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

Minutes of the meeting held on **Tuesday 25th May 2021** at **12:00** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Mr VI G Fenton-May
Professor D Goldblatt
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
Dr A Riordan
Professor C Robertson[1]
Professor T Solomon
Professor K M G Taylor
Dr R Thorpe
Dr S Walsh
Mrs M Wang
Professor C Weir

Apologies

Professor G Dougan
Professor N French
Sir M Jacobs
Professor M Turner

Visiting Experts

[redacted]

Observers (left after item 4)

[redacted]

Secretariat

[redacted]

[1] Left during item 5

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted] - VRMM

Presenters supporting specific items

[redacted] - LD

MHRA Observers

[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
Dr S Branch - VRMM
[redacted] - VRMM
[redacted] - VRMM
[redacted] - Comms
[redacted] - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD
Dr J Raine - MHRA CEO
[redacted] - VRMM
Mr P Tregunno - VRMM
[redacted] - LD
Dr K Wydenbach - LD

[redacted]

4th February 2022

Key
LD = Licensing Division
VRMM = Vigilance & Risk Management of Medicines
MHRA CEO = Chief Executive
Comms = MHRA Communications

1. Introduction and Announcement

1.1 The Chair reminded Members, invited Experts and observers that the content of papers and proceeding of the meeting are strictly confidential and should be treated as 'Official – sensitive commercial' and should not be disclosed. There is no consent for members / participants to record the meeting, take screenshots or photographs of presentations. The meeting was recorded by the MHRA Secretariat for minute taking purposes only. The Chair & Members including all participants gave full consent to the recording prior to the start of the meeting.

1.2 Conflict of Interest Policy (Annex I to the minutes)

The Chair reminded members and participants that, in accordance with the CHM Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members were also reminded to declare any other matter which could reasonably be perceived as affecting their impartiality.

1.3 Participants declared interests and other relevant interests for this meeting listed at **Annex II** to the minutes.

1.4 Apologies were received from Professors Dougan, French, Turner and Sir Michael Jacobs for this meeting.

1.5 The Chair welcomed the following Visiting Experts:

Dr [redacted]
[redacted] Public Health England

Professor [redacted]
[redacted] University of Oxford

Professor [redacted] MA MPH BMBCh PhD FRCP FRCPath FMedSci
Professor of Clinical Microbiology, Wellcome Senior Fellow in Clinical Science
[redacted]

Professor [redacted] ChB MD FRCP DRCOG FRCGP
Professor of Clinical Epidemiology and General Practice
Professorial Fellow, [redacted]

1.6 The Chair welcomed the following observers:

Dr [redacted]
[redacted], Public Health Agency

Dr [redacted]
[redacted]

2. Update from COG-UK on Spread of the Variant first identified in India

2.1 The EWG was presented with information on the emergence and biological properties of SARS-CoV-2 B.1.617. The EWG heard that lineage B.1.617 is now of global significance. There are two main lineages of B.1.617 (B.1.617.1 and B.1.617.2). A furin cleavage mutation (P681R) that increases host cell-cell fusion is common to both. The B.1.617.1 lineage has two mutations (L452R and E484Q) in the receptor binding domain (RBD) that partially evade mRNA elicited neutralising antibody. Evidence of additive / synergistic effects of the two mutations in the RBP has not been found.

2.2 The EWG heard Cambridge Institute for Therapeutic Immunology and Infectious Disease are investigating the effect of patient age on T-cell immunity but only with Wild Type (WT) virus. Other groups are exploring T-cell immunity and vaccine escape, where the data show that the variant B.1.351 includes escape mutations in T-cell epitopes, but the relevance of this finding is less clear. The findings in the literature indicate that to prevent infection with SARS-CoV-2, antibodies are required because the virus is highly infectious. The role of T-cells in COVID-19 most likely occupies the later phases of infection and may contribute to hindering the progression of disease and severity of disease.

2.3 The EWG heard the samples were taken from healthcare professionals (HCPs) who were recently vaccinated (earliest January 2021) and the vaccine interval was understood to be 4 weeks, but the specific interval data is due. The Chair noted the interval used in the UK is 12 weeks for ChadOx1. The invited expert was uncertain if the higher peak antibody levels observed with an interval of 12 weeks would be sustained.

2.4 The EWG commented that serum samples of breakthrough cases have shown very high antibody levels (Hacisuleyman et al, 2021; NJEM 2021). The invited expert segued into a question, do the variant studies provide greater understanding of vaccine breakthrough considering that there are a number of other factors aside from phenotypic changes involved in the process of breakthrough (such as viral load). The EWG heard that by way of example the mutation at the furin cleavage site mutation (P681) potentially promotes the ability of the virus to tolerate neutralising antibodies through modulation of S1/S2 cleavage. The EWG heard there also appears to be good consistency between in vitro data and trial data, whilst the invited expert acknowledged multiple mechanisms would be involved in vaccine breakthrough. Reassuringly the fold changes in a reduction of neutralisation seen with the B.1.617 lineages do not yet confer a loss of vaccine efficacy in terms of severe disease.

2.5 The EWG noted interpretation of the molecular epidemiology data from India requires careful consideration of the limitations, since approximations of transmissibility are known to be affected by the number of samples versus the extent and evenness of geographical coverage. In India, sequencing is currently very concentrated in a few areas. The data from India may indicate that B.1.617.2 is outcompeting B.1.617.1, but it is not known if it is also outcompeting B.1.1.7. The most robust data on transmission is UK based, covering almost all positives to a high level of viral genome coverage and the data show a fairly steady rise of B.1.617.2 that has spread outside areas of travel, and is therefore, less likely to be an artefact of people movement and more likely due to increased transmissibility as a trait of B.1.617.2.

2.6 The EWG noted that vaccine breakthrough data are not reliable due to the absence of unvaccinated sera controls. Without this, the level of breakthrough cannot be assessed compared to the other variants or WT virus, but hitherto can only show that the variant circulating in and around the period of sample collection is able to breakthrough. The EWG also noted that B1.617.2 is representative of a selective sweep and thus would not reveal adequate information about transmissibility. The EWG noted that interpretations from the

data should be conservative, with careful consideration of denominator data. The UK HAS England data do not appear to show that B.1.617 lineages are producing more events of vaccine breakthrough. However, if this understanding changes, it also needs to be understood if lineages of B.1.617 are associated with more severe cases of COVID, i.e. result in more hospitalisations and deaths.

2.7 The EWG noted that mutations altering the phenotype are common in respiratory viruses and tend to become part of the background variation not often associated with more severe disease. Norovirus maybe one of a number of exceptions where disease can become more severe seasonally as the viral genome acquires mutations.

2.8 The Invited expert agreed that due to sweep of B1.617.2, from these data it is not possible to determine if B1.617.2 is more able than other variants or WT to breakthrough. The expert however, maintained that the consistency of findings in the in vitro and in vivo data supports a hypothesis that phenotypic variation enables a biological mechanism for B1.617 to breakthrough, but caveated this by noting that further data would be required to substantiate this claim.

2.9 The EWG heard that B1.617.2 is concentrated in discrete locations in the UK, and therefore, until there is a more generalised B1.617.2 epidemic, analysis of UK epidemiological data will carry limitations. As the time expires awaiting this scenario, as well as that required to confirm that the infectivity and virulence of B1.617.2 is greater—the human cost will likely have already been accrued. The EWG noted that an exception may be if there is a clear signal.

2.10 The EWG heard, in terms in importations from other locations in the subcontinent, that in a current outbreak in Nepal, 33 out of 35 randomly sampled sequences were B1.617.2, but data from other countries was not readily available.

2.11 The EWG heard that bamlanivimab loses binding affinity for B1.617.2 completely, but, the other Regeneron antibody cocktail (dual therapy) still has neutralising activity. In terms of the real world situation, this is currently not a pressing issue as access to monoclonals is very limited.

3. Presentation form Prof [redacted] on thrombocytopenia/thrombosis

3.1 The EWG was presented with data on the short-term risks of thrombocytopenia and thromboembolism associated with vaccination or natural infection during the vaccine roll out in the 2nd and 3rd pandemic waves in England. The study was in a population that was the largest, most representative, and diverse to date. The main limitations of the study included the short exposure window (28 days), a reliance on clinical coding and therefore, an absence of formal adjudication of outcomes, study of 1st vaccine dose only, and those still in hospital not included with the potential for misclassification or under-ascertainment of outcomes—likely to be non-differential with regard to each vaccine.

3.2 The key findings consisted of:

- increased risk of thrombocytopenia, venous thromboembolism VTE, and other rare arterial thrombotic events following first dose of the AstraZeneca vaccine
- increased risk of arterial thromboembolism (ATE) and ischemic stroke following a first dose of Pfizer/BioNTech. Increased risk of cerebral venous sinus thrombosis (CVST) was found following a first dose of both AstraZeneca vaccine or Pfizer/BioNTech in the 8-14 day and 15-21 risk windows respectively.

- importantly the risk of these outcomes following vaccination were much lower than those associated with SARS-CoV-2 infection in the same population.

3.3 To contextualise their findings the group estimated the number of exposures needed for one excess event and the excess number of events per 10 million exposed for each outcome.

3.4 For the AstraZeneca vaccine the excess events were 107 for thrombocytopenia, 66 for VTE and 7 for CVST. For the Pfizer/BioNTech vaccine there were 143 extra cases of ischemic stroke and 5 of CVST. For SARS-CoV-2 infection, there were an estimated 934 additional cases of thrombocytopenia, 12,614 of VTE, 1,699 of ischemic stroke and 20 of CVST.

3.5 The EWG was presented with a draft visualisation of a lay summary of findings from the study.

3.6 Question and Answer

3.6.1 The EWG heard that the analysis of thrombocytopenia was conducted separately to that of thrombosis. The diagnosis of thrombocytopenia but without platelet counts work is being undertaken to obtain this information from hospital systems for future analysis in real-time. The study data on thrombocytopenia with thrombosis can be analysed together but will not be linked to platelet counts.

3.6.2 The EWG heard a sub-group analysis grouped by age (below 50 year and 50 and over) produced results that were fairly consistent but with wide confidence intervals.

3.6.3 The EWG noted the association of Pfizer with ischemic stroke appears to be a novel finding and highlighted a distinction in the US where despite wider use of this vaccine in the US, a signal of stroke has not been identified by the FDA. The EWG heard there was a possibility that the finding of stroke could possibly be due to chance, another possibility is that CVST was mis-coded as ischemic stroke. The Chair noted this may apply particularly to the elderly where a CT venogram may not have been completed. The EWG heard the group did not identify any particular bias that applied to stroke but not the other outcomes. The EWG heard there were some cases of stroke in younger people <50 years, but to give a specific number the data would be required to be checked.

3.6.4 The EWG heard in the self-controlled case series the 28 days before vaccination was removed from the baseline comparator risk period to limit risk of bias due to prior VTE. When studying the 28-day period data, there was a reduced risk of VTE, indicating that the patients were postponing vaccination until recovery or discharge from hospital following a VTE event. The expert noted that the same period in the Scottish study was 14 days, in the age stratified analysis an association with VTE was not identified for either of the two vaccines.

3.6.5 The EWG heard a call is planned with haematologists with an aim of improving validation of clinical outcomes against hospital coded data, which if successful will help to substantiate the study outcomes.

3.6.6 The EWG noted with a self-controlled case series one limitation is the end of follow-up in conjunction with the person time beyond 28 days. If there is lack of completion in the cases, cases may be missed from the analysis that otherwise would have been included in the study period - if it were not for the delay to obtain the information. This could result in a case deficit / underreporting of adverse outcomes. Similarly, for the pre-period if there was a permanent deferral or contraindication, the pre-data is prone to a lower incidence in that period. The invited expert acknowledged when compared to other options there are strengths and weaknesses of using a self-controlled case series and mentioned that the

scope for biases needs to be controlled as well as possible. In terms of the beyond 28 days, the vaccination outcomes drop to ~1 (22-28 days post-vaccination) but there could still be some increased risk, more particularly with SARS-CoV-2 infection the increased risk had not reduced by 28 days.

3.6.7 The EWG heard the study included individuals with SARS-CoV-2 infection pre-vaccination and after vaccination numbers were considered insufficient to explore the interactions between the two. The EWG noted that the invited experts may revisit this and remarked that this would be of benefit because the effect of infection lasts for longer in terms of the risk of thrombosis.

3.6.8 The invited experts confirmed they have not yet evaluated the potential causes or mechanisms that may account for the differing dates of onset of CVST in the period following vaccination, for each of the two vaccines.

3.6.9 The invited experts confirmed that an analysis of thrombocytopenia with thrombosis as combined outcome could be undertaken, and these results could be included in the same publication. The invited experts also confirmed that once completed the analysis and results would be made available to the EWG.

3.6.10 The EWG noted that the term 'slight risk' in the lay messaging may exaggerate the risk given the rate is per 10 million exposed, for example for CVST with is 5 additional cases for Pfizer. The EWG suggested terminology that maintains a context of an exceedingly rare event. The invited experts volunteered to refer the comments / subject to the patient group.

4. Update on PHE analysis of thrombosis with thrombocytopenia

4.1 The EWG was presented with upon on cohort analysis of Secondary Uses Service SUS data after COVID-19 vaccines from PHE.

4.2 The EWG heard the PHE data shows that following vaccination with the AZ vaccine, there is an increased risk of: dose specific thrombotic events, thrombocytopenia, and concurrent thrombocytopenia with thrombotic events. The EWG heard that the longer follow-up time increases the confidence in these associations. However, coding changes could occur due to prior awareness of these potential associations amongst medical professionals. This denotes a caveat to the results, though it is likely to be minor.

4.3 The EWG heard it was not possible to adjust for known SARS-CoV-2 infection when using the cohort analysis approach, and therefore, changing infection risk can only be evaluated in relation to the time period by number of weeks in the study.

4.4 The EWG heard from the MHRA, that there has been indication of signal of myocarditis in the Israeli data particularly after the second dose and in males (age ~30 and below).

4.5 In the US, the CDC have not detected an imbalance in their observed-expected figures of myocarditis, but they have identified a clustering of reports post second dose in a very similar demographic to that of Israel for both mRNA vaccines (Moderna and Pfizer). The CDC do not stratify their observed expected by age. The MHRA observed expected data have also not shown any imbalance with respect to myocarditis age-related or generally.

4.6 The invited expert mentioned acute myocarditis was included in the PHE analysis in direct response to the indication of a signal from Israel. The EWG heard events of arterial thromboembolism were also included in the UK PHE analysis.

5. COVID-19 Vaccine AstraZeneca (ChAdOx1-S [recombinant]), 1 x 1011vp-mL, solution for injection

5.1 The EWG heard a presentation on the submission of a conditional marketing authorisation (CMA) for Covid-19 vaccine AstraZeneca (AZD1222) in Great Britain (GB). Covid-19 Vaccine AstraZeneca has been granted a temporary authorisation under Regulation 174 of the Human Medicines Regulations 2012 (Regulation 174 authorisation) on 29 December 2020.

5.2 Similarly, to the Regulation 174 authorisation, no quality major objections have been raised with this conditional marketing authorisation (CMA) application as all other concerns have been appropriately addressed. The EWG heard, that initially there will be concurrent supply of the regulation 174 authorisation packs alongside the CMA packs in order to ensure uninterrupted supply to Northern Ireland.

5.3 The EWG heard there were no new clinical trial data received since the last update of the Reg. 174 public assessment report. The United Stated (US) trial data, very recently submitted by the Company, will be assessed in the near future. Of interest are two pre-prints provided by the Company, which describe similar immune response in people living with human immunodeficiency virus (HIV) (under treatment and immunocompetent) compared to healthy subjects.

5.4 The EWG heard about the non-clinical assessment of the product. An updated biodistribution study showed no unexpected results, i.e. the replication incompetent virus does not travel far from the injection site. Separately, the report from GLP inspection for the reproductive toxicity study was satisfactory.

5.5 The EWG heard the content of the product information and conditions require consideration. The assessment team have aimed to abide by two principles: to align as far as possible with the EU/NI product information, and where the UK has additional data /experience in the Regulation 174 authorisation to carry this over to the CMA as 'additional text'.

5.6 The EWG agreed that the SmPC sections 1 & 2 should updated to be brought closer in line with the EU/NI SmPC. It was also agreed to remove the negative statement regarding routes of administration present in section 4.2 of the EU/NI SmPC

5.7 Of note, the EWG heard that, in-line with the R174 product information, it is not proposed to include a recommendation for a15-minute observation period post vaccination in Section 4.4 of the GB SmPC. The EU/NI SmPC includes this recommendation, in keeping with all Covid-19 vaccines approved in the EU to date. The EWG noted that, in view of the significant clinical experience accrued in the UK with over 30 million COVID-19 Vaccine AstraZeneca ChAdOx1 (AZD1222) vaccinees, in terms of a broad recommendation for protocols in mass vaccination centres it was considered appropriate not to include this recommendation.

5.8 The EWG noted that, in-line with the R174 product information, a cautionary statement about use in individuals with a history of heparin-induced thrombocytopenia and thrombosis (HITT or HIT type 2) was to be retained in the GB SmPC due to the possibility of an interconnected pathophysiology with Thrombosis with Thrombocytopenia Syndrome (TTS). However, the EWG heard this information is now to be located under section 4.4, special warnings and precautions, rather than in section 4.3, contraindications.

5.9 Given the quantity of accruing data that does not show any evidence for an association between APS and TTS, it was considered to be an overly cautious approach to include APS in section 4.4, noting it places an unnecessary burden on haematologists, i.e. a resource

cost to other patients. Therefore, the EWG agreed that the cautionary statement about use in individuals with anti-phospholipid syndrome (APS) that was previously included in the R174 PI, can be removed from section 4.4. because there are no confirmed cases of patients with a history of anti-phospholipid syndrome developing TTS following vaccination.

5.10 The EWG noted cerebral venous sinus thrombosis (CVST) is a far rarer condition and it would be practical to recommend a patient with a history of CVST seeks an alternative vaccine. The EWG noted that they would welcome confirmation from neurology experts on the CHM as to whether they agree with the EWG view that, on a precautionary basis, the text on administration of the vaccine in individuals with a past history of CVST included in the R174 PI, should be retained in section 4.4 of the GB SmPC.

5.11 The EWG agreed with the Agency's proposals to largely harmonise text in section 4.4.with the EU/NI SPC, but with a slight divergences in some areas: a) to include angioedema under the umbrella of hypersensitivity reactions, b) to reflect clinical parameters from cases of TTS rather than the average age at onset of TTS which was not reflective of UK experience of b) to give national advice on the healthcare pathway for patients with TTS and c) to include a statement about real-world efficacy data in elderly subjects.

5.12 The EWG heard that fertility and pregnancy information in the EU/NI SmPC is not yet furnished with information on animal studies; the proposal for the UK SPC is to include the outcomes of relevant animal studies in the fertility, pregnancy, and lactation (section 4.6).

5.13 The EWG heard all figures in the tabulated summary of ADRs in section 4.8 have been updated in accordance with the December safety analysis—EU/NI text has not yet been updated.

5.14 The EWG supported the proposal to include the recommendation on use of analgesic and/or anti-pyretic medicinal products if required to manage symptomatic relief from post vaccination ADRs that is already in the R174 product information, in the GB SmPC.

5.15 On rare and very rare ADRs, the EWG heard that defined frequency designations must be followed, which can lead to difficulties when trying to contextualise the likelihood of a particular ADR/s and to avoid what could be interpreted as contradictions between the ADR frequency range and the paragraphs of text in the SmPC and PIL. The EWG noted the need to reassure patients that these events are extremely rare by adding context to the frequency of events of thrombosis with thrombocytopenia syndrome in the PIL. The EWG acknowledged the potential limitations but asked the agency to aim to minimise any disconnect between the ADR table designated frequency and the contextualised information / retain as much clarity as possible.

5.16 The EWG heard the approximate frequency in figures of TTS proposed by the company has not been included in the EU/NI SmPC. The EWG noted it would be favourable to adopt the same position because the frequency is evolving, and the distribution of cases by age is also uneven.

5.17 The EWG noted there was a risk that 'influenza like illness' could be misconstrued by readers to be related to an active infection acquired through vaccination, which is obviously not the case. However, EWG concluded that the text should remain because this terminology has been present in the regulation 174 authorisation for many months without causing any notable issue. The EWG also considered there to be some added descriptive value in using the term to healthcare professionals.

5.18 The EWG noted text in section 4.8 on neuroinflammatory disorders should be retained because there is data emerging on GBS.

5.19 The EWG agreed that section 5.3 of the SmPC contained an appropriate level of detail was commensurate with the scope of studies submitted.

5.20 The EWG heard that both the former and proposed versions of the GB SmPC still refer to advice on 6 hour in use times (section 6.6), text in the proposed SmPC also includes a statement to align with the EU/NI SmPC that the product may be kept in-use at temperatures up to 30°C for a single period of up to 6 hours, but due to the inclusion of the word may, this does not contradict the UK recommendation for use up to 25°C.

5.21 The EWG supported the specific obligations for the CMA and the obligations to conduct post-authorisation measures.

6. Any Other Business

None.

7. Date and time of next meeting

The next Ad Hoc meeting on Thromboembolic events with COVID-19 Vaccines is scheduled to take place on **Tuesday 1st June at 3.15pm**.

The next scheduled meeting is to take place **on Friday 4th June** at **10.30am**.

The Meeting today started at 12:01 and ended at 14:14.

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).

Ms Hunneyball - Other relevant interest – writes articles published in the Chemist and Druggist magazine, a trade magazine for pharmacists, but receives no payment for these articles. The information referred to in the articles is in the public domain. Ms Hunneyball makes it clear that these are her personal views and reflections and references all sources of information used.

Professor Hyrich – NPNS - Professor Hyrich was co-I on an investigator-initiated research grant exploring predictors of outcome in rheumatoid arthritis. NPNS Pfizer- she is a Co-I on a grant exploring adherence to JAK inhibitors in rheumatoid arthritis. NPNS in Abbvie, Professor Hyrich gave some lectures at an education conference on effectiveness of treatment for rheumatoid arthritis.

Professor Lachmann – Other relevant interest as a volunteer participant in the Oxford vaccine study and no other involvement in the study.

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 Perrie - NPNS in Pfizer & AstraZeneca arising from a contract for a grant (March 2018), which includes contributions from these companies to the University of Strathclyde, Janssen in writing a grant for a PhD (now funded), GSK – arising from an EU grant to University of Strathclyde (Jan 2019-Dec 2019).

Professor Price - NPNS in GSK and AstraZeneca – which relates to donations provided by both companies to the British Toxicology Society (BTS) to support their Annual Congress and Education and Training of which Professor Price is currently President of the Society (2020-2022).

Dr Riordan - Other relevant interests - Participant in Oxford University's ChAdOx1 nCoV-19 clinical trial –received immunisation 27/8/2020. NPNS - Postgraduate External Examiner for Oxford University (Postgraduate Diploma in Paediatric Infectious Diseases).

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