COMMISSION ON HUMAN MEDICINES (CHM)

COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Thursday 25th February 2021** at **12:30** via videoconference

Participants Present

Members

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

Apologies

Professor P Shah

Member 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[3]
Professor K M G Taylor (Chair of CPS)
Dr S Walsh

Invited Expert

[redacted][4]

Secretariat

[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD

Presenters supporting specific items[4]

[redacted] - PHE
[redacted] - VRMM
[redacted] - LD
Dr P Bryan - VRMM
[redacted] - MHRA-NIBSC

MHRA Observers

[redacted] - VRMM
[redacted] - LD
Dr S Branch - VRMM
[redacted] - LD
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[redacted] - LD
[redacted] - MHRA-NIBSC
[redacted] - LD
Ms N Rose - MHRA-NIBSC
[redacted] - LD
[redacted] - VRMM
Mr P Tregunno - VRMM
[redacted] - MHRA-NIBSC
[redacted] - LD
[redacted] - LD

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
PHE = Public Health England

[1] Left during item 3
[2] Joined during item 4
[3] Joined during item 3
[4] supporting specific items

1. Introduction and Announcement

1.1 The Chair reminded Members and invited Experts 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 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 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.

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 – NPNS interest. Professor Turner is a Non Executive Director (non-remunerated) on the Board of the Cell and Gene Therapy Catapult (CGT) until the end of March. 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. Rentschler have signed a contract with the Cell and Gene Therapy Catapult (CGT) to rent one of the manufacturing clean room suites at the Stevenage Centre. Professor Turner understands that this will be for contract AAV manufacture.

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

Invited Experts for this meeting

[redacted] – Other relevant interest – The Immunisation Dept at PHE does sell surveillance reports on Meningococcal and Pneumococcal vaccination and disease on cost recovery basis to GSK and Pfizer. [redacted] does not have any personal conflicts of interest.

[redacted] – None

1.4 Apologies were received from Dr Riordan for the meeting today.

1.5 The Chair welcomed [redacted] from PHE as an Invited expert for Item 2 - Update from PHE. [redacted] left the meeting after his presentation.

1.6 The Chair also welcomed [redacted], Consultant Haematologist and Professor of Lymphoma Biology, Kings College Hospital as an Invited expert for Item 4 - COVID-19 Vaccines and risk of immune thrombocytopenia. [redacted] participated for this item only.

2. Update from PHE on the effectiveness of vaccines (Pfizer and AZ)

2.1 The EWG heard an update from [redacted] of Public Health England on vaccine effectiveness data gathered following deployment of Pfizer/BioNTech and AstraZeneca vaccines. The facets of the presentation covered data collected from the following sources: routine testing, SIREN study, General Practitioner cohort study (from Royal College of GPs), hospitalisations, SARI watch, and vaccine impact data.

2.2 In summary, Pfizer vaccine effectiveness against symptomatic disease in older adults shows dose 1 reaches 60-70%, dose 2 reaches 85-90%. AZ vaccine effectiveness against symptomatic disease in older adults shows dose 1 reaches 60-75% and this has not yet

plateaued. The national data provide suggestive evidence of population level impact on hospitalisations and deaths.

2.3 The Chair noted it is reassuring that the results from England, Scotland and Israel on vaccine effectiveness show a great degree of consistency. The Chair also noted that extended interval data on the Pfizer vaccine from Scotland was an exception in that a decline in vaccine effectiveness with an increased interval between first and second doses was present in the data. The EWG noted the analysis plan for the dataset from Scotland will be honed to study the result. The present assumption that the result is not representative of a true effect, but rather an error due to the smaller sample size. The invited expert noted that the longer follow-up data (post 60 days second dose) shows that the Pfizer vaccine takes longer to generate effectiveness in the older subjects, and the uptrend in cases with a longer interval is too minor to produce any concerns. The Chair noted the recent data from the Real-time Assessment of Community Transmission (REACT-2) study show antibody levels are sustained after the first dose of the Pfizer vaccine to at least 36 days, further supportive of that vaccine efficacy reflects a sustained immune response, with no indication that protection is declining.

2.4 The EWG noted that outside of specific studies, systematic sequencing of samples from hospitalised cases in pillar 1 is not being undertaken. The EWG noted the measures to track potential escape variants in the UK datasets was currently limited. The EWG discussed the importance of enriching the sampling (viral genome sequencing) of vaccinated individuals admitted to hospital ("breakthrough cases"), in particular those with symptom onset beyond the date where protection from the vaccine is estimated to occur. Enrichment of sampling in this manner would likely serve to track potential vaccine escape variants of clinical concern more effectively. The invited expert agreed to refer the suggestion to PHE and noted that targeting severe populations (for example hospitalised individuals) would indeed, likely offer over advantages over the random sampling approach.

3. Marketing Authorisation requirements for new COVID-19 vaccines

3.1 Existing guidance on the development of new vaccines when effective vaccines are available and approved was presented. Three situations are possible. 1) There is an established correlate of protection. In that case, no comparative study to an approved vaccine is required. 2) A specific immune response is reasonably likely to predict protection. In that case, a comparative immunogenicity trial may be acceptable. The design of a non-inferiority immunogenicity trial was detailed, including its endpoints (neutralising/binding antibodies, T-cell response), its parameters (geometric mean titre, seroconversion rate), its non-inferiority margin. In addition, safety data (at least 3000 subjects) and post-approval effectiveness studies would be required. However, it was questioned whether this strategy is possible across different manufacturing platforms. 3) There is no approved vaccine of a similar platform. In that case, if a placebo-controlled trial is not feasible, a comparative efficacy trial is required (superiority or non-inferiority). It was questioned whether it might still be possible to justify an immunogenicity comparison between vaccines of "similar" platforms, e.g., inactivated vaccine vs subunit vaccine, and finally whether animal studies or human challenge studies might help support the choice of a comparator.

3.2 The EWG noted that new approaches to define correlates of protection are available which study more than a single antibody level, but comparison between trials is hindered by a lack of standardisation. Ratios of neutralising or binding antibodies to convalescent sera antibodies are being calculated to aid comparative analyses across trials. The EWG noted that the MHRA will most likely need to collaborate with international bodies to facilitate a broader understanding of, and to gather the information required to reliably define the correlates of protection.

3.3 The EWG noted correlates of protection are difficult to establish across different vaccine platforms. For viral vector and mRNA vaccines, in addition to inducing antibody responses these COVID-19 vaccines also provoke fairly potent T-cell responses, whereas theory suggests sub-unit vaccines may trigger lower levels of T-cell responses. The challenge will be to qualify the implications of such differences for immunity in vaccinated subjects and this may be an unrealistic goal.

3.4 The EWG noted standardised assays on variants could promptly be launched at NIBSC, and potentially could be used to assess immunity across vaccine platforms. The EWG heard that NIBSC are exploring using the international standard to compare neutralising assays across various platforms when challenged with different viral variants, but this work is presently hindered by the absence of normalisation of variants in the assays. Therefore, it cannot be ruled out that the intrinsic behaviour of the variant is responsible for any difference in the titres. One of the members of the EWG, offered to assist NIBSC to identify groups that could share provide relevant expertise on variant assays.

3.5 The MHRA informed the EWG that in the absence of correlates of protection, companies are seeking scientific advice from the MHRA with regard to their trial designs. The Chair signposted the trial design proposed by Valneva SE. The company are proposing an immunogenicity and safety trial of 4000 participants, 600 of which will have immunogenicity data collected, with efficacy as a secondary endpoint.

3.6 The EWG noted a method to evaluate a vaccine would be to study equivalent responses in convalescent sera. To benchmark vaccine efficacy, the vaccine should perform better in the same assay / assays when compared to sera of patients that have recovered from natural COVID-19 infection. The EWG noted neutralisation is only one component of the immune response but that T-cell responses are also likely to be important, and as such should also be evaluated. A member raised the data on variants from neutralisation activity compared to efficacy data from clinical trials, the correlation between the two appears clear. The expert also noted the currently emerging consensus is that T-cell responses are unlikely to contribute to protection in the immediate post-vaccination period but will be key for longer-term protection and potentially also in lowering the likelihood of progression to severe disease or death.

3.7 The EWG noted in the absence of correlates of protection, it is best to measure both antibody and T-cell responses as surrogate measures of efficacy.

3.8 The EWG noted that establishing robust measures of the durability of the immune responses caused by COVID vaccines is critical to understanding vaccine efficacy.

3.9 The Chair informed the panel that the EMA appear to be supportive of companies pursuing a non-inferiority approach to immunogenicity trial designs. The EWG statistical expert noted that ascertaining clinical meaning from a non-inferiority margin of a surrogate scale such as neutralising titres is challenging, however non-inferiority studies of other vaccines such as the flu vaccines could be used as an exemplar to follow. The statistical expert continued that more data would be needed for COVID-19 vaccine candidates and suggested that trial designs factor-in the gathering of data that would likely support the discerning of correlates of protection.

3.10 The EWG noted a potential future perspective is to test vaccine efficacy in human challenge models.

3.11 The MHRA informed the EWG that the rationale for the choice of the AZ vaccine as a comparator in the planned Valneva SE trial is not substantiated. The MHRA had also

considered whether a sub-unit vaccine may represent a better choice of comparator in the absence of any licensed vaccine using the same platform technology as Valneva.

3.12 The MHRA informed the EWG that at minimum a regulatory perspective is required on the choice of comparator ahead of the next scheduled meeting with Valneva. The Chair acknowledged that the company should justify the choice of comparator, the dose interval, and the trial age range / group (as the majority of the older population in the UK are, or will be vaccinated by the recruitment period), the company also need to be informed it will be mandatory to undertake a post-authorisation vaccine effectiveness study.

3.13 The MHRA informed the EWG that there are limited countries where placebo-controlled studies would be possible due to the varied national vaccination campaigns in progress.

3.14 The EWG were invited to consider the choice of comparator. The EWG noted that assessing the advantages and disadvantages of using comparators that utilise different platform technologies (from sub-unit vaccines, whole inactivated vaccines, mRNA, to vector vaccines) is problematic as none seem ideal, including sub-unit vaccines, and substituting comparators would not solve the issue. The EWG noted a paper comprising the views of regulators and scientists on non-inferiority challenges in different settings is expected to be published shortly. The Chair acknowledged that regulatory alignment on the global stage will be important in the near future, and it would be beneficial to promptly commence discussions with other regulatory bodies. In the immediacy, Valneva should justify their choice of comparator, including that it is a different platform technology and the proposed dosing interval.

4. COVID-19 Vaccines and risk of immune thrombocytopenia

4.1 The EWG heard reports of immune thrombocytopenia (ITP) for the Pfizer/BioNTech vaccine, AZ vaccine and the international data on the same topic for the Moderna vaccine which is not currently used in the UK. The reports were heard in the context of vaccination coverage in the UK, which at the time of the meeting, it was estimated that over 10 million doses of the Pfizer/BioNTech vaccine have been administered in the UK as of 21 February 2021 and over 8.4 million doses of the AstraZeneca COVID-19 vaccine have been administered in the UK as of 21 February 2021.

4.2 Pfizer/BioNTech have also reviewed events of immune thrombocytopenia in the context of observed vs expected analyses for international usage of their vaccine and did not identify an increased rate in excess of that expected. The meeting also heard that a review by the US Centre for Disease Control (CDC) covered data to 27th of January 2021 and also did not identify a signal of ITP.

4.3 The EWG focused on two key questions a) if the vaccine is causally related to de novo cases of ITP, and b) If there is a signal to suggest the vaccine could exacerbate pre-existing ITP.

4.4 The EWG noted that diagnosis of ITP requires a thorough clinical assessment; however the details within the reports are varied in terms of the level of assessment of the patient as undertaken by the healthcare professionals. The EWG discussed the limited influence that one particular case should have on the considerations, because this patient's low haemoglobin was suggestive of other haematological disease. This case aside, overall the number of plausible ITP cases appears sufficient to justify continued monitoring.

4.5 The EWG discussed the biological plausibility of the potential signal. The EWG noted that vaccines used in other diseases have been causally linked with cases of thrombocytopenia (TP); in some of these instances the adjuvant has been theorised to be responsible, but the identification of TP cases across different vaccine preparations and technologies somewhat

challenges this view. The EWG also noted that COVID-19 infection can also cause thrombocytopenia not only by means of increased platelet turnover, but direct platelet infection by SARS-CoV-2. Therefore, concomitant COVID-19 infection needs to be thoroughly evaluated as potential confounding factor. It was confirmed that the majority of the reports state 'negative' for concomitant COVID-19. In summarising remarks, the EWG noted it was plausible that ITP could potentially be associated with each of the three vaccines discussed.

4.6 The EWG noted the number of ITP cases likely represents a borderline signal with the Pfizer/BioNTech and the Moderna vaccine, and perhaps a more likely signal for the AZ vaccine. Further details of individual cases are required, and any new reports need to be carefully evaluated and incorporated to on-going analyses. Mechanistic data could also be used to interrogate the likelihood of a causal relationship. At present, the EWG noted that the level of information and the proportionately low number of cases of TP preclude making any robust judgements on causality.

4.7 On the topic of exacerbation of pre-existing ITP as potential side effect triggered by the vaccine, the EWG considered that viral infections can lead to flare ups in patients with ITP. Mixed outcomes are also reported with other vaccines in the literature, with some studies suggesting a causal link to the vaccine and others not. It was also considered by the EWG that unvaccinated patients who have a sub-clinical IPT may advance to clinically diagnosable IPT more rapidly following vaccination. The EWG noted a proposed mechanism involved the downstream processes of inflammation in response to vaccination, leading to up-regulation of pre-existing types of autoantibodies. The EWG determined that it was plausible that the time of onset to ITP could potentially be accelerated due to use of COVID-19 vaccines but that an association with the vaccines could not currently be established.

4.8 The EWG noted the detailed narrative regarding the case of fatal cerebral venous sinus thrombosis (CVST) in a 32 year old patient, and that there was no evidence of confounding. The EWG noted thrombotic events or bleeding is rare in cases of ITP, but bleeding can occur in cases of wet ITP. Further information on this case, and any other similar cases, should be obtained as follow-up.

4.9 The EWG noted a number of reports of ITP and thrombocytopenia do not appear to include any confounding factors and which decreased the likelihood these reports represent a chance finding.

4.10 The EWG considered the proposed follow up forms to gather additional information on these cases, and systemic lupus should be added to the list of other potential causes of TP.

4.11 The EWG discussed whether vulnerable patient groups, in particular patients with auto-immune disease, would be more susceptible to ITP. The meeting considered that this could be plausible but there is no evidence to suggest that this is the case at the moment. Monitoring platelet counts in the period prior to vaccination in patients with auto-immune disease was not recommended by the EWG, as there is presently only a potential signal, and also because results would be difficult to interpret especially when considering that some immune conditions can cause low-platelets, e.g. lupus. The EWG agreed the topic of vulnerable patients including those with auto-immune diseases, should be revisited in the near future /when further data may have become available. The EWG discussed ITP in the paediatric population and confirmed that if the vaccination schedule is broadened to include children, there will be a need to rapidly monitor and review potential haematological signals in children, particularly as 40% of ITP cases occur in children mostly under the age of 10 years.

4.12 The EWG noted the need to conduct very in-depth assessments of individual cases that include no apparent confounding factors and communicate with other international regulators to gain further insights, and establish a basis for a coordinated regulatory response.

4.13 The EWG noted future studies should explore platelet activation in vaccinated patients, and although initiating these studies falls outside of the MHRA's purview, the EWG could form a recommendation to researchers.

4.14 The EWG considered that initiation of risk minimisation for ITP would be premature at this stage and the addition of warnings on ITP in the product information for the vaccines would be (currently) unfounded and may only unnecessarily contribute to vaccine hesitancy.

4.15 The EWG concluded that cases of immune and non-immune thrombocytopenia should continue to be monitored.

5. Update on COVID-19 vaccine AstraZeneca safety

5.1 The EWG heard an update on safety data for the AstraZeneca vaccine up to 19th February 2021. 41,157 reports of suspected ADRs in association with COVID-19 Vaccine AstraZeneca had been received in the context of roughly 8 million doses given. The most frequently reported reactions were consistent with expected reactogenicity reactions and were present in the product information. 227 fatal cases had been received, the majority of which were in patients aged over 80 years. An update of cases received for adverse events of interest Bell's palsy and transverse myelitis was provided. Analysis of individual cases as well as epidemiological analysis did not indicate a signal.

5.2 The EWG discussed cases reporting transverse myelitis and the plausibility of cases where patients reporting the condition with very quick recovery, without input from a healthcare professional. The EWG considered these cases to be less plausible to be true transverse myelitis than those where medical review and treatment have been sought.

5.3 The EWG discussed the importance of acquiring more information on the reported cases to allow further assessment of cases although the difficulties in obtaining this with established follow up measures were acknowledged.

5.4 The EWG advised that no regulatory action was required currently but further information for assessment was required.

6. Review of potential risk of encephalitis with Pfizer/BioNTech and AstraZeneca COVID-19 vaccines

6.1 The EWG heard an overview of an ongoing report regarding a recipient of the AstraZeneca Covid-19 vaccine who experienced encephalopathy, multi-organ failure and paralysis with an onset between 24-48hours post vaccination. The patient had a complex medical history, significant for reactions to viral and bacterial infections as well as a previous reaction to a vaccine.

6.2 A review of cases of encephalopathy and encephalitis and related terms reported to the Yellow Card database was presented, to a data lock point of 15th February 2021 and from clinical trials with the Astra Zeneca and Pfizer vaccines.

6.3 The EWG noted that as per the product information, a previous reaction to a vaccine (other than a prior COVID-19 vaccine) does not contraindicate use of any COVID-19 vaccine. A

search of the Yellow Card database for other cases mentioning previous reactions to vaccines found only reports of reactogenicity type reactions to the COVID-19 vaccines.

6.4 The EWG discussed the most recent information regarding the index case and commented on the complexity of the patient's medical history.

6.5 The EWG commented on previous reports of fatal reactions to the use of adenoviral vectors used therapeutically (rather than as a vaccine) and stated that it was important to be clear that these events are not similar to the events being discussed currently and that the adenovirus vectors used in these therapies were live adenovirus vectors, rather than a replication-deficient adenovirus vector, as used in COVID-19 vaccine AstraZeneca.

6.6 The EWG concluded that more information was needed on this case, however it was not possible to establish causality with vaccination for this patient and that there wasn't wider evidence of similar reactions currently. The EWG considered there is no need for any updates to the product information or communications at this time.

7. Core Risk Management Plan for COVID-19 vaccines – requirements for update following strain

7.1 The EWG heard MHRA proposal to principles and requirements of an updated pharmacovigilance system and core Risk Management Plan for COVID-19 vaccines strain variations and agreed of the principles laid down in the proposal.

7.2 Update on the Guideline

7.2.1 MHRA-NIBSC updated the EWG on recent revisions of the guideline that were made in consultation with stakeholders and other regulators. Experts approved all proposals made and strongly encouraged timely publication.

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

8.1 None.

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

The next meeting is scheduled to take place on Tuesday 2nd March 2021 at 11:30.

The Meeting today started at 12:32 and ended at 15:00.

[redacted]

19th July 2021

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