Witness Name: Munir Pirmohamed
Statement No.: 01
Exhibits: MP/1 – MP/238
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UK COVID-19 INQUIRY – MODULE 4

FIRST WITNESS STATEMENT OF PROFESSOR SIR MUNIR PIRMOHAMED

I, **PROFESSOR SIR MUNIR PIRMOHAMED**, of the Institute of Systems, Molecular and Integrative Biology at the University of Liverpool, Liverpool, L69 3GL, will say as follows:

Introduction

1. I make this statement pursuant to the COVID-19 Inquiry's Module 4 Rule 9 request of 13 September 2023.

2. The matters I set out in this statement are within my own knowledge except where I state otherwise. If the facts I refer to are not within my own knowledge, I will provide the source for these facts. I also provide other sources of evidence where necessary. The contents of this statement are true to the best of my knowledge and belief.

3. I will cover the period of time between 30 January 2020 and 28 June 2022, as requested in the Rule 9 letter. However, where additional evidence has become available after 28 June 2022, and it is relevant to the issues discussed in my statement, I will provide the source for this evidence.

4. Between 30 January 2020 and 28 June 2022, I was a Chair or member of the following committees (relevant to this Rule 9 request): I make this statement as

Chair of the CHM but where indicated I provide my personal views and observations.

5. My relevant memberships are as follows:
    a. **Commission on Human Medicines**: Member between 30 January 2020 and 31 December 2020. I attended the CHM meeting on 21 January 2021 as an invited expert.
    b. **Commission on Human Medicines:** appointed Chair on 12 February 2021 for a 4-year term (I remain Chair of the Commission to the present day).
    c. **COVID-19 Vaccine Safety Surveillance Methodologies Expert Working Group**: Member from 28 May 2020 to 27 October 2020.
    d. **COVID-19 Vaccine Benefit Risk Expert Working Group:** Chair from 25 August 2020 to 5 May 2023.
    e. **COVID-19 Therapeutics Expert Working Group**: Member from 20 March 2020 to 5 May 2023.

Professional Background

6. I qualified in Medicine from the University of Liverpool in July 1985. Since then, I have undertaken clinical work in the NHS, and have been a Consultant Physician since 1996. I am listed on the General Medical Council Specialist Register for Clinical Pharmacology and Therapeutics (CPT), and General Internal Medicine (GIM), both from 19 July 1996 **(MP/01 – INQ000408395)**.

7. I am also a clinical academic researcher, and currently hold the David Weatherall Chair of Medicine at the University of Liverpool (since July 2013). I was awarded a Personal Chair in Clinical Pharmacology in 2001 and the NHS Chair of Pharmacogenetics in 2007.

8. My main area of research is in the safety of medicines, and factors that determine the variability in response to medicines that we use in everyday practice in the NHS. The aim of my research is to optimise the use of medicines in clinical practice, improving their effectiveness and minimising adverse drug reactions,

thereby improving the benefit-risk ratio of medicines. I am recognized as an international leader in this field, the aim of which is to personalise medicines, so that people get the right medicine for their disease, at the right dose and at the right time. I have published over 660 academic papers in this area, and my work has been cited more than 66,000 times by other researchers **(MP/02 – INQ000408396)**. I was awarded a Knights Bachelor in the Queen's Birthday Honours list in 2015 for services to Medicine.

9. My expertise in clinical pharmacology and drug safety was the main reason I first became a member of the Pharmacovigilance Expert Advisory Group, a sub-committee of the Commission on Human Medicines, in 1996. I subsequently became a member of the Commission on Human Medicines in 2005. I therefore have had over 25 years of experience in advising on the regulation of medicines.

Committee structure, terms of reference and people

Commission on Human Medicines (CHM)

10. The CHM was established in the Human Medicines Regulations 2012. Its predecessor, the Committee on Safety of Medicines, was established under section 2 of the Medicines Act 1968. Prior to that, the main advisory committee was the Committee on Safety of Drugs (also known as the Dunlop Committee) which was set up in 1963 in response to the Thalidomide tragedy. Thalidomide was prescribed during the late 1950s and early 1960s to relieve morning sickness, but it resulted in serious birth defects. In 1964, the Committee on Safety of Drugs established the first iteration of the Yellow Card Scheme to monitor the side effects of marketed medicines.

11. The members of the CHM are appointed by the Ministers, and the Ministers also appoint the Chair of the CHM. It functions as an independent advisory body. The CHM must give advice to the Ministers if they request it, or if the CHM considers it appropriate to give it, in relation to (a) the execution of duties imposed by the Human Medicines Regulations 2012 or the Medicines for Human Use (Clinical Trials) Regulations 2004 (the Clinical Trials Regulations); (b) the exercise of any

power conferred by Human Medicines Regulations 2012 or the Clinical Trials Regulations; and (c) medicinal products. The CHM gives advice with respect to the safety, quality and efficacy of medicinal products; and promotes the collection and investigation of information relating to adverse reactions, for the purposes of enabling such advice to be given. The CHM must also advise the licensing authority (MHRA) if (a) the licensing authority is required under Schedule 11 (advice and representations) of the Clinical Trials Regulations to consult the Commission about any matter arising under those provisions; or (b) the licensing authority consults the Commission about any matter arising under those provisions. I am not aware of any instances during the pandemic where the MHRA, as the licensing authority (LA), did not follow the CHM's advice. The CHM takes collective responsibility for the advice it gives to the licensing authority and the Secretary of State.

12. The CHM's role is purely advisory. The MHRA is the UK wide LA; however, in respect of Northern Ireland, the effect of the Northern Ireland Protocol is that medicines licensed by the European Medicines Agency (EMA) are automatically licenced for use in Northern Ireland but not the rest of the UK.

13. Advice from CHM can also be sought or given to the DHSC and its Ministers (directly) on issues relating to quality, safety and efficacy of medicinal products, but most of the CHM's work is with the MHRA. While the CHM is supported by a secretariat within the MHRA, importantly, the CHM remains an independent body. This secretariat has no influence on any of the advice given by members of the CHM or its expert groups. The agenda for the CHM meetings is drawn up by the secretariat in the MHRA in conjunction with the committee chair based on products where licensing decisions need to be made and where there are quality, safety or efficacy issues with existing products.

14. The CHM provides advice based on papers that are presented to the CHM itself, or its expert advisory groups, after discussion at committee meetings, or occasionally, through written comments. The advice is recorded in committee meeting minutes which are signed off by the Chair. The advice given by the CHM

is also not binding and ministers and/or the licencing authority are not bound to follow it.

15. Where representations are made to the CHM, they are for the purposes of obtaining advice on the quality, efficacy and/or safety of a medicinal product.

16. The CHM considers applications which lead to LA action if there are particular circumstances where the MHRA is of the view that already licenced products need specific consideration by CHM. By applications which lead to LA action, I am referring to: circumstances where the licence needs to be amended (for example, when another indication is added); where there are safety issues which may need amendment to license; strengthening of pharmacovigilance to protect public health; or licensing of generic compounds (established medicines). Specific consideration by the CHM for licensed products would be required for variations to the licence for safety issues, and for the licensing of generic medicines. The MHRA can bring forward any item to the CHM in relation to medicines as long as it is within the remit of CHM to evaluate the efficacy, safety and quality of medicinal products.

17. Commissioners are appraised annually by me (on the basis of criteria provided by DHSC), as Chair of the CHM, or by the Vice Chair. I also appraise the Vice Chair. I, as the Chair of the CHM, am annually appraised by the chair of the MHRA, who is accountable to ministers. However, the CHM is independent, as is its advice. I have been asked to explain the impact of the Chair of CHM being appraised by the Chair of the MHRA on CHM's independence from MHRA. I do not think the appraisal process affects the independence of the CHM for the following reasons: (a) satisfactory appraisal involves assessment of evidence of achievements of pre-defined objective goals; (b) individual CHM members do not report to the MHRA Chair; and (c) appraisal documentation is sent to DHSC for further scrutiny and challenge.

18. As an advisory body, the CHM is required to provide to Ministers a report each year about the performance of its functions, and the performance of the functions of any expert advisory group that it appoints, as per Regulation 12(2) of The Human Medicines Regulations 2012.

19. The independence and perceived independence of the CHM is necessary for both industry and public confidence in medicines regulation. There is a close working relationship between the CHM and the MHRA, but the CHM is independent of the MHRA, and prepares its advice at arm's length from the MHRA. Furthermore, the advice of the CHM is not binding on the MHRA. The Chair of the CHM does not take part in any MHRA committees, or its executive structure, and does not attend MHRA Board meetings. The CHM is allowed to debate all items and reach its advice without undue pressure from any other organisation including the MHRA, DHSC or Government.

20. Many experts in the field of medicines and medical devices have, or have had, connections with the pharmaceutical, medical device and/or biotechnology industry and other commercial organisations whose business may be considered relevant to their expertise and role in the committee but may also have an impact on perceptions of their impartiality. To build and maintain confidence that the advice on which decisions about the regulation of medicines and medical devices are based is impartial and to maintain confidence in the work of the committees, it is essential to have a robust policy to identify and effectively manage any potential conflicts in the interests of transparency and accountability.

21. Members of the CHM are subject to a strict Code of Practice **(MP/03 – INQ000409496)** which sets out the rules and process to be followed for identifying and declaring interests which are relevant to the work of the commission. For the purposes of the Code of Practice, interests are divided into personal and non-personal interests and 'other relevant' interests. The types of interest that must be declared are an individual's own financial or other interests in any relevant industry for that committee (examples are set out in the Code of Practice, along with definitions of each interest); these may be:
    a. Personal or non-personal;
    b. Specific or non-specific to the product under discussion;
    c. Financial interests of immediate family in the relevant industry, or;
    d. Any other matter that could affect impartiality, or that could reasonably be perceived as affecting impartiality.

22. The Chair and members are required to make a full declaration of interests when applying for an appointment and to update that declaration annually. All Commissioners' interests are published in the Annual Report **(MP/04 – INQ000502034)**. They are also required to inform the Secretariat and provide an updated declaration promptly as and when there are any changes or updates to their interests. The Chair and members are also required to declare relevant interests prior to and at meetings, whether or not those interests have been previously declared. Invited experts, patient experts and co-opted members also make a declaration on the item under consideration when invited to contribute advice or participate at a CHM meeting. Observers also make a declaration on the items under consideration when invited to attend a meeting.

23. I have been asked to explain how the CHM determines whether or not a declared interest constitutes a conflict of interest sufficient to require action, such as (for example) recusal from involvement in a particular issue. As per the Code of Practice, no member of CHM is allowed to hold *personal* interests in the pharmaceutical industry. Personal interests are financial interests that involve a payment, in any form, to an individual personally from a relevant industry whose business maybe directly affected by the advice of the committee. These can be specific or non-specific, depending on if the payment relates to a product that is under consideration. For the EWGs or EAGs, personal interests can be held by members, and in such circumstances, they are asked to leave the room while that item is being discussed. A Commissioner who has a specific interest in a particular item will not be able to take an active part in the discussion of that item, but can stay in the room, and the Chair is able to ask him/her specific questions. The vast majority of interests declared by Commissioners are categorised as "non-personal, non-specific". For the COVID-19 vaccines and therapeutics considered by the CHM during the pandemic, all interests, which were again largely non-personal and non-specific, were declared for every meeting and have been published in the annual report.

24. The Code of Practice, which was last updated on 8 September 2022, works well in respect of declaration of conflicts of interest, and ensures the independence and

impartiality of the CHM. If membership of the CHM was restricted to individuals who did not have any interests or connections with Industry, we would have difficulty in recruiting to the Commission, and it is unlikely that it would be constituted by the best experts in the field. To note, all Commissioners are expected to uphold the Seven Principles of Public Life.

25. The terms of reference of the CHM are as follows:
    a. to advise the Health Ministers and the Licensing Authority (LA) on matters relating to human medicinal products including giving advice on the safety, quality and efficacy of human medicinal products where either the Commission thinks it appropriate or where it is asked to do so.
    b. to consider those applications that lead to LA action as appropriate (e.g., where the LA has a statutory duty to refer or chooses to do so);
    c. to consider representations made (either in writing or at a hearing) by an applicant or by a licence or marketing authorisation holder in certain circumstances;
    d. to promote the collection and investigation of information about adverse reactions to human medicines so advice can be given.
    e. The Commission is similarly involved in respect of medicinal products to which relevant EC legislation applies.

26. The members of the CHM are appointed by the ministers as per the New Code of Practice for ministerial appointments **(MP/05 – INQ000409467)**. The Chair and Commissioners are appointed in accordance with the Code of Practice for Ministerial Appointments to public bodies, issued by the Commissioner for Public appointments. The ultimate responsibility for public appointments lies with Ministers as appointing authorities, who are accountable for their decisions. Where these appointments fall within the commissioners' remit, ministers may be involved in the public appointments processes, provided that the procedures set out in this code are followed.

27. The **current membership** of the Commission on Human Medicines is as follows:

Chair

Professor Sir Munir Pirmohamed MB ChB (Hons) PhD FRCP FRCP (Edin) FBPhS, FFPM (Hon) FMedSci

David Weatherall Chair of Medicine, University of Liverpool, NHS Chair of Pharmacogenetics, Director of the Wolfson Centre for Personalised Medicine, Director of the Centre for Drug Safety Science

Members

Professor Amanda Adler MD PhD FRCP
Professor of Diabetic Medicine and Health Policy, University of Oxford **(started: 01/05/2021)**

Professor Jamie Coleman MD MA (Med Ed) FRCP FBPhS
Consultant Physician, University Hospitals Birmingham NHS Foundation Trust and Honorary Professor in Clinical Pharmacology and Medical Education, University of Birmingham **(started 01/09/2018)**

Mrs Julia Cons
Lay Representative **(started 01/07/2022)**

Mr David Crundwell
Lay Representative **(started 12/06/2023)**

Professor Steven Cunningham MBChB PhD FRCPCH
Professor of Paediatric Respiratory Medicine, University of Edinburgh and Honorary Consultant, Royal Hospital for Children and Young People, NHS Lothian, Edinburgh **(started 01/05/2021)**

Professor Paul I Dargan MB BS FRCP Edin FACMT FRCP ERT FAACT FEAPCCT FBPhS MAE
Consultant Physician and Professor of Clinical Toxicology, Guy's and St Thomas' NHS Foundation Trust, London
Professor of Clinical Toxicology, King's College London **(started 01/07/2022)**

Professor David Dockrell MB BCh MD FRCPI FRCP (Glas) FACP
Professor of Infection Medicine, University of Edinburgh **(started 01/07/2022)**

Dr Jamie Fraser BSc (Hons) MBChB MRCGP
GP Partner, Southside Surgery, Inverness **(started 01/11/2012)**

Professor David Hunt MB BChir FRCP PhD
Consultant Neurologist, NHS Lothian
Professor of Neuroinflammatory Medicine, University of Edinburgh **(started 01/07/2022)**

Professor David Moore MBChB MD MSc DTM&H
Professor of Infectious Diseases and Tropical Medicine, London School of Hygiene and Tropical Medicine and Consultant in Infectious Diseases and Tropical Medicine, Hospital for Tropical Diseases, University College London Hospital **(started 15/12/2022)**

Dr Gerri Mortimore PhD; MSc Advanced Practice; PgCert (IPPE); Ba(Hons) Health Studies; iLM. RGN; NMP; FHEA
Associate Professor in Advanced Clinical Practice; NICE Nurse Expert Advisor **(started 01/07/2022)**

Professor Sandosh Padmanabhan MBBS MD PhD FRCP(Glasg) FRCP(Edin) FBPhS FBIHS
Professor of Cardiovascular Genomics and Therapeutics, University of Glasgow **(started 01/05/2021)**

Professor Poulam Patel PhD, MBBS, FRCP
Professor of Clinical Oncology, University of Nottingham **(started 06/07/2020)**

Professor Yvonne Perrie BSc Hons MRPharmS FAPS FSB PhD

Chair in Drug Delivery, Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, Scotland **(started 01/05/2021)**

Professor Rui Providencia MD PhD
Institute of Health Informatics Research, University College London Consultant Cardiologist & Cardiac Electrophysiologist, Barts Health NHS Trust (**started 01/07/2022)**

Dr Vanessa Raymont MBChB MSc MRCPsych
Senior Clinical Researcher, University of Oxford and Honorary Consultant Psychiatrist, Oxford Health NHS Foundation Trust **(started 01/07/2022)**

Professor Marc Turner MB ChB PhD MBA FRCP FRCPath FRSE
Professor of Cellular Therapy; Director Scottish National Blood Transfusion Service (SNBTS) (**Started 06/07/2020)**

Professor Heather M Wallace PhD FRCPath FRSC FRSB FBTS FBPhS ERT
Professor Emerita of Biochemical Pharmacology and Toxicology, University of Aberdeen **(Started 01/09/2022)**

Professor Christopher Weir BSc (Hons) PhD MSc FRSS C.Stat
Personal Chair in Medical Statistics and Clinical Trials, Usher Institute, University of Edinburgh (**Started 06/07/2020)**

Professor Anthony Williams BSc MSc MRCP, FRCPath, PhD
Professor of Translational Medicine and Honorary Consultant in Clinical Immunology and Allergy, University of Southampton and University Hospital Southampton NHS Trust **(Started 01/07/2022)**

Dr Martin Wilson MB ChB, MPhil (Glasgow), FRCP(Edin)
Consultant Physician in Care of the Elderly, Raigmore Hospital, Inverness **(Started 28/03/2016)**

28. **Commissioners whose term ended during the period** from 30 January 2020 and 28 June 2022, were as follows:

Mrs Helen M Ward MSc, BSc (Hons), Senior Fellow HEA, RGN, RCN Nurse Practitioner, PGCEA, PG Cert NMP, Queens Nurse, Advanced Nurse Practitioner (**Term ended 27/03/2020)**

Professor Sarah Meredith Professor of Clinical Trials, MRC Clinical Trials Unit at UCL, Institute of Clinical Trials and Methodology, University College London (**Term ended 14/12/2020)**

Professor Sir Munir Pirmohamed MB ChB (Hons) PhD FRCP FRCP (Edin) FBPhS, FFPM (Hon) FMedSci, David Weatherall Chair of Medicine, University of Liverpool, NHS Chair of Pharmacogenetics, Director of the Wolfson Centre for Personalised Medicine, Director of the Centre for Drug Safety Science (**Term as Member ended 31/12/2020)**

Professor Stuart Ralston MB ChB MD FRCP FMedSci FRSE FFPM (Hon)
Professor of Rheumatology, University of Edinburgh (**Term as Chair ended 11/02/2021).**

Professor Jonathan S Friedland MA PhD FRCP FRCPE FRCPI FESCMID FMedSci, Deputy Principal, St. George's, University of London (**Term ended 31/03/2022)**

Professor Malcolm R Macleod BSc MBChB MRCP PhD FRCP (Edin)
Professor of Neurology and Translational Neurosciences, University of Edinburgh and Honorary Consultant Neurologist, NHS Forth Valley (**Term ended 31/03/2022).**

Dr Rebecca Mann BMBS FRCPCH

Consultant Paediatrician, Taunton and Somerset NHS Foundation Trust (**Term ended 31/03/2022)**

Dr Siraj Misbah MBBS (Hons) MSc FRCP FRCPath
Consultant Clinical Immunologist, Lead for Clinical Immunology, Oxford University Hospitals (**Term ended 30/06/2022)**

Professor Richard J C Gilson MD FRCP
Professor of Sexual Health & HIV Medicine, Director of the UCL Centre for Clinical Research in Infection & Sexual Health & Deputy Director of the UCL Institute for Global Health (**Term ended 14/12/2022)**

29. The CHM has the ability to create sub-groups (sub-committees) which can evaluate relevant areas in more depth, and report back to the CHM. In order to prepare for the development of new or repurposed therapeutics, and new vaccines, the CHM set up the following expert working groups (the membership of these groups is shown sections 3.6, 3.7 and 3.8):

    a. **Covid-19 Therapeutics Expert Working Group:**
    Established: 20/03/2020
    Disestablished: 05/05/2023

    b. **Covid-19 Vaccine Safety Surveillance Methodologies Expert Working Group:**
    Established: 28/05/2020
    Disestablished: 27/10/2020

    c. **Covid-19 Vaccine Benefit Risk Expert Working Group:**
    Established: 25/08/2020
    Disestablished: 05/05/2023

30. The **Covid-19 Therapeutics Expert Working Group** was established on 20/03/2020. Its remit was as follows:

a. To advise on the safety and efficacy of candidate anti-viral agents, immune-based therapies and repurposed agents for the treatment and prevention of COVID-19 infection, based on available scientific data.
b. To review the robustness of the evidence of supporting agents used for the treatment of COVID-19 complications, including agents based on putative mechanisms, as currently available and based on emerging data.
c. To advise on strategies and study designs to collect efficacy and safety data including novel trial designs.
d. To advise on measures to minimise risks and optimise the benefit-risk balance of anti-viral agents, supportive therapies (e.g., corticosteroids, NSAIDS, chloroquine, immune modulators, etc) proposed for the treatment of COVID-19 infection and its complications.
e. To advise on the benefits and risk of concomitant medications (e.g., ACE inhibitors/ AT-II blockers or immunosuppressants).
f. To advise on measures to monitor safety and effectiveness of risk minimisation measures relating to these medicinal products.
g. To advise the Commission on Human Medicines.

31. Its membership included a Chair who was a member of the CHM (to facilitate reporting back to CHM), while individuals with the required expertise were identified by the CHM and the MHRA, and invited to become members.

Chair

Professor Jonathan S Friedland MA PhD FRCP FRCPE FRCPI FESCMID FMedSci
Deputy Principal, St. George's, University of London

Members

Professor Kenneth Baillie BSc(Hons) MBChB PhD FRCA FRCP FFICM
Professor of Experimental Medicine, Roslin Institute, University of Edinburgh

Ms Susan Bradford Lay Representative

Professor David Dockrell MB BCh MD FRCPI FRCP (Glas) FACP
Professor of Infection Medicine, University of Edinburgh

Professor Richard J C Gilson MD FRCP
Professor of Sexual Health & HIV Medicine, Director of the UCL Centre for Clinical Research in Infection & Sexual Health & Deputy Director of the UCL Institute for Global Health

Sir Michael Jacobs MA PhD MB BS FRCP FRCP Edin DTM&H
Consultant in Infectious Diseases, Royal Free London NHS Foundation Trust; Hon. Senior Lecturer, University College London and Liverpool School of Tropical Medicine

Professor Nigel Klein BSc MBBS MRCP PhD FRCPCH
Consultant, Great Ormond Street Hospital for Children NHS Trust; Professor of Infectious Diseases and Microbiology, Institute of Child Health, UCL

Dr Siraj Misbah MBBS (Hons) MSc FRCP FRCPath
Consultant Clinical Immunologist, Lead for Clinical Immunology, Oxford University Hospitals

Professor Deenan Pillay
Professor of Virology, UCL Pro-Vice-Provost International (**Stepped down 09/2022).**

Professor Sir Munir Pirmohamed MB ChB (Hons) PhD FRCP FRCP (Edin) FBPhS, FFPM (Hon) FMedSci
David Weatherall Chair of Medicine, University of Liverpool, NHS Chair of Pharmacogenetics, Director of the Wolfson Centre for Personalised Medicine, Director of the Centre for Drug Safety Science

Professor Shirley Price MSc, PhD, FBTS, FRSB, ERT, FHEA, FRSC, MBPharmacolSoc
Emerita Professor of Toxicology, University of Surrey
Visiting Professor of Toxicology, University of Hertfordshire

32. The **Covid-19 Vaccine Safety Surveillance Methodologies Expert Working Group** was established on 28/05/2020. Its remit was as follows:
    a. **Pre-deployment phase:**
        i. To landscape the different healthcare datasets that are currently available in the UK to capture near real-time information on COVID-19 vaccine exposure and study endpoints relevant to vaccine safety and potential for disease enhancement (and effectiveness). This should take into account a range of potential scenarios for vaccine deployment (i.e. the point of administration and any prioritised/targeted immunisation), and should advise on the need for further data capture and linkage.
        ii. To advise on the most suitable study endpoints and design(s) to monitor COVID-19 vaccine safety, and potential for disease enhancement (and effectiveness).
        iii. To support engagement with UK institutions who may be planning/in a position to conduct COVID-19 vaccine safety studies. This is to encourage and facilitate studies that are complementary in terms of objective and design, to avoid duplication and to accommodate a suitable range of study endpoints and scenarios for vaccine deployment.
        iv. To advise on proposals for enhanced passive surveillance.
        v. To advise on communications in support of the pharmacovigilance strategy.
    b. **Post-deployment phase:**
        i. To advise on the emerging evidence from all data sources on the risks and benefits of vaccine(s) during the course of any COVID-19 immunisation campaign in the UK. This includes measures to

minimise risks, and optimise the benefit-risk balance for individual vaccines, such as any new precautions or restrictions on use.

i. To advise on any communications to health professionals and the public.

ii. To advise on measures to monitor impact/effectiveness of any additional risk minimisation.

33. Its membership included a Chair who was a member of the CHM (to facilitate reporting back to CHM), while individuals with the required expertise were identified by the CHM and the MHRA, and invited to become members.

Chair

Dr Siraj Misbah MBBS (Hons) MSc FRCP FRCPath Consultant Clinical Immunologist, Lead for Clinical Immunology, Oxford University Hospitals & Chair of the Clinical Trials, Biologicals & Vaccines Expert Advisory Group (CTBVEAG) & Member of the Commission on Human Medicines (CHM)

Members

Professor Ian J Douglas BSc MSc PhD Senior Lecturer in Pharmacoepidemiology, London School of Hygiene & Tropical Medicine & Member of the Pharmacovigilance Expert Advisory Group (PEAG)

Professor Jonathan S Friedland MA PhD FRCP FRCPE FRCPI FESCMID FMedSci Deputy Principal, St. George's, University of London & Chair of the Infections Expert Advisory Group (IEAG) & Member of the Commission on Human Medicines (CHM)

Sir Michael Jacobs MA PhD MB BS FRCP FRCP Edin DTM&H Clinical Director of Infection, Royal Free London NHS Foundation Trust & Hon. Senior Lecturer, Liverpool School of Tropical Medicine

Professor Simon De Lusignan Professor of Primary Care and Clinical Informatics, University of Oxford

Professor Rupert Payne MB ChB PhD MRCGP FRCPE FBPhS FHEA Professor of Primary Care & Clinical Pharmacology, University of Exeter. Member of the Pharmacovigilance Expert Advisory Group (PEAG)

Professor Sir Munir Pirmohamed MB ChB (Hons) PhD FRCP FRCP (Edin) FBPhS, FFPM (Hon) FMedSci David Weatherall Chair of Medicine, University of Liverpool, NHS Chair of Pharmacogenetics, Director of the Wolfson Centre for Personalised Medicine, Director of the Centre for Drug Safety Science

Professor Siobhan Quenby MBBS BSc MD FRCOG Professor of Obstetrics, Warwick University & Member of the Medicines for Women's Health Expert Advisory Group (MWHEAG)

Professor Chris Robertson PhD MSc BSc Professor of Public Health Epidemiology, University of Strathclyde

Professor Calum Semple PhD FRCPCH FRCPE FHEA Professor of Outbreak Medicine University of Liverpool

34. The **Covid-19 Vaccine Benefit Risk Expert Working Group** was established on 25/08/2020. Its remit was as follows:
    a. To advise CHM on the quality, safety and efficacy of COVID-19 vaccines and on the balance of benefit and risks prior to authorisation.
    b. To coordinate safety evaluation with the Clinical Trials, Biologicals and Vaccines Expert Advisory Group.
    c. To report its conclusions and recommendations to the Commission on Human Medicines.
    d. To advise on the emerging evidence from all data sources on the risks and benefits of vaccine(s) during the course of any COVID-19 immunisation campaign in the UK. This includes measures to minimise risks, and

optimise the benefit-risk balance for individual vaccines, such as any new precautions or restrictions on use.

e. To advise on any communications to health professionals and the public.
f. To advise on measures to monitor impact/effectiveness of any additional risk minimisation.

35. Its membership included a Chair who was a member of the CHM (to facilitate reporting back to CHM), while individuals with the required expertise were identified by the CHM and the MHRA, and invited to become members.

Chair

Professor Sir Munir Pirmohamed MB ChB (Hons) PhD FRCP FRCP (Edin) FBPhS, FFPM (Hon) FMedSci
David Weatherall Chair of Medicine, University of Liverpool, NHS Chair of Pharmacogenetics, Director of the Wolfson Centre for Personalised Medicine, Director of the Centre for Drug Safety Science.

Members

Professor Judith Breuer MD FRCPath FmedSci
Professor of Virology, University College London (UCL), Division of Infection and Immunity, London

Professor Gordon Dougan FRS
Department of Medicine, Cambridge Infectious Diseases, University of Cambridge

Professor Ian J Douglas BSc MSc PhD
Professor of Pharmacoepidemiology, London School of Hygiene & Tropical Medicine (**Stepped down on 17/11/2020 because of workload issues)**

Mr V'Iain G Fenton-May BPharm MIPharm FRPharmS

Pharmaceutical Microbiologist

Professor Neil French MB ChB FRCP PhD
Head Department of Clinical Infection Microbiology and Immunology, Chair of Infectious Diseases & Global Health, Hon Consultant Infectious Diseases, Royal Liverpool & Broadgreen University Hospitals Trust

Professor David Goldblatt MB ChB FRCPCH FRCP PhD
Professor of Vaccinology and Immunology, Consultant in Paediatric Immunology, NIHR Senior Investigator, Great Ormond Street Hospital & University College London

Ms Susan Hunneyball BSc(Hons)
Lay Member, Member of the Pharmacovigilance Expert Advisory Group (PEAG) and Advisory Board on the Registration of Homeopathic Products (ABRHP)

Professor Kimme Hyrich MD PhD FRCPC Professor of Epidemiology and Honorary Consultant in Rheumatology, Centre for Musculoskeletal Research, Faculty of Biology Medicine and Health, University of Manchester and Kellgren Centre for Rheumatology, Manchester University NHS Foundation Trust

Sir Michael Jacobs MA PhD MB BS FRCP FRCP Edin DTM&H
Consultant in Infectious Diseases, Royal Free London NHS Foundation Trust; Hon. Senior Lecturer, University College London and Liverpool School of Tropical Medicine **(stepped down on 25/07/2022 because had taken on a new role)**

Professor Helen J Lachmann MA MB BChir MD FRCP FRCPath
Professor of Medicine & Honorary Consultant Nephrologist

Clinical Director UCL Division of Medicine & Clinical Lead for National Amyloidosis Centre, University College London & Royal Free Hospital London NHS Foundation Trust

Professor Paul J Lehner PhD FRCP FMedSci FRS
Professor of Immunology and Medicine, Wellcome Trust Principal Research Fellow. Honorary Consultant Infectious Diseases, Cambridge Institute of Therapeutic Immunology and Infectious Disease (CITIID), Jeffrey Cheah Biomedical Centre Cambridge Biomedical Campus

Mr Robert Lowe BPharm FRPharmS -
Practising Hospital Pharmacist, Specialist Pharmacy Services - East of England

Dr Siraj Misbah MBBS (Hons) MSc FRCP FRCPath
Consultant Clinical Immunologist, Lead for Clinical Immunology, Oxford University Hospitals

Professor B Kevin Park BSc PhD FMedSci HonFRCP FBTS HonFBPhs
Professor of Pharmacology, University of Liverpool (**Retired on 18/03/2021)**

Professor Yvonne Perrie BSc Hons MRPharmS FAPS FSB PhD
Chair in Drug Delivery, Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, Scotland

Professor Shirley Price MSc, PhD, FBTS, FRSB, ERT, FHEA, FRSC, MBPharmacolSoc
Emerita Professor of Toxicology, University of Surrey, Visiting Professor of Toxicology, University of Hertfordshire

Dr Andrew Riordan MD FRCPCH DTM&H
Consultant in Paediatric Infectious Diseases and Immunology, Honorary Clinical Lecturer, University of Liverpool, Alder Hey Children's NHS Foundation Trust, Liverpool

Professor Chris Robertson PhD MSc BSc
Professor of Public Health Epidemiology, University of Strathclyde

Professor Pallav Shah MD, MB BS, FERS, FRCP Consultant Physician, Royal Brompton Hospital and Chelsea & Westminster Hospital, Professor of Respiratory Medicine, Imperial College (**Stepped down 09/04/2021 as expertise in area not required or covered)**

Professor Tom Solomon FRCP PhD Chair, Neurological Science, Director, NIHR Health Protection Research Unit in Emerging and Zoonotic Infections, Associate Pro-Vice-Chancellor for Infrastructure and Environment, Faculty of Health and Life Sciences, University of Liverpool & Honorary Consultant Neurologist, Walton Centre NHS Foundation Trust **(stepped down on 17/05/2022 because of workload issues)**

Professor Kevin M G Taylor BPharm PhD FRPharmS
Chair of the British Pharmacopoeia Commission and Emeritus Professor of Clinical Pharmaceutics, UCL School of Pharmacy, London

Professor Kevin M G Taylor BPharm PhD FRPharmS
Emeritus Professor of Clinical Pharmaceutics, UCL School of Pharmacy, London

Dr Robin Thorpe BSc PhD FRCPath

Retired, Head, Division of Biotherapeutics, National Institute for Biological Standards and Control (NIBSC) & Member of the Clinical Trials, Biologicals & Vaccines Expert Advisory Group (CTBVEAG)

Professor Marc Turner MB ChB PhD MBA FRCP FRCPath FRSE
Professor of Cellular Therapy; Director Scottish National Blood Transfusion Service (SNBTS)

Professor Susannah E Walsh PhD BSc MBA
Head of School, Professor of Pharmaceutical Microbiology, Pharmacy and Life Sciences, Robert Gordon University

Mrs Madeleine Wang BA (Hons)
Lay Member & Patient Advocate

Professor Christopher Weir BSc MSc PhD FRSS Cstat Professor of Medical Statistics & Clinical Trials, Edinburgh Clinical Trials Unit, Usher Institute, University of Edinburgh & Member of Commission on Human Medicines (CHM)

36. In addition to the above expert working groups which were set up because of the pandemic, the CHM also has a number of pre-existing Expert Advisory Groups (detailed on the GOV.UK website **(MP/06 – INQ000408397**) which can provide advice to the CHM. For example, the Infection Expert Advisory Group was frequently consulted on various issues over the pandemic, but mostly in relation to clinical trial study protocols for COVID therapeutics and vaccines.

37. The Clinical Trials, Biologicals and Vaccines Expert Advisory Group was also important in providing advice on clinical trials and vaccines over the pandemic. Its remit is as follows:
    a. first time in human (FTIM) studies with new compounds acting (directly or indirectly) via the immune system with a novel target or a novel mechanism of action or having a secondary potential effect on the immune system via a mechanism of action which currently is not well characterised.

b. FTIM studies with novel compounds acting via a possible or likely species-specific mechanism.

c. Any FTIM studies which are otherwise seen as requiring expert advice.

d. Other clinical trials involving classes of compound where MHRA may wish to seek external expert advice or CHM may wish to have oversight.

e. Whether a product's mechanism of action is novel and comes within the scope of the EAG.

f. Pre-meeting scientific advice documentation for within scope compounds.

b. Other clinical trials where MHRA may wish to seek advice or where there is a difficult risk benefit balance.

c. Other clinical trials involving products where a new class safety issue has been identified.

d. The quality, safety and efficacy of medicinal products of biological or biotechnological origin including vaccines which are the subject of marketing authorisation applications; and to advise on such other matters as are referred to it.

38. Its membership included a Chair who was a member of the CHM (to facilitate reporting back to CHM), while individuals with the required expertise were identified by the CHM and the MHRA, and invited to become members.

Chair

Professor Marc Turner MB ChB PhD MBA FRCP FRCPath FRSE
Professor of Cellular Therapy; Director Scottish National Blood Transfusion Service (SNBTS)

Members

Professor Farzin Farzaneh DPhil FRCPath FRSB
Professor of Molecular Medicine, King's College London
Honorary Consultant in Specialist Medicine, King's College Hospital NHS Trust

Professor Chris Goldring BSc PhD PGCert FBPhS,
Professor of Pharmacology, Department of Pharmacology and Therapeutics, The University of Liverpool.

Professor Andrew Pollard PhD FRCPCH FMedSci
Chair of the Joint Committee on Vaccination and Immunisation; Professor of Paediatric Infection and Immunity, University of Oxford

Dr Kirstie Shearman LLB MA PhD **(Lay member)**
Policy Manager, Health Research Authority

Dr Robin Thorpe PhD FRCPath
Retired, Head, Division of Biotherapeutics, National Institute for Biological Standards and Control (NIBSC)

Professor Christina Yap MSci PhD Cstat,
Professor of Clinical Trials Biostatistics, Team Leader in Early Phase and Adaptive Trials Team, ICR-Clinical Trials and Statistics Unit, The Institute of Cancer Research

39. There were several members whose term ended during the period between 30 January 2020 and 28 June 2022. These members were:

Professor B Kevin Park BSc PhD FMedSci HonFRCP FBTS HonFBPhs
Professor of Pharmacology, University of Liverpool (**Retired on 18/05/2020)**

Professor Christopher Weir BSc (Hons) PhD MSc FRSS C.Stat
Personal Chair in Medical Statistics and Clinical Trials, Usher Institute, University of Edinburgh (**Term ended 08/12/2020)**

Professor Helen J Lachmann MD FRCP FRCPath
Professor of Medicine & Honorary Consultant Nephrologist

Clinical Lead National Amyloidosis Centre
Clinical Service Lead Immunity & Rare Diseases Division
University College London & Royal Free Hospital London NHS Foundation Trust (**Term ended 11/11/2021)**

Mrs Madeleine Wang BA (Hons), Lay Representative. Patient Advocate (**Term ended 11/11/2021)**

Dr Siraj Misbah MBBS (Hons) MSc FRCP FRCPath
Consultant Clinical Immunologist, Lead for Clinical Immunology, Oxford University Hospitals (**Term ended 30/06/2022)**

40. Given the structure of CHM and its sub-committees, and the wide range of expertise available, CHM is able to discharge its responsibilities in providing independent advice to ministers and the licensing authority on matters relating to the safety, efficacy and quality of medicinal products. The CHM can also request expert witnesses to provide evidence on specific issues.

41. During the pandemic, the CHM and its subcommittees interacted with different individuals and organisations to ensure we (a) had access to all the relevant information; (b) were aware of policy decisions which were being undertaken and how regulatory advice may impact on those decisions; and (c) were able to discuss with and question researchers who were undertaking research on different aspects of the COVID-19 pandemic. The list of invited experts and observers who were invited to the committees is given in appendix 1. However, it is important to note that these individuals were not involved in the decisions taken by CHM or its expert working groups.

42. Observers from NICE, DHSC, Public Health England and NHS England and NHS Improvement attended the COVID-19 therapeutics expert working group. Observers from NHS England, UK HSA, Public Health Scotland, Public Health Wales and Health and Social Care Northern Ireland attended the Covid-19 Vaccine Benefit Risk Expert Working Group.

43. The CHM advice is relevant to the whole of the UK and does not differ between England and the devolved nations, except when medicinal products have already been approved by the European Medicines Agency, when the Northern Ireland protocol comes into play with respect to the licence in Northern Ireland which may differ compared to the licence in Great Britain.

44. All members of the CHM and its expert working groups contributed equally to the deliberations of the relevant committees, and the decisions that were taken. We acted according to the processes set out in the Human Medicines Regulations 2012 with all the work being undertaken in committee.

Therapeutic agents

45. The therapeutic issues which arose during the pandemic, and which were considered by the CHM and its expert working groups, can be categorised into 3 areas, each of which will be discussed separately:

    a. Concerns about pre-existing drugs being taken by people and how this may impact on the severity of COVID-19 disease.
    b. Drugs which were repurposed for the treatment of COVID-19.
    c. New therapeutics which were developed during the pandemic to treat COVID-19.

Pre-existing drugs

46. **Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers**: These were covered by the COVID Therapeutics EWG on 20 March 2020 **(MP/07 – INQ000409475)**, 17 April 2020 **(MP/08 – INQ000409547)** and 12 June 2020 **(MP/09 – INQ000409470)**, and by the CHM on 20 March 2020 **(MP/10 – INQ000409483)**. These drugs are widely used for cardiovascular disease including hypertension and heart failure. Because the SARS-CoV-2 virus was shown to bind to the ACE2 receptor to get into the cell, some authors had suggested that these drugs which act via the same receptor systems may be harmful to patients, while conversely, others had suggested that the drugs may be

beneficial. The situation was further complicated by the fact that a prominent academic paper published in the New England Journal of Medicine **(MP/11 – INQ000408398)** was subsequently withdrawn because the authenticity of the data included in the studies could not be verified. The EWG and the CHM reviewed all the evidence available at the time and concluded that (a) the studies were largely observational, of varying quality, had many confounding factors and often reported conflicting findings; and (b) the biological rationale for either a beneficial or adverse effect was theoretical with limited supportive experimental data. The EWG and CHM therefore supported the advice from national **(MP/12 – INQ000408399)** and international **(MP/13 – INQ000408400)** bodies that these drugs should be continued for the treatment of cardiovascular diseases. Subsequent studies have shown that ACE-inhibitors and angiotensin receptor blockers had neither a beneficial nor adverse effect on COVID-19 infection **(MP/14 – INQ000408381)**.

47. **Non-steroidal anti-inflammatory drugs (NSAIDs):** These are drugs that are widely used for pain relief. Ibuprofen is available over the counter. Early in the pandemic, there were concerns in the media that the use of NSAIDs might increase the risk of severe COVID-19. This was based on the premise that NSAIDs increase the levels of the ACE2 receptor which is used by the virus to gain entry to the cell and may potentially inhibit an immune response. This was reviewed by the COVID-19 Therapeutics EWG **(MP/07 – INQ000409475)** and CHM **(MP/10 – INQ000409483)** on 20 March 2020. The conclusion was that there was insufficient evidence or theoretical basis currently to recommend discontinuation of NSAIDs in people requiring prescriptions for comorbid conditions, but who might develop COVID-19. This was confirmed by a rapid evidence summary by NICE on 14 April 2020 **(MP/15 – INQ000408401)**. A subsequent analysis from the UK ISARIC (International Severe Acute Respiratory and emerging Infection Consortium) study showed that NSAID use did not worsen outcomes in patients with COVID-19 **(MP/16 – INQ000231497)**.

Drugs repurposed for the treatment of COVID-19

48. At the beginning of the pandemic, as COVID-19 was a new disease, there were no treatments available. Understandably, there was intense activity to identify

currently existing drugs which could be re-purposed for either the treatment of COVID-19, or as prophylactic treatments to prevent COVID-19. Unfortunately, much of the science conducted to identify these treatments was of poor quality and often irreproducible. It was published either in pre-print servers or in press releases (without peer review), which often led to a media frenzy, and in some cases, political polarisation (which occurred particularly outside the UK). Given the fear of catching COVID-19, there was sometimes a rush by members of the public to obtain these medicines, often without prescription, sometimes via the internet, which led to shortages of these medicines for diseases which they were already licensed for. Given this frenzy, it was therefore important for the CHM and its working groups to objectively evaluate the evidence for the benefits and risks of using these medicines in COVID-19.

49. **Hydroxychloroquine**: The use of this drug was reviewed by the COVID-19 Therapeutics EWG on 20 March 2020 **(MP/07 – INQ000409475)**, 3 April 2020 **(MP/17 – INQ000409546)**, 24 April 2020 **(MP/18 – INQ000400278)**, 12 June 2020 **(MP/9 – INQ000409470)**, 26 June 2020 **(MP/19 – INQ000283540)**, 7 August 2020 **(MP/20 – INQ000409473)**, and 16 October 2020 **(MP/21 – INQ000409549)**. It was also assessed by the CHM on 20 March 2020 **(MP/22 – INQ000409468)**, 24 April 2020 **(MP/23 – INQ000409469)**, 21 May 2020 **(MP/24 – INQ000409486)**, 1 June 2020 **(MP/25 – INQ000400206)**, 5 June 2020 **(MP/26 – INQ000400207)**, 18 June 2020 **(MP/27 – INQ000409487)**, 26 June 2020 **(MP/28 – INQ000409471)** and 21 October 2020 **(MP/29 – INQ000409474)**. Hydroxychloroquine, and the related drug chloroquine, were shown to have activity against the virus in *in vitro* studies, but there were no animal or human studies early in the pandemic. It was therefore important that CHM and its EWG were able to review new data as it was being published, as well as have sight of clinical trials which were being conducted.

50. One of the early studies reviewed by the EWG and CHM (published online on 20 March 2020) was a trial in 20 patients from France which showed that hydroxychloroquine treatment together with an antibiotic called azithromycin, was associated with an improvement of COVID-19 parameters **(MP/30 – INQ000408441)**. However, this was a poorly conducted study with a small sample

size, and was heavily criticised **(MP/31 – INQ000409472)**, but nevertheless was used as evidence for the efficacy of hydroxychloroquine.

51. Another prominent study in 96,000 patients, published in the Lancet, showed that hydroxychloroquine or chloroquine, when used alone or with a macrolide, did not show a benefit on in-hospital outcomes for COVID-19. However, the authenticity of the data could not be verified, and the article was subsequently retracted **(MP/32 – INQ000408402)**.

52. Many other studies were reviewed most of which showed lack of effectiveness of hydroxychloroquine in the treatment of COVID-19, and some of which suggested the potential for hydroxychloroquine to cause harm given its known adverse effects on conduction of electrical waves in the heart, and the potential for this to lead to heart rhythm abnormalities.

53. With the review of the emerging data, the view of the CHM and its EWG remained that there was no evidence of effectiveness of hydroxychloroquine in the treatment of COVID-19, and any use of hydroxychloroquine should be in the context of randomised controlled trials where its efficacy and safety could be properly assessed.

54. The remit of CHM is also to advise the MHRA on clinical trials being conducted in the UK under regulation 31(5) of The Medicines for Human Use (Clinical Trials) Regulations 2004. This regulation also enables the MHRA to suspend or terminate a trial, with advice taken from the CHM, where appropriate. To this end, the CHM reviewed the clinical trials being conducted in the UK with hydroxychloroquine either for treatment or prophylaxis. Because of the risk of potential harm from hydroxychloroquine (especially with regard to heart rhythm abnormalities), combined with the lack of any convincing data on effectiveness, on 21 May 2020, the CHM advised that there should be a re-assessment of the benefit-risk balance of the 8 on-going trials and justify any proposed continuation.

55. Subsequently, the MHRA communicated with investigators of the 8 trials that it was minded to suspend their trials pending provision of the information relating to the safety of the trial subjects. Investigators from seven trials confirmed that

recruitment would be paused, while investigators from the RECOVERY trial provided preliminary answers to the questions posed by the MHRA, and recruitment was allowed to continue.

56. On 1 June 2020, the CHM invited the Chair of the RECOVERY trial data monitoring committee (DMC) to provide a summary of the review of safety being undertaken by the DMC, and was generally reassured by the responses, but asked for further safety information, and in addition, also asked for a futility analysis. While in session on 5 June 2020, the CHM was informed of a press release from the RECOVERY trial indicating that there was "no clinical benefit from use of hydroxychloroquine in hospitalised patients with COVID-19" and that enrolment of participants to the hydroxychloroquine arm of the RECOVERY Trial had been stopped by the trialists with immediate effect (this was subsequently published on 8 October 2020 in a peer-reviewed journal **(MP/33 – INQ000408403)**).

57. The CHM considered that the lack of benefit of hydroxychloroquine in RECOVERY had implications from both the regulatory and clinical equipoise perspective for the other on-going trials. Most of the trials on hydroxychloroquine or chloroquine were never re-started after the pause imposed by MHRA, although one study evaluating the use of chloroquine for prophylaxis of COVID-19 was allowed to resume on 26 June 2020, although has not yet (at time of writing this statement) reported its results.

58. **Ivermectin**: Ivermectin is another drug which has been the subject of media frenzy, fraudulent scientific activity and political polarisation. It was reviewed by the COVID-19 Therapeutic EWG on 16 March 2021 **(MP/34 – INQ000409551)** and 15 October 2021 **(MP/35 – INQ000409554)**. It was also reviewed by CHM on 28 October 2021 **(MP/36 – INQ000400267)**. Our conclusion based on the review of all the available data was that there was insufficient evidence for use of ivermectin in COVID-19 and further data were needed from appropriate studies to draw informed conclusions regarding its benefits. We also recommended that any use of ivermectin in COVID-19 should only be in the setting of a clinical trial, which was consistent with the advice from the WHO **(MP/37 – INQ000408442)**.

<u>Other repurposed agents</u>

59. As part of the ongoing review of therapeutics for COVID-19, the CHM and its EWG advised on a number of other products, as below:

a. **Remdesivir (MP/08 – INQ000409547) (MP/10 – INQ000409483) (MP/38 – INQ000409484) (MP/39 – INQ000409485) (MP/24 – INQ000409486) (MP/27 – INQ000409487) (MP/29 – INQ000409474) (MP/40 – INQ000409482) (MP/41 – INQ000400215)**: this is an antiviral originally developed to treat Ebola. This was repurposed for COVID-19, and gained an early access to medicines approval on 21 May 2020, and a conditional marketing authorisation following the CHM meeting on 18 June 2020. Since then, it has been widely used in the NHS **(MP/42 – INQ000408404)**.

b. **Azithromycin (MP/18 – INQ000400278) (MP/20 – INQ000409473) (MP/43 – INQ000409548)**: this is a widely used antibiotic which was trialled either in combination with hydroxychloroquine or by itself. The EWG was kept informed of the findings of global trials which showed no benefit of azithromycin on COVID-related clinical parameters, a finding confirmed by the RECOVERY study which showed that azithromycin did not improve survival **(MP/44 – INQ000408368)**.

c. **Nicotine (MP/45 – INQ000400279)**: there were some preliminary findings early on during the pandemic that suggested that cigarette smoking was protective against COVID-19, which led the French government to restrict the sales of nicotine substitutes **(MP/46 – INQ000408405)**. Studies relating to nicotine were reviewed by the EWG, and overall, given the contradictory findings in the literature, it was concluded that no recommendation could be made.

d. **Anakinra (MP/46 – INQ000408405) (MP/47 – INQ000409493) (MP/48 – INQ000409552) (MP/49 – INQ000409495) (MP/50 – INQ000409506) (MP/51 – INQ000409509) (MP/52 – INQ000400282)**: Anakinra, a product used for treatment in rheumatoid arthritis, which works by blocking the actions of interleukin-1, a molecule that is pro-inflammatory, was assessed on several occasions by the EWG and CHM. On 2 Sept 2021, the CHM considered and discussed an application to extend the indication for anakinra to include the treatment of COVID-19 in adult patients with

pneumonia who are at risk of developing severe respiratory failure. The CHM advised against the grant of the extension of the indication on the grounds relating to safety and efficacy. The applicants had proposed the use of a non-standard biomarker, suPAR (soluble urokinase plasminogen activator receptor) to enable the use of anakinra, but we were not convinced that a patient population could be identified in which anakinra would provide a clear benefit.

e. Other drugs evaluated by the COVID-19 Therapeutics EWG at various stages of development included Vitamin D **(MP/9 – INQ000409470)**, Boceprevir **(MP/43 – INQ000409548)**, 1% methylene blue **(MP/21 – INQ000409549)**, Favipiravir **(MP/53 – INQ000409550)**, Itolizumab **(MP/53 – INQ000409550)**, Povidone iodine **(MP/47 – INQ000409493)**, and Lenzilumab **(MP/35 – INQ000409554)**. The EWG felt that there was no evidence of effectiveness or further investigations were required before the drugs could be progressed to licensing or included in guidelines.

Clinical trials

60. Throughout the pandemic, the CHM and its EWGs were kept informed of on-going clinical trials for either prophylactic use or for treatment of COVID-19. Indeed, in many cases, members of CHM and its working groups were asked to provide independent advice to the trials in terms of the design, and potential benefits and risks. This included the large UK based trials including RECOVERY **(MP/54 – INQ000408406)**, REMAP-CAP **(MP/55 – INQ000408407)** and PRINCIPLE **(MP/56 – INQ000408408)**, and SOLIDARITY **(MP/57 – INQ000408409)**, a trial run by the WHO. Some of the specific drugs assessed by CHM and its working groups included:

    a. **Dexamethasone (MP/58 – INQ000408410), tocilizumab (MP/59 – INQ000408369)** and **baricitinib (MP/60 – INQ000408386)**, all of which showed beneficial effects on mortality in the RECOVERY trial, and were licensed for use in severe COVID-19.

    b. **Colchicine**, a drug used for gout, was reviewed by CHM on 1 February 2021 **(MP/61 – INQ000409497)** – although initial data were promising based on a Canadian trial **(MP/62 – INQ000408373)** conducted in

community-treated patients, they were not conclusive. Subsequently, the RECOVERY failed to show any improvement in mortality in hospitalised patients with severe COVID-19 **(MP/63 – INQ000408376)**.

c. **Budesonide (MP/64 – INQ000409490) (MP/65 – INQ000409504)**: this is an inhaled steroid, which was investigated in patients in the community who were at high risk of complications, hospitalisation or death. The trial showed that inhaled budesonide reduced recovery time from 14.7 days to 11.8 days but had no effect on hospitalisation or death **(MP/66 – INQ000408374)**. However, the CHM felt that based on the totality of the evidence, there was insufficient evidence to support inclusion of budesonide as standard of care for COVID-19 patients.

61. I have been asked to provide a summary of key points arising out of the advice provided by CHM and its working groups in respect of trial design, benefits and risks, including any reflections on lessons learned for the future. Any trial involving a medicinal product in the UK needs approval from the MHRA before it can be undertaken. The CHM and its expert groups therefore provide a pool of expertise that the MHRA can ask for advice on trial design, benefits and risks. The Infection Expert Advisory Group and The Clinical Trials, Biologicals and Vaccines Expert Advisory Group were particularly involved in providing advice on trial design prior to the commencement of the trials.

62. For clinical trials, the investigators need to report adverse events to the clinical trials unit at the MHRA. If there are concerns about drug safety, the clinical trials unit can ask the CHM for advice, which may in some cases, lead to a temporary pause in the trial (until the safety has been mitigated) or in some cases, stopping of the trial. This is exemplified by the advice given by CHM on trials involving hydroxychloroquine (see paragraph 54).

63. In terms of lessons learned for the future, clinical trials are pivotal for assessing the safety and efficacy of medicines. The MHRA therefore plays a vital role in assessing these trials, and subsequently providing clinical trials authorisation. Trials need to be assessed and eventually approved within required timeframes. During the pandemic, all clinical trial unit resources were directed towards approving the COVID trials as quickly as possible. This

led to delays in the timelines for the non-COVID trials, resulting in a massive backlog in trial approvals – this backlog has now been cleared. It is important that the clinical trials unit and therefore MHRA are provided adequate resources to ensure that the timelines for approving trials can be met, and exceeded, if possible. The clinical trials unit also needs access to relevant expertise so that it can get advice on the design and potential utility of the trials.

New drugs for COVID-19

64. During the course of the pandemic, new therapeutic agents, directly targeting the SARS-CoV-2 virus were developed. These can be divided into monoclonal antibodies and antivirals.

Monoclonal antibodies

65. These are antibodies directed against the viral spike protein which then prevent the entry of the virus into the cell. The following antibodies were reviewed by the COVID-19 Therapeutics EWG and the CHM:

66. **Bamlanivimab (MP/67 – INQ000409476) (MP/68 – INQ000409477) (MP/69 – INQ000409489)**: This was a single monoclonal antibody where the evidence of efficacy was insufficient to support its use. Furthermore, the product also seemed to promote the development of new variants of the virus. Although the product had initially received a PIM (promising innovative medicine) designation, it was felt that the benefit-risk was negative because of its limited efficacy and the potential to promote the development of new viral variants, and its application for an Early Access to Medicines approval was therefore declined.

67. **Ronapreve (Casirivimab and imdevimab) (MP/70 – INQ000409505) (MP/71 – INQ000400266)**: This is a combination of two antibodies, which was given a conditional marketing authorisation for the prophylaxis and treatment of acute Covid-19 infection **(MP/72 – INQ000408411)**, based on data from three studies

from the company. Data from the RECOVERY trial showed that Ronapreve reduced 28-day mortality in hospitalised COVID-19 patients, but this was limited to those who were seronegative (i.e., had not mounted an antibody response to the virus) at baseline **(MP/73 – INQ000408380)**. The CHM noted that the participants in the earlier trials were largely unvaccinated, whereas vaccine coverage in the UK at the time of authorisation was over 70%. The effect of this combination monoclonal antibody was therefore likely to be less than that observed in the original trials. Furthermore, the COVID variants circulating at the time of the trial were different to those circulating at the time of authorisation. It was therefore important to monitor for escape variants in Ronapreve-treated patients (see below). The conditional marketing authorisation was only applicable in GB, and not in Northern Ireland as per the Northern Ireland protocol. As the product had not been licensed by the EMA, in order to make it available to Northern Ireland, the CHM endorsed the recommendation from the MHRA to grant temporary authorisation in Northern Ireland under Regulation 174 of the Human Medicines Regulations (Regulation 174 of the Human Medicines Regulations 2012 provides for the supply of a medicinal product on a temporary basis in response to a public health emergency which may cause harm to human beings. The spread of COVID-19 was considered to meet this criterion).

68. **Sotrovimab (MP/74 – INQ000409510) (MP/75 – INQ000400268) (MP/76 – INQ000409559):** Authorisation of this single monoclonal antibody product was based on a rolling review and was supported by data from one clinical study **(MP/77 – INQ000408412)**. This showed that the product was effective in the treatment of symptomatic adults and adolescents (aged 12 years and over weighing at least 40kg) with acute COVID-19 infection who do not require oxygen supplementation and who are at increased risk of progressing to severe covid infection. At the time of conditional marketing authorisation, the company was asked to provide data on the effect of sotrovimab on the Omicron variant, which was not circulating at the time the clinical trial was undertaken. On 20 April 2022, the CHM considered a proposal from the marketing authorisation holder to increase the dose from 500mg to 1000mg in order to combat the emergence of the Omicron BA.2 variant. However, this was declined because of inadequate pharmacokinetic data, lack of data on tissue penetration of the antibody (where the

virus causes the disease) and lack of clinical data on the effectiveness of the 1000mg dose compared with the 500mg dose.

69. **Evusheld (Tixagevimab, cilgavimab) (MP/78 – INQ000409556) (MP/79 – INQ000409557) (MP/52 – INQ000400282) (MP/80 – INQ000409558) (MP/81 – INQ000409560) (MP/82 – INQ000409564) (MP/83 – INQ000409563)**: This product was also evaluated through a rolling review. Evusheld consists of two monoclonal antibodies which bind distinct parts of the viral spike protein. The marketing authorisation holder (MAH) applied for a conditional marketing authorisation. This was reviewed by the CHM on 3 occasions, before a limited indication for pre-exposure prophylaxis was agreed in March 2022. The main concern was about dosing, and whether the dose would be adequate to neutralise the Omicron variants circulating at the time – wording was therefore included in the product licence to use higher doses (600mg) for some of the Omicron variants, where in vitro data had shown reduced neutralisation capacity. A subsequent application to remove the 300mg dose altogether was declined because of lack of robust data characterising the need for 600mg for all variants of concern. The MAH was also asked to provide real-world data on the effectiveness of Evusheld against the Omicron variants as a post-authorisation commitment. In October 2022, Evusheld was also approved for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.

Emergence of resistant variants:

70. With all these monoclonal antibody products, the CHM had concerns about the possibility of mutations in the virus leading to the emergence of escape variants, i.e., variants which could not be neutralised by the monoclonal antibodies. Theoretically, this could occur more commonly in individuals who were immunosuppressed where the virus could not be eliminated by the patient's own immune system. Therefore, for all the products, the CHM asked for monitoring for new 'escape' variants as a post-authorisation commitment. The companies were able to do this by forming collaborations with the UKHSA and NIHR.

Viral variants:

71. We learned very early on in the pandemic that the virus had a propensity to mutate leading to new variants which could lead to a rise in infections in the population, and hospital admissions and deaths. When the monoclonal antibodies were trialled by the manufacturers, the variants which were circulating were different to those which were circulating when the products were licensed. This meant that we had to rely on in vitro data which showed the capacity of the antibodies to neutralise the different variants but did not have any real world data in patients. Hence it was important for all real-world data to be collected following authorisation by the manufacturers, and by the healthcare system, to ensure that the drugs would be used in the most effective way, and their use would be stopped if the circulating variants were resistant to the product. This is very similar to how antibiotics are licensed – the licence is based on the original data from the trials undertaken at the time of the authorisation, but monitoring of resistant strains allows the NHS to modify prescribing recommendations by clinicians through local and national formulary management. These monoclonal antibody products are no longer used in the NHS (or elsewhere in the world) because the current heavily mutated strains of the virus are resistant. However, it is still important to maintain the licence so that the products are available in the future should there be the emergence of a new variant which is susceptible to the antibodies.

Deployment of the monoclonal antibodies:

72. Deployment is not within the remit of the MHRA or CHM. Deployment of the monoclonal antibodies was a function of the NHS (and of NICE guidance), and it therefore needed the flexibility to make the antibodies available in the most efficient way (given the limited supplies) taking into account the need to identify members of the population who would most benefit from the monoclonal antibodies, while at the same time staying within the product licence. Furthermore, the NHS needed the ability to make deployment decisions based on new mutational patterns in the virus which would render the antibodies ineffective. Thus, for Ronapreve, the NHS was able to deploy the antibodies in those who were considered to be the most vulnerable **(MP/71 – INQ000400266)**. Similarly for sotrovimab, it was available for

patients at greatest risk of serious illness from COVID-19 **(MP/84 – INQ000408413)**.

73. For Evusheld, which was initially licensed for prevention (pre-exposure prophylaxis) of COVID-19, in the summary of product characteristics **(MP/85 – - INQ000497049]** it was highlighted that "Circulating SARS-CoV-2 viral variants may be associated with resistance to monoclonal antibodies such as tixagevimab and cilgavimab and Evusheld does not neutralise BA.4.6 and is unlikely to be active against this variant. Due to the observed decrease in in-vitro neutralisation activity against the Omicron subvariants BA.1, BA.1.1, BA.4 and BA.5, the duration of protection of Evusheld for these subvariants is currently not known". Table 5 in the summary of product characteristics lists the neutralisation capacity of the antibodies in isolation, and in combination, against the different SARS-CoV-2 variants. Evusheld was not procured by the Government based on independent clinical advice (provided by the Rapid C-19 oversight group ((**MP/86 – INQ000502036)** taking into account the epidemiological context of the pandemic and doubt about its effectiveness against the variants circulating at the time **(MP/87 – INQ000408414)**, a decision further supported by a NICE technology appraisal **(MP/88 – INQ000408415)**. In my personal opinion, this was the correct decision. Evusheld was developed at the time when the ancestral and early strains of the COVID virus were circulating. By the time it came to market, the predominant circulating strain was Omicron and its sub-variants. As highlighted in this paragraph, the efficacy of Evusheld against these variants was reduced, and how long it would protect for was not known. The virus continued to evolve, and by the time the XBB 1.5 strain emerged, the neutralisation capacity of Evusheld decreased even further. This led to the FDA withdrawing authorisation in the US in January 2023. Because of the lack of data on the efficacy of Evusheld against the circulating COVID variants, even at higher doses, and the lack of inclusion of sufficient numbers of immunosuppressed patients (the target group for protection) in the pivotal PROVENT trial **(MP/89 – INQ000502037)**, it was the right decision not to procure it. This is a personal opinion and not that of CHM; it is important to note that procurement is not within the remit of CHM. A real-world effectiveness paper published in April 2023 stated that "due to the presence of

changing vaccine coverage, multiple therapies, and changing variants, the effectiveness of T/C (Evusheld) in the Omicron era remains difficult to assess" **(MP/90 – INQ000502032)**.

Antiviral agents

74. Towards the latter part of the pandemic, new antivirals were introduced into the therapeutic armamentarium – these were Molnupiravir and Paxlovid.

75. **Molnupiravir**: The CHM assessed an application for a conditional marketing authorisation for molnupiravir on 28 October 2021 **(MP/36 – INQ000400267)**, after it had been reviewed by the COVID-19 Therapeutics EWG on 17 August 2021 **(MP/48 – INQ000409552)**, 20 September 2021 **(MP/91 – INQ000409553)** and 15 October 2021 **(MP/35 – INQ000409554)**. The drug was assessed by the MHRA as part of a rolling review. Based on the data provided by the company, the CHM concluded that the balance of benefits and risks of the drug with regard to quality, safety and efficacy was positive and the conditional marketing authorisation could be granted provided a number of conditions were met, including revised wording for the indication, and a number of post-authorisation commitments including collection of information on pregnancy outcomes in women exposed to molnupiravir during pregnancy.

76. **Paxlovid**: This is a combination product containing nirmatrelvir and ritonavir. The former is an antiviral preventing the growth and spread of the virus, while the latter acts as an "enhancer" preventing nirmatrelvir from being broken down too quickly in the body. The CHM reviewed the application for a conditional marketing authorisation at an ad hoc meeting on 30 December 2021, and also an application for the same product under Regulation 174 in Northern Ireland **(MP/92 – INQ000409510)**. The CHM advised that the benefit-risk was positive for Paxlovid, and agreed to recommend the grant of a conditional marketing authorisation for Paxlovid in GB and authorisation under regulation 174 in Northern Ireland. The CHM advised that authorisation was dependent on a commitment from the company to undertake thorough and pro-active monitoring of viral resistant variants post-deployment. The CHM also discussed the ability of the drug to be

involved in drug-drug interactions with other drugs commonly being taken by patients, and highlighted the need to ensure that guidance on avoidance or minimisation of these potentially serious drug-drug interactions was followed in the NHS.

Vaccines

77. The COVID-19 Vaccines Benefit Risk (VBR) Expert Working Group first met on 25 August 2020 **(MP/93 – INQ000409491)**, with the remit as outlined in section 3.8. The VBR EWG met 93 times, the last meeting being on 5 May 2023 **(MP/94 – INQ000409573)**. All the meetings were conducted online apart from the last meeting.

78. A pivotal event in the race to develop a vaccine against SARS-CoV-2 was the online publication of the genome of the virus that caused the Wuhan pneumonia outbreak **(MP/95 – INQ000408417)**. This provided researchers in academia and in industry the ability to analyse the characteristics of the virus; understand its biology; develop diagnostic tests to contain spread of the virus; and importantly started a global race to develop a vaccine. Many of the vaccine manufacturers also worked at risk, developing the manufacturing capabilities for mass scale vaccine production, even though there was no guarantee that the vaccines would be effective.

79. Although the VBR EWG and CHM worked within their terms of reference, given that this was a public health emergency, it was important for us to be aware of plans for vaccine deployment by the JCVI, the public health bodies in the 4 nations and the NHS. Therefore, colleagues from these bodies were invited to give evidence to the committees, and also invited to attend as observers (see appendix 1). In addition, the committees were able to invite companies and academic researchers developing the vaccines to give presentations.

80. An important innovation was to undertake a rolling review of the vaccines. Traditionally, vaccines and other therapeutic products are reviewed after the development programme is completed, and a consolidated document submitted. However, with a rolling review, the manufacturer was able to share data (i.e., share

modules of the dossier) as it was being generated for evaluation by the MHRA, and by the CHM and its committees. In turn, the MHRA and CHM were able to ask questions as the different parts of the dossier were reviewed and receive responses from the companies. This reduced delays in being able to assess the quality, safety and efficacy of the vaccines, prior to any marketing authorisation.

81. This innovation of undertaking a rolling review should be applied in the future to new products where there is an unmet medical need. Indeed, this is consistent with the guidance from the MHRA ("Rolling review for marketing authorisation applications") published on 31 December 2020 **(MP/96 – INQ000408418)**. There are many advantages to a rolling review including streamlining the development of novel medicines, and enhanced regulatory interactions, which hopefully reduces the risk of failure. However, it is resource intensive, and in my opinion, requires investment into an adequate specialist workforce in the regulatory agency that can deal with both the rolling and conventional reviews. In retrospect, it was possible in the pandemic to undertake the rolling reviews because work on other diseases was either temporarily discontinued or slowed down, which allowed different parts of the system to primarily focus on the development of the vaccines.

82. The VBR EWG and CHM were kept informed by the MHRA of the plans for regulatory submissions from the vaccine manufacturers. For confidentiality reasons, code names were initially used for the different vaccines **(MP/97 – INQ000409492)**. The MHRA also kept the VBR EWG and CHM informed of the vaccine trials being conducted in the UK.

83. While the vaccines were being developed, in initial work, the VBR EWG addressed the issue of monitoring vaccine safety and efficacy when (and if) any vaccines were authorised. The safety issues are covered in section 6 following on from the work of the Covid-19 Vaccine Safety Surveillance Methodologies Expert Working Group. For efficacy, it was important to have a definition of what would constitute an effective vaccine. Assessment of the clinical trial protocols for the different vaccines showed that there were differences in calculating vaccine efficacy, but all were acceptable. In simple terms, this is a measure of how many people who got vaccinated developed symptomatic COVID-19 compared with how many people who got the placebo developed the disease **(MP/98 – INQ000408419)**. The VBR

EWG and CHM agreed that the success criteria for the primary endpoint of vaccine efficacy should be 50%, in keeping with WHO/FDA criteria **(MP/99 – INQ000408383)**, with a lower bound of the confidence interval for vaccine efficacy being above 30% **(MP/97 – INQ000409492)**.

84. The CHM was informed that the vaccine authorisation would be under Regulation 174 of The Human Medicines Regulation 2012. This would allow the MHRA to grant authorisation for a temporary period without having to wait for the European Medicines Agency.

85. Throughout the course of the pandemic, a number of vaccines were authorised; the efficacy of each of the vaccines is considered below (for safety aspects, please refer to the vaccines safety section 6).

Pfizer/BioNTech COVID-19 vaccine (BNT162b2, later called Comirnaty)

86. This vaccine was approved on 2 December 2020, following a CHM meeting on 30 November 2020 **(MP/100 – INQ000409481)**. This approval was based on scrutiny of the quality (including large scale manufacturing), nonclinical, effectiveness and safety data that was shared with the MHRA as part of the rolling review process. The ability to approve this vaccine was based on the success of the rolling review process and the hard work of the MHRA staff, and its expert committees to rigorously scrutinise the data, without bypassing the expected standards of safety, quality, and effectiveness.

87. The BNT162b2 vaccine was the first mRNA vaccine to be approved. Therefore, quality aspects were comprehensively assessed, including the need to store the vaccine at -80^{0}C, and the need to maintain the cold chain during transport, and stability at 2-8^{0}C prior to administration to people. All these issues were satisfactorily addressed, including the processes that had been put into place to enable vaccine administration to the most vulnerable individuals, including those who were housebound.

88. The BNT162b2 mRNA COVID-19 vaccine was assessed in an international placebo-controlled double blind efficacy trial in a total of 43,448 participants (21,720 with BNT162b2 and 21,728 with placebo) **(MP/101 – INQ000408420)**.

There were 8 cases of COVID-19 in the BNT162b2 group compared with 162 cases amongst those assigned placebo, giving an overall efficacy rate of 95%, well above the WHO-stipulated standard of 50% vaccine efficacy. Severe COVID-19 occurred in 1 participant in the vaccine arm compared with 9 participants in the placebo arm, giving a vaccine efficacy against severe COVID-19 of 88.9%.

89. A real-world effectiveness study of the BNT162b2 vaccine, published by Public Health England on 13 May 2021, showed that a single dose of the vaccine was about 80% effective at preventing admission to hospital and 85% effective at preventing death with COVID-19 **(MP/102 – INQ000408421)**.

90. Subsequent to the authorisation and use of the original BNT162b2 vaccine in 2020 and 2021, with the development of new variants of SARS-CoV-2, the vaccine was modified to cover the Omicron BA.1 variant. This bivalent vaccine (containing the mRNA sequence of the original Wuhan strain of the virus, and the mRNA sequence of viral spike protein of the Omicron BA.1 virus in a 1:1 ratio) was assessed by the CHM on 1 September 2022 as a booster dose. Based on the safety and immunogenicity (i.e., the antibody response to the vaccine) data, the product was approved, and subsequently deployed by the NHS.

91. Although outside the reporting period for this witness statement, it is important to state that since then, with the continued evolution of the virus, new variant vaccines produced by Pfizer BioNTech have been approved targeting BA.4 and BA.5 Omicron variants (on 9 November 2022) **(MP/103 – INQ000408422)**, and most recently, Omicron XBB1.5 **(MP/104 – INQ000408423)**.

<u>AstraZeneca Oxford Vaccine (also known as AZD1222, and later named Vaxzevria)</u>

92. This vaccine was also subject to a rolling review and was first discussed by the VBR EWG on 25 August 2020 **(MP/93 – INQ000409491)**. It received authorisation for emergency supply under regulation 174 on 30 December 2020 **(MP/105 – INQ000408424)**, after a CHM meeting on 29 December 2020 **(MP/106 – INQ000409488)**.

93. AZD1222 was developed using more conventional technology compared with the mRNA vaccines. It is an adenoviral vaccine containing the chimpanzee

adenovirus (ChAdOx1), which has been rendered replication deficient. Following intramuscular administration, the SARS-CoV-2 protein is expressed locally stimulating an immune response which consists of both antibody formation and a cellular response (T-cells).

94. The VBR EWG and CHM assessed the quality data, the nonclinical data, the efficacy data (including the immunogenicity studies), the safety data and the risk management plan prior to authorisation. The safety aspects will be covered in the safety section.

95. The efficacy data for this vaccine based on 4 studies which included 17,178 participants (8597 received AZD1222, while 8581 received the placebo) showed that after two doses, the vaccine efficacy was 66.7%. Importantly, it also showed that the vaccine efficacy based on hospitalisations was 100% (9 hospitalisations in the control group and 0 in the active group) indicating that it was more effective against severe disease. The clinical efficacy was consistent with the immunogenicity data which indicated that the vaccine was generating a protective antibody and cellular response.

96. Another trial of AZD1222 conducted in 32,451 participants from the United States, Chile, and Peru, published on 16 December 2021 **(MP/107 – INQ000408425)** confirmed the efficacy of the vaccine (vaccine efficacy 83.5%). Furthermore, no severe or critical symptomatic COVID-19 cases were observed among the 17,622 participants in the AZD1222 group, compared with 8 cases of severe disease in the placebo group.

97. Real-world evidence published online on 23 April 2021 from Scotland showed that the first dose of the vaccine reduced the likelihood of hospitalisation by 88% (most of the vaccine recipients being over the age of 65 years) **(MP/108 – INQ000147546)**. Many other real-world studies have been published since then from the UK and other countries which have shown the real-world effectiveness of the vaccine against severe disease.

Moderna mRNA-1273 SARS-CoV-2 Vaccine (later known as Spikevax)

98. Like the Pfizer/BioNTech vaccine, this is an mRNA vaccine which was also subject to a rolling review. It was reviewed by both the VBR EWG and CHM several times before review on 31 December 2020 by CHM, when it was recommended for a Regulation 174 authorisation **(MP/109 – INQ000400263)**. It received regulatory approval from the MHRA on 8 January 2021 **(MP/110 – INQ000408426)**.

99. As with the other vaccines, the CHM and the VBR EWG reviewed the quality, nonclinical, efficacy and safety data and the risk management plan for this vaccine before authorisation. As with the BNT162b2 vaccine, the CHM reviewed the conditions required for storage and stability at different temperatures so that the relevant information was included in the product label for deployment and administration of the vaccine.

100. In terms of efficacy, the trial was conducted in 30,420 participants. The vaccine efficacy was 94.1% (Symptomatic Covid-19 illness was confirmed in 185 participants in the placebo group, and in 11 participants in the mRNA-1273 group) **(MP/111 – INQ000408427)**. This was again in keeping with the immunogenicity data.

101. Severe Covid-19 occurred in 30 participants in the trial, with one fatality; all 30 were in the placebo group, again highlighting the protection against severe disease.

102. Real-world data has shown that the Moderna mRNA 1273 mRNA vaccine was 98.1% effective after deployment in different parts of the world **(MP/112 – INQ000408377)**.

103. With the emergence of the Omicron SARS-CoV-2 variants, the Moderna bivalent original/Omicron vaccine was assessed by CHM on 12 August 2022, and authorisation recommended as a booster vaccine based on the immunogenicity and safety data **(MP/113 – INQ000409561)**. The Moderna BA.4/5 vaccine was subsequently authorised on 21 February 2023 **(MP/114 – INQ000408394)** for use as a booster dose and subsequently for primary vaccination as well. A Moderna vaccine targeting the XBB1.5 sub-variant was authorised on 15 September 2023

based on an assessment of the quality, safety and effectiveness **(MP/115 – INQ000408428)**.

Booster doses of vaccines

104. As the pandemic progressed, and as experience with the vaccines increased, it became clear that immunity was waning, which would necessitate booster doses of the vaccines. Using data generated by the companies, and academically-led trials such as COV-BOOST **(MP/116 – INQ000412452)** and Com-COV **(MP/117 – INQ000408375)** trials, the VBR EWG and CHM were able to recommend the following **(MP/50 – INQ000409506) (MP/118 – INQ000409507) (MP/119 – INQ000409508)**:

    a. Use of homologous third doses could be supported for both the BNT162b2 and the AZD1222 vaccines. Homologous refers to the fact that the person would have received the same first two doses of the vaccine as the third dose.
    b. Use of a heterologous third dose could be supported for the BNT162b2 vaccine. Heterologous refers to the fact that the person will have received a vaccine which was different from the BNT162b2 vaccine for the first two doses.
    c. Use of a heterologous third dose of AZD1222 vaccine could not be supported because the benefit-risk was negative. The main reason for this was that if AZD1222 had been approved for heterologous administration, many people would have been exposed to the vaccine for the first time. However, by that time, we were aware of the serious adverse reaction of clotting with lowered platelets that could occur with AZD1222, most individuals had already received two doses of a mRNA vaccine, and there was adequate supply of mRNA vaccines.
    d. Use of a homologous or heterologous third dose of the Moderna mRNA-1273 vaccine could be supported. The third dose would be half the dose (50µg) that was used for primary vaccination (100µg).

Nuvaxovid vaccine (Novavax; NVX-CoV2373)

105. This vaccine was also subject to a rolling review – it was first reviewed by the VBR EWG on 24 March 2021 **(MP/120 – INQ000409519)**, and several times after

that. When all the data had been received, and queries answered by the Company, it was reviewed by CHM on 27 January 2022 **(MP/78 – INQ000409557)**.

106. Nuvaxovid is a protein nanoparticle vaccine which is combined with an adjuvant, the function of the latter being to enhance the immune response. The EWG and CHM were able to review the quality, nonclinical and clinical data for this vaccine. Given the novelty of the protein nanoparticles, and the novel adjuvant (Matrix M1) being used for the vaccine, there were many quality issues which had to be resolved prior to any authorisation.

107. In terms of efficacy, the Nuvaxovid vaccine was investigated in a randomised controlled trial of 29,582 participants who received at least one dose of vaccine or placebo (19,714 received vaccine and 9868 placebo) **(MP/121 – INQ000408429)**. The vaccine efficacy was 90.4%. Ten moderate and 4 severe cases occurred, all in placebo recipients, yielding vaccine efficacy against moderate-to-severe disease of 100%.

108. The CHM recommended approval of the conditional marketing authorisation of Nuvaxovid vaccine on 27 January 2022 for adults over the age of 18 years, with some specific obligations to be fulfilled post-authorisation.

109. Subsequently, on 4 August 2022 **(MP/81 – INQ000409560)**, the CHM advised the grant of a variation to the licence to lower the indication age from 18 years and older to 12 years and older. On 29 September 2022 **(MP/122 – INQ000409562)**, the CHM advised that the variation to introduce a homologous and heterologous booster dose in individuals aged 18 years and older was approvable.

<u>COVID-19 vaccine Janssen (Ad26.COV2-S)</u>

110. This vaccine was reviewed by the VBR EWG on 23 April 2021 **(MP/123 – INQ000409523)** and by the CHM on 6 May 2021 **(MP/124 – INQ000409503)** for a conditional marketing authorisation via the European Commission Decision Reliance Procedure (ECDRP) **(MP/125 – INQ000408430)**. It had been licensed by the European Commission on 11 March 2021 **(MP/126 – INQ000408431)**. This is an adenoviral vector vaccine (containing adenovirus type 26) which required single dose administration. A randomised controlled trial had shown that the

vaccine efficacy was 67% (there were 116 cases out of 19,630 people who received the vaccine compared with 348 of 19,691 people given placebo). This vaccine was approved by the MHRA on 28 May 2021 following the CHM review which concluded that the overall benefit-risk balance was positive. As far as I am aware, this vaccine has never been deployed in the UK.

Valneva COVID-19 vaccine

111. This vaccine was reviewed by the VBR EWG on 29 March 2022 **(MP/127 – INQ000409540)** and by CHM on 7 April 2022 **(MP/80 – INQ000409558)**. This was the first whole-virus inactivated COVID-19 vaccine to gain MHRA approval on 14 April 2022 **(MP/128 – INQ000412457)**. Furthermore, it was approved on the basis of immunobridging data, i.e. there was no clinical trial to demonstrate efficacy, but an immunogenicity study was conducted focusing on the immune responses with this vaccine compared with the Vaxzevria vaccine. This showed that the level of neutralising antibodies was significantly superior after 2 doses of Valneva vaccine compared to 2 doses of Vaxzevria. However, the proposed indication was restricted to individuals aged between 18 to 50 years because only 3 subjects over 50 years of age had been included in the immunobridging study. In addition to the immunobridging study, the manufacturer had to provide safety data, usually in about 3000 individuals, which provided some reassurance of safety in comparison to already authorised vaccines; the safety data from the trial were comparable with the safety of Vaxzevria (AZD1222). There will also have been the usual post-marketing commitment to gather safety data. It is also important to note that many non-COVID vaccines are authorised on the basis of immunobridging data.

112. At the later stages of the pandemic when the majority of the population in the UK had been vaccinated, it would not have been possible to undertake conventional efficacy trials. Thus, the approval of the Valneva COVID-19 vaccine on the basis of immunobridging data was consistent with the statement from the ACCESS consortium (which includes the MHRA) on 15 September 2021 which stated that "well-justified and appropriately designed immunobridging studies are an acceptable approach for authorising COVID-19 vaccines" **(MP/129 –**

INQ000408433). This followed a workshop held by the International Coalition of Medicines Regulatory Authorities (ICMRA) on 24 June 2021 **(MP/130 – INQ000408434)**.

VidPrevtyn Beta

113. This vaccine was submitted through the European reliance procedure and was assessed by the VBR EWG on 13 December 2022 **(MP/131 – INQ000400277)**, and by CHM on 15 December 2022 **(MP/132 – INQ000409565)**. It is a protein-based vaccine which was authorised by the European Commission on 10 November 2022 for booster immunisation to prevent COVID-19 in adults who had previously received an mRNA or adenoviral-vector vaccine. Positive immunobridging data in comparison to the BNT162b2 vaccine were presented to the EWG and CHM. It was recommended that the product could be given authorisation in GB using the same indication approved in the EU (approved by MHRA on 20 December 2022 **(MP/133 – INQ000408435)**. The CHM was also asked if this vaccine could be used for primary immunisation for some individuals who had either refused the mRNA vaccines or could not receive them. Based on the data available to them from the booster dose, its safety profile, the nonclinical and in vitro data, the biological plausibility as well as the immunogenicity, the CHM considered that use of VidPrevtyn Beta for primary immunisation may be an acceptable clinical option. This opinion was aligned with European Commission decision.

Approval of the COVID-19 vaccines for the paediatric population

114. The initial authorisations of the COVID-19 vaccines focused on people over the age of 16-18 years based on the data that was presented to the regulatory agency by the vaccine manufacturers. This was consistent with the fact that COVID-19 had been shown to cause the most severe disease in older people, particularly those who had underlying diseases. Although in most children, infection is either asymptomatic or causes mild disease, in some children and adolescents, particularly those with underlying illnesses, it can cause severe, and rarely fatal disease (infection fatality ratio of less than 1 in 100,000 infections in 0-19 year-olds **(MP/134 – INQ000408389)**. However, infection with SARS-CoV-2 can also lead

to Paediatric multisystem inflammatory syndrome, and in some cases long COVID – one systematic review has suggested that the prevalence of long-COVID may be as high as 25% in children **(MP/135 – INQ000408384)**. There might also be a protective effect on long-COVID from the use of COVID vaccines in adults **(MP/136 – INQ000408416)**. A more recent study published in November 2023 from Sweden has shown that the effectiveness of vaccination against long COVID was 21%, 59% and 73% for one, two or three doses, respectively **(MP/137 – INQ000408443)**. Although studies in children are needed, there is no reason to believe that there would not be a proportionate beneficial effect of vaccination on long COVID.

115. The data that was evaluated for approval in children was immunobridging and safety data, but in some cases, there were also small-scale efficacy studies. All these showed positive effects, with the immune responses in children being better than in adults **(MP/138 – INQ000409494)**. Based on the evaluation of safety, quality and effectiveness, the COVID vaccines have been approved for use in children. Some representative examples are shown below in terms of dosing, but please note that this can vary depending on whether the child had been vaccinated before, or whether it is the original vaccine or the newer bivalent/XBB1.5 vaccine:
    a. Comirnaty 30µg/dose in children 12+ years; Cominarty 10µg/dose in children 5-11 years old; and Cominarty 3µg/dose for infants and children 6 months to 4 years.
    b. Spikevax 100µg/dose for children 12 years of age or older; 50µg/dose for children 6-11 years; 25µg/dose for 6months-4 years of age.
    c. Nuvaxovid is licensed for individuals 12 years of age and older.

Vaccines Safety Monitoring

116. Given the likely scale of vaccination that would be needed during the pandemic, pro-active steps were taken to develop a pharmacovigilance strategy that would enable the capture and assessment of vaccine-related adverse reactions as quickly and efficiently as possible, so that risk mitigation strategies could be put into place, if and when appropriate. The initial step was the formation of COVID-19 Vaccine Safety Surveillance Methodologies expert working group, which met

on four occasions **(MP/139 – INQ000409569) (MP/140 – INQ000409572) (MP/141 – INQ000409570) (MP/142 – INQ000409571)** and considered proposals and methodologies for MHRA-led vigilance activities. Following these four meetings, it was felt that the work of this group had concluded as evidenced their report **(MP/143 – INQ000409480)**. The COVID-19 Vaccine Benefit Risk Expert Working Group had been formed on 25 August 2020 – this group had a broader remit, and was able to follow on from the work of the COVID-19 Vaccine Safety Surveillance Methodologies expert working group, without any detriment to the overall programme of work.

117. The final report of the EWG was presented to the CHM on 27 November 2020 **(MP/144 – INQ000408436)** and was published on 5 February 2021 **(MP/143 – INQ000409480)**. There were 4 strands to the strategy.

118. ***Strand 1 - Enhanced passive surveillance:*** The cornerstone of pharmacovigilance in the UK is the Yellow Card scheme (see below). Members of the public, healthcare professionals and industry can submit reports of suspected adverse reactions. The MHRA encourages anyone to report suspicions of adverse reactions, but this does not necessarily mean that the medicine or vaccine caused the reaction. The MHRA developed a COVID-19 interface to the Yellow Card scheme **(MP/145 – INQ000408437)**, undertook continual review of potential safety signals using up-to-date statistical approaches, and also undertook an observed-expected analysis: this is an evaluation of the observed number of reports of a suspected adverse reaction compared with what would be expected in a population, based on the naturally-occurring rate that would normally happen in a given time period in the same sized cohort and in the absence of vaccination.

119. ***Strand 2 – Rapid cycle analysis and ecological analysis***: This is a method which supplemented the Yellow Card scheme. Rapid cycle analysis involves proactive, weekly analysis of a range of theoretical side effects to quickly identify safety signals – it again involves 'observed vs expected' analyses (i.e., comparing rates after vaccination to rates in unvaccinated comparator groups). However, it does not rely on people directly reporting any concerns through the Yellow Card scheme, but instead uses anonymised electronic health care records. Ecological

analysis involves the monitoring of trends of particular events within a certain population, for example those who were prioritised for vaccination, compared with the same population pre-vaccination.

120. ***Strand 3 – Targeted active monitoring through the Yellow Card vaccine monitor***: This is a form of active monitoring in some people who have received vaccines (for example, those who may have been under-represented in the vaccine clinical trials). This required invitations of a random selection of vaccinees to register on the Monitor, and then pro-active follow up to ascertain whether any suspected adverse reactions had occurred.

121. ***Strand 4 – Formal epidemiological studies***: The above 3 strands can be used to identify an association, but this may not necessarily be causal, i.e., it may be coincidental. In order to determine causality, other studies such as formal epidemiological studies with different designs are needed where an adequate number of people can be studied in an unbiased way to provide a quantitative estimate of the adverse reaction and if it is causally related to the administration of the vaccine. It was envisaged that these epidemiological studies could be undertaken by the MHRA using the Clinical Practice Research Datalink **(MP/146 – INQ000408439)** which captures daily data from ~20% of GP practices in England and includes 13 million currently registered patients. However, these studies may also be undertaken by academic groups either in collaboration with MHRA, or separately. It was important to capture data from these studies to provide an evaluation of the adverse reactions which were occurring, whether they were caused by the vaccines, a quantitative estimate of the adverse reaction, and identification of any risk factors which could then be used as part of a risk mitigation strategy.

122. The MHRA was able to share data from these 4 strands of work with the VBR EWG and with the CHM throughout the pandemic.

<u>Yellow Card Scheme</u>

123. The Yellow Card scheme is an important part of medicines safety surveillance in the United Kingdom. It was established in 1964. It is used to monitor and collect information around safety concerns and incidents involving all medicinal products, including medicines, vaccines, medical devices and e-cigarettes. It is operated jointly by the CHM and the MHRA. The purpose of the scheme is to provide an early warning that the safety of a product may require further investigation.

124. Information is gathered through reports that are made to the scheme. These reports can be made online through the Yellow Card website **(MP/147 – INQ000408440)**, via the Yellow Card App, by telephone and on paper. The scheme relies on voluntary reporting of problems by the public (including patients, parents and care givers) as well as from healthcare professionals. In May 2020, a dedicated Yellow Card portal was set up (as mentioned in section 6.1) for reporting incidents related to COVID-19 and its treatment, including vaccination.

125. The MHRA use Yellow Card data in range of different ways including:

a. Highlighting the report in their database as a possible safety issue and keeping a close watch on the issue by monitoring similar reports.
b. Noting the patient perspective of the issue reported to help develop a better understanding of the impact on patients using the product.
c. The report can be used as a basis for requesting additional information from the reporter to build a better understanding of the reported issue.
d. Analysing similar reports to identify new safety signals.
e. The reports can also be used as a basis for requesting further information from other sources such as the manufacturer.
f. The reports can be used to open a dialogue to discuss the reported issues with other regulatory agencies and experts in the field.

126. Yellow Card reports of suspected issues are evaluated by MHRA staff with expertise in medicines safety, together with additional sources of evidence, to identify any new safety issues or side effects. Statistical techniques are applied to work out whether more events are being seen that would be expected to be seen in the absence of use of the vaccine, medicine or device. Clinical characteristics are also looked at to see if new patterns of illness are emerging that could indicate

a new safety concern. This safety monitoring is supplemented with other epidemiology studies including analysis of data on national usage, anonymised GP-based electronic healthcare records and other healthcare data to proactively monitor patient safety. Account is also taken of international experience based on data from other countries. These signals can also be shared with the CHM and its expert advisory/working groups in order to obtain independent advice. As outlined in sections 6.1-6.4, an enhanced surveillance strategy was put into place for the COVID vaccines.

127. The nature of Yellow Card reporting means that reported events are not always proven side effects. Some events may have happened anyway, regardless of vaccination. This is particularly the case when millions of people are vaccinated, and especially when vaccines are being given to the most elderly people and people who have underlying illness.

128. Analysis of the Yellow Card reporting to the vaccines was regularly published by the MHRA on the Yellow Card Website **(MP/148 – INQ000408438)**. On 7 July 2022, the MHRA published a Summary of Yellow Card reporting covering the period from 9 December 2020 to 29 June 2022 **(MP/149 – INQ000408385)**. As of 29 June 2022, for the UK, 171,913 Yellow Cards had been reported for the COVID-19 Vaccine Pfizer/BioNTech, 245,771 had been reported for the COVID-19 Vaccine AstraZeneca, 39,809 for the COVID-19 Vaccine Moderna and 1,768 had been reported where the brand of the vaccine was not specified. For the COVID-19 Vaccine Pfizer/BioNTech, COVID-19 Vaccine AstraZeneca and COVID-19 Vaccine Moderna the overall reporting rate is around 2 to 5 Yellow Cards per 1,000 doses administered.

129. For all COVID-19 vaccines, the overwhelming majority of Yellow Card reports relate to injection-site reactions (sore arm, for example) and generalised symptoms such as 'flu-like' illness, headache, chills, fatigue (tiredness), nausea (feeling sick), fever, dizziness, weakness, aching muscles, and rapid heartbeat. Generally, these happen shortly after the vaccination and are not associated with more serious or lasting illness. These types of reactions reflect the normal immune response triggered by the body to the vaccines. They are typically seen with most types of vaccines and tend to resolve within a day or two. The nature of reported suspected

side effects is broadly similar across age groups, although, as was seen in clinical trials and as is usually seen with other vaccines, they may be reported more frequently in younger adults.

130. The MHRA report concluded that "The expected benefits of the vaccines in preventing COVID-19 and serious complications associated with COVID-19 far outweigh any currently known side effects." But noted that "As with all vaccines and medicines, the safety of COVID-19 vaccines is continuously monitored and benefits and possible risks remain under review **(MP149 – INQ000408385)**."

131. The Yellow Card database can be interrogated for trends in adverse drug reaction (ADR) reporting, and this can be related to batch numbers, but there are caveats (as outlined at paragraph 213).

132. In respect of individual Yellow Card reports, when the report is sent in by the reporter, the patient may be at a certain stage or severity of the adverse reaction. In most cases, the adverse reaction will improve with time (after the culprit medication has been removed, or the patient has had treatment), but in some cases the adverse reaction can be long-lasting. The MHRA can follow up any Yellow Card report and ask for more information, in terms of more details of the reaction, or on the outcome of the adverse reaction. The main limitation with this is that reporters may be difficult to trace and even if they do receive the request from the MHRA, they may not reply.

133. Of course, it is also possible to follow trends in reporting of a specific adverse reaction over time, but this may not necessarily mean that the symptoms have improved or worsened over time because the characteristics of the patient group receiving the medication may have changed over time, or the nature of the disease may have changed over time (as it did with the COVID pandemic). Any trends identified therefore need careful evaluation and interpretation.

134. There are many different ways of completing a Yellow Card report, including through a website, an app, by paper or by telephone. The MHRA has tried to make this as inclusive as possible.

135. The Yellow Card has a large number of fields which should be completed when reporting an adverse reaction. Ethnicity has been added as a field more recently. The form asks for "other drugs" including the reason for taking these drugs, which allows for the collection of data on comorbidities. A copy of the Yellow Card report form is exhibited at **(MP/150 – INQ000502035)**.

136. Coroners can report any deaths associated with vaccine use (irrespective of causality) using the Yellow Card system. They can also write directly to the MHRA about adverse reactions associated with any drug.

137. The Yellow Card system is a voluntary reporting scheme. Other countries do have a mandatory reporting scheme, but their reporting is no better than that in the UK. In fact, it is acknowledged that the UK has one of the best ADR reporting schemes in the world. I think rather than making reporting mandatory, it is important to continually raise awareness of the reporting scheme amongst all reporters. Education and training for healthcare professionals is important and ensuring that the public know of the existence of the yellow card reporting scheme, and how reports can be submitted.

138. The Yellow Card Vaccine Monitor (YCVM) for the COVID vaccines was introduced as one of the components of the strategy for vaccine safety monitoring. The MHRA is no longer recruiting members to the YCVM, but is still receiving and monitoring follow up. During the pandemic, close to 1.5 million invitations were sent, yielding over 33,000 registrations, including roughly 12,000 individuals over the age of 70 years and 2,500 pregnant women. The overall results of the vaccine monitor, and the value it added to the safety surveillance programme, have not yet been presented to the CHM. A large amount of data was also collected through the Yellow Card reporting system (strand 1), the rapid cycle analysis (strand 2) and the formal epidemiological studies (please see paragraphs 118-121).

<u>Safety assessments from clinical trials</u>

139. The large COVID vaccine trials allowed an assessment of the safety of the COVID vaccines. The advantage of the trials was that adverse events could be compared between the active (i.e., vaccine arm) and the placebo arms, and if there was any imbalance between the two arms, this provided an indication that the adverse event was due to the vaccine. Importantly, they also provided an assessment of the occurrence of adverse events in the placebo arm – this can be termed the nocebo response (a detrimental effect produced by negative expectations of the vaccine).

140. Despite the large number of participants in the COVID vaccine trials, the trials still did not have adequate statistical power to detect the rare adverse events. I have been asked whether this indicates that the clinical trial process was insufficiently robust. The ability to detect an adverse event depends on the number of people included in the trial. Thus, for example with the Moderna COVID vaccine, approximately 15000 received the vaccine, while about 15000 received placebo. This provides statistical power to detect 1 adverse reaction which has a frequency of 1 in 5000 – i.e. it occurs in 1 in 5000 people exposed to the vaccine. Thus, any adverse event which is less common than in 1 in 5000, is unlikely to be detected. To detect an adverse event which occurs in 1 in 50,000 individuals, the trial would need to have 150,000 participants. Of course, regulators could insist on much larger trials, but this is unlikely to work because (a) it would be difficult to conduct such trials; (b) it would take too long meaning that we would never get new drugs on the market; and (c) it is unlikely that the pharmaceutical industry would fund it. It is therefore important to have appropriately (statistically) powered trials, with a robust post-marketing surveillance programme after the drug is licensed to identify rare and very rare adverse events (as outlined in sections 6.2-6.4). Consequently, the trials were robust and this was considered during the assessment for the marketing authorisation.

141. Injection site reactions, also termed reactogenic events, were the most common adverse reactions identified in the trials. These consisted of local effects such as pain, swelling, and redness, and systemic effects such as fatigue, headache, muscle pains, chills, joint pains and pyrexia. Most were mild or moderate in

intensity and resolved within a few days. These reactogenic events were slightly less common in older age groups. Figure 2 in the BNT162b2 mRNA COVID-vaccine trial (published in the New England Journal of Medicine **(MP/151 – INQ000408420)** highlights the different events, with a comparison between the active and placebo arms. A similar picture has been observed with the other vaccines, with some small differences in incidence.

142. A systematic review and meta-analysis **(MP/152 – INQ000408387)** comparing the reactogenicity of the COVID-19 vaccines has suggested that both doses of the mRNA vaccines, the second dose of the protein subunit vaccines and the first dose of adenovirus vectored vaccines were the most reactogenic.

143. A recent systematic review and meta-analysis covering 45,380 participants (22,578 on placebo and 22,802 on vaccine) **(MP/153 – INQ000408445)** showed that nocebo responses accounted for 76% of the systemic adverse events after the first COVID-19 vaccine dose and for 51.8% after the second dose.

Anaphylaxis

144. Anaphylactic reactions can occur with vaccines, but at the time of authorisation there was no indication that the BNT162b2 mRNA COVID vaccine caused this reaction. There was one case of anaphylaxis reported in the original trial which was shown to be due to a bee sting. However, on the first day of the vaccination campaign with the BNT162b2 mRNA COVID vaccine, there were two reports of anaphylaxis. Urgent advice was provided for the vaccination centres (prior to the second day of the vaccination campaign), and a warning was included in the product information (in section 4.4) **(MP/154 – INQ000408446)** which stated that "Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine" and "Close observation for at least 15 minutes is recommended following vaccination".

145. As a precaution, advice on a 15-minute observation period was included for all the vaccines that were subsequently authorised.

146. The 15-minute observation period had the effect of slowing down the number of vaccines which could be administered each day. In addition, there were concerns that it may increase the risk of spread of the virus through close contact of individuals waiting in the observation area. For this reason, the VBR EWG was asked about relaxation of the 15-minute period. However, the EWG declined to waive the 15-minute period at its meetings on 31 March 2021 **(MP/155 – INQ000409520)** and on 5 July 2021 **(MP/156 – INQ000409530)**, but asked for more data "to support an evidence-based review of the requirement (or not) for the 15-minute observation period".

147. In September 2021, the booster vaccination campaign was about to start, and there were concerns with the rapid spread of virus variants, which were further heightened by the emergence of the Omicron variant in November 2021. On 17 September 2021 **(MP/157 – INQ000409535)**, the EWG agreed that the 15-minute observation period could be removed only for homologous third doses. Subsequently, data were presented to the EWG **(MP/158 – INQ000409538)** which showed that the suspension of the 15-minute period had not adversely affected patient safety and had increased throughput through the vaccine centres.

148. As experience with the vaccines increased, and there was more data available about the need for a 15-minute observation period, the wait period was suspended for all COVID-19 vaccines. Monitoring by the UKHSA and NHS England has not shown any adverse consequences of suspending the 15-minute observation period for the COVID-19 vaccines.

149. It is important to note that there was no change in the summary of product characteristics of the vaccines when the 15-minute period was relaxed in order to keep this information consistent with the European label. The decision was taken at a policy level through information provided to the vaccine centres via the UK HSA and the NHS. It is also important to note that an observation period of 15-minutes or longer is still required for individuals with a past history of allergy (see table 5, The Green Book, chapter 14a) **(MP/159 – INQ000425558)**.

<u>Thrombotic Thrombocytopaenia Syndrome (TTS)</u>

150. In the middle of a mass vaccination campaign, the challenge of identifying a very rare adverse event amongst the many thousands of reports of adverse events being received, and distinguishing these events as being due to the vaccine rather than the underlying disease being prevented (or due to a background disease) is highlighted by the thrombotic thrombocytopaenia syndrome. The timeline of events associated with this syndrome are shown in table 1.

Table 1: Timeline of events associated with TTS

Date	Narration
Feb-21	3 reports (3rd, 11th and 18th Feb of CVST (cerebral venous sinus thrombosis) with Thrombocytopaenia following the AZ vaccine reported.
25 February 2021	AZ Vaccine safety considered by the VBR EWG - Advised MHRA events should be closely monitored but no regulatory action advised **(MP/160 – INQ000409515) (MP/161 – INQ000409479) (MP/162 – INQ000409478).**
Early March 2021	Series of European states suspended use of AZ vaccine based on reports of thrombosis: Denmark, Norway, Iceland, Italy, Estonia, Latvia, Luxembourg, Lithuania **(MP/163 – INQ000408447)**
07-Mar-21	Austria suspended use of a single batch of AZ vaccine based on reports of thrombosis at more general sites **(MP/164 – INQ000408448).**
11-Mar-21	Denmark, Norway & Iceland suspend vaccinations after reports of thromboses and death of a 60-year-old. Estonia, Lithuania, Luxembourg, Italy and Latvia followed suit **(MP/165 – INQ000408470)**. The Pharmacovigilance Risk Assessment Committee (PRAC) stated that "There is currently no indication that vaccination has caused these conditions, which are not listed as side effects with this vaccine. The position of EMA's safety committee PRAC is that the vaccine's benefits continue to outweigh its risks and the vaccine can continue to be administered while investigation of cases of thromboembolic events is ongoing **(MP/166 – INQ000408449)**.
14-Mar-21	Netherlands & Ireland suspended AZ (response to death and 3 hospitalisations in Norway the previous day) **(MP/167 – INQ000408449).**
15-Mar-21	Germany suspended vaccination temporarily pending EMA review following 7 cases of thrombosis **(MP/168 – INQ000408451)**; Italy widened ban (from particular batch to all batches); Spain; Slovenia & Cyprus also banned on the same day.
16-Mar-21	Sweden suspended use of AZ vaccine.
17-Mar-21	MHRA consults COVID-19 VBR EWG **(MP/169 – INQ000409517)** on a review of venous thromboembolism and thrombosis with thrombocytopaenia in order to discuss the emerging evidence. At this point the MHRA had received 5 reports of CVST cases occurring following AZ vaccine; concluded that no evidence of increased risk of peripheral venous thromboembolism. Evidence did not support

	increased risk of thrombocytopaenia alone. As a very serious condition, further information should be rapidly gathered on the events where thrombosis is accompanied by thrombocytopaenia. The benefit/risk of the vaccine still overall positive, although may vary in different age groups and clinical vulnerability. Further data to be evaluated and next steps taken. 2 extra reports received between 25 Feb & 17 March 2021.
18-Mar-21	MHRA publishes press statement saying no evidence between AZ and blood clots but further review into 5 reports of rare blood clot in the cerebral veins occurring with thrombocytopaenia is being investigated **(MP/170 – INQ000408457).**
March 2021	2 further reports on 13th March 2021 and 15th March 2021.
23-Mar-21	VBR EWG considered thrombosis with thrombocytopaenia again **(MP/171 – INQ000409518)** - concluded that there was insufficient evidence to establish causality at present, and that the events reported had been rare. Highlighted that information needed to be gathered on possible risk factors in cases.
24-Mar-21	VBR EWG updated: MHRA had received further information from haematology experts and were now reconciling cases with Yellow Card reports - EWG noted that there were now over 30 cases of thromboembolic/thrombocytopenic events **(MP/120 – INQ000409519)**
26-Mar-21	Independent panel convened to agree definition of what constitutes a case of thrombosis with thrombocytopaenia and to adjudicate Yellow Card reports.
27-Mar-21	CHM meeting **(MP/172 – INQ000409498)** - advised that while there is a temporal association with vaccination; no causal association could be established on currently available evidence; appears to be more cases in younger age groups but significance of this finding needs to be further investigated as case numbers are low; current trials in children should continue.
31-Mar-21	VBR EWG **(MP/155 – INQ000409520)** - The EWG considered that the overall risk of thrombosis with thrombocytopaenia remains low but there is concern of significant harm for individual patients. In younger age groups, the risk of COVID-19 and associated complications might not be as high and so the benefit risk from the vaccine in these groups may be different to older groups.
01-Apr-21	CHM **(MP/173 – INQ000409499)** considered thrombosis with thrombocytopaenia: acknowledged that while causality had not yet been established, and the incidence remains very rare, the number of cases continues to rise and that the association appears to be stronger as more data become available. Discussed that information on the risk should be communicated to healthcare professionals and the public. Advised that overall benefit-risk of the AZ vaccine remains favourable but acknowledged that situation is rapidly evolving and should be kept under review.
04-Apr-21	CHM Meeting **(MP/174 – INQ000409500)** - The benefit risk balance remained favourable in recipients aged over 40 but was less so for those under 40; data on second dose was lacking. On a precautionary basis, advised AZ shouldn't be used in pregnant woman.

06-Apr-21	VBR EWG **(MP/175 – INQ000409521)** - The EWG noted that the data had consistently showed a higher incidence in younger individuals in both the MHRA and company data. The EWG concluded that it was important to communicate on the available evidence in the younger age groups and allow informed consent, but that an age cut off for usage would not be proposed at present from a regulatory perspective. Also given presentation from AZ at this meeting.
06-Apr-21	CHM Meeting **(MP/176 – INQ000409501)** - The data presented no longer supported an age-based restriction for the use of the AZ vaccine; also advised that it was important that the public was made aware of the available data and that decisions made on benefits and risks could change as more data becomes available.
07-Apr-21	MHRA published advice **(MP/177 – INQ000408453)** on the signs and symptoms of thrombosis with thrombocytopaenia and stated that there was a reasonably plausible link between these events and administration of the AZ vaccine (but stressed that these were rare and still outweighed the risks for the majority of people). Also updated the information for healthcare professionals to include the evidence of age-related risks.
07-Apr-21	JCVI advises that it was preferable for people under 30 years without underlying health conditions to be offered an alternative vaccine if available **(MP/178 – INQ000413051).**
08-Apr-21	CHM noted that limiting AZ in under 30 year old population will not impact on the predicted peak of the 3rd wave **(MP/179 – INQ000409502).**
15-Apr-21	MHRA updated information to UK vaccine recipients advising that those with a history of heparin-induced thrombocytopaenia and thrombosis (HITT or HIT type 2) should not receive AZ vaccine and those who have experienced major venous and/or arterial thrombosis occurring with thrombocytopaenia following vaccination with any COVID-19 vaccine should not receive a second dose of the AZ vaccine.
15-Apr-21	Paper using US data shows risk of CVST after COVID infection higher than from mRNA COVID-19 vaccines vaccine **(MP/180 – INQ000408372)**.
19-Apr-21	VBR EWG meeting **(MP/181 – INQ000409522)** - Overall benefit-risk profile for AZ remains positive; however, benefits of immunisation in individuals under 30 is more equivocal and may begin to be outweighed by potential risks should incidence rate further increase.
26-Apr-21	VBR EWG **(MP/182 – INQ000409524)** - The EWG noted that the data had consistently showed a higher incidence in younger individuals in both the MHRA and company data. The EWG concluded that it was important to communicate on the available evidence in the younger age groups.
04-May-21	VBR EWG **(MP/183 – INQ000409525)** - The EWG advised that the overall benefit-risk profile of the AstraZeneca COVID-19 vaccine remains positive. However, the benefits of immunisation in individuals aged under 30 years may be outweighed by the potential risks, depending on the status of the COVID-19 pandemic, its severity and impact on hospitalisation.

06-May-21	CHM meeting **(MP/124 – INQ000409503)** – presented with the latest data where the overall incidence rate of TTS was 10.5 cases per million for first/unknown doses and the overall fatal incidence rate was 2.1 per million doses. The CHM noted that the risks may be higher in individuals aged under 40 (also see note from 4 April).
07-May-21	MHRA issues updated statement on latest data on case reports of thrombosis with thrombocytopaenia associated with AZ and the age gradient risk **(MP/184 – INQ000408455)**.
07-May-21	JCVI advises that alternative vaccines to AZ should be offered for people aged under 40 **(MP/185 – INQ000408456).**
05-Jan-22	Information for healthcare professionals and vaccine recipients for AZ amended to include a warning about CVST without Thrombocytopaenia.

151. On 25 February 2021 **(MP/160 – INQ000409515)**, the EWG was presented with a paper on COVID-19 vaccines and risk of immune thrombocytopaenia (lowering of platelets). At that time, over 10 million doses of the Pfizer/BioNTech vaccine and over 8.4 million doses of the AstraZeneca COVID-19 vaccine had been administered. The main focus of the paper was on ITP (Immune thrombocytopenic purpura), and whether this could either be precipitated or exacerbated by COVID vaccines. The EWG was also cognisant of the fact that COVID-19 infection itself had been reported to lead to thrombocytopaenia. The EWG concluded that this issue needed to be closely monitored, but at that time, no regulatory action was needed. This paper also highlighted a report of a 32-year-old man who had unfortunately died of cerebral venous sinus thrombosis (CVST) together with thrombocytopaenia – the EWG advised that "Further information on this case, and any other similar cases, should be obtained as follow-up".

152. On 17 March 2021 **(MP/169 – INQ000409517)**, the EWG met together with a group of expert haematologists. The focus of the meeting was to review reports of thrombosis with thrombocytopaenia following vaccination with the AstraZeneca COVID-19 vaccine. Analysis had shown that rates of isolated peripheral venous thromboembolism and immune thrombocytopaenia were not higher than historical background rates. However, 7 reports of thrombotic events occurring in conjunction with thrombocytopaenia, predominantly in younger patients, had been reported following vaccination with the AZ COVID vaccine. The EWG was also notified that the AZ vaccine had been temporarily suspended in several EU

member states including Ireland, Norway, Iceland, Austria, Estonia, Lithuania, Luxembourg, Italy, Latvia, and most recently, France, Spain and Germany. This was not an action taken by the European Medicines Agency, but locally within each country. The experts noted that "the co-existence of a prothrombotic state with thrombocytopaenia is rare. Although this is seen to occur rarely with certain conditions, at present it is unclear if a causal association exists with the vaccine. Nevertheless, given the close temporal association and the rare nature of the event, the meeting concluded this should be promptly evaluated further as a signal." The EWG advised on further steps including the development of a case definition, to continue working with the expert haematologists, to promote reporting of these cases via the Yellow Card system, develop risk minimisation strategies, and treat this as an urgent matter and keep it under review.

153. I have been asked whether the UK should have suspended the use of the AstraZeneca vaccine on a precautionary basis in early March 2021 like other European countries. By 17 March 2021, the MHRA had received only 5 reports of TTS in the UK. As highlighted at paragraph 176, there is a background incidence of TTS, and at that stage, it was very difficult to be sure that this reaction was causally related to the AZ vaccine. At that time, real-world evidence was beginning to appear on the effectiveness of even one dose of the vaccine in preventing hospitalisation and deaths. Therefore, the benefit-risk was considered to be positive. With the benefit of hindsight, it could be argued that we should have suspended the use of the AZ in early March. However, a decision to do so at a critical stage of the pandemic ran the risk of undermining public confidence in the vaccine not only in the UK, but across the developing world where the AZ vaccine was directly responsible for saving millions of lives. Furthermore, given our population size, and the limited availability of vaccines during the early stages of the pandemic, together with increasing evidence of the effectiveness of the AZ vaccine, suspension at that time would likely have led to an increased number of deaths from COVID. It is also important to highlight the morbidity that has been caused by COVID infection beyond the initial acute symptoms. A recent analysis in OpenSAFELY (**MP/186 – INQ000502033)** has shown that people who have had COVID-19 before or without being vaccinated are at higher risk of cardiovascular events for

at least two years, the risk being greatest in weeks 1-4 after infection, while COVID-19 vaccination reduces the risks of cardiovascular events after COVID-19 infection. Furthermore, a paper in the New England Journal of Medicine, published on 7 August 2024 **(MP/187 – INQ000502039)**, shows that the risk of long COVID (now called Postacute sequelae of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (PASC)) has decreased since the beginning of the pandemic, and 72% of this decrease can be attributed to vaccination, while 28% is attributable to change in the virus from the ancestral strain to Omicron. Although we did not definitively know about the effect of vaccination on long COVID at the time, the CHM commented in its minutes of 27 March 2021 **(MP/172 – INQ000409498)**, point 2.18: "It was however noted that while Long COVID is still not well understood, that this is an important risk in young people and a decrease in the risk would be an additional benefit of vaccination".

154. On 18 March 2021, there was a communication from the MHRA highlighting that cases of thrombosis together with thrombocytopaenia were being investigated, but the communication also advised "anyone with a headache that lasts for more than 4 days after vaccination, or bruising beyond the site of vaccination after a few days, to seek medical attention" **(MP/188 – INQ000408457)**.

155. Subsequent to this, there was intense activity with many meetings of the VBR and CHM which evaluated the rapidly changing situation of reports of thrombosis occurring together with thrombocytopaenia following the administration of the AZ vaccine (please see table 1 for timelines). The following are important issues to emphasise:

    a. There was a need to have a case definition which was agreed with the help of haematologists on 23 March 2021 **(MP/171 – INQ000409518)**. I have been asked why a case definition wasn't agreed sooner. This was a complicated and a completely unforeseen new syndrome in association with adenoviral vaccine administration, and the fact that the haematologists were able to develop a case definition within one month should be commended. Clearly, the process could have been even

faster if we had better data infrastructure which allowed easier access to accurate clinical, radiological and laboratory data. Publication of guidance on the diagnosis and management of TTS by the UK Expert Haematology Panel on 1 April 2021 preceded guidance from most other countries and international societies (France, Thrombosis and Haemostasis Society of Australia and New Zealand, International Society for Thrombosis and Haemostasis) **(MP/189 – INQ000502042)**.

b. However, assessment of the cases was difficult because Yellow Card reports lacked the essential information. The MHRA was advised to obtain additional information by contacting the individuals who had reported but this was difficult, resource intensive, and information was not always forthcoming. Independent adjudication by a haematologist was also hampered by the lack of information in the reports.

c. A major limitation was that we did not have reliable data on background rates of the occurrence of thrombosis together with thrombocytopaenia. We were able to ascertain that the background rate of cerebral venous sinus thrombosis (in isolation) was 15 per million per year, with a 5% mortality **(MP/172 – INQ000409498)**. I have addressed how improvements could be made in the future at paragraph 173.

d. Another issue which had to be taken into account was the effect of COVID-19 infection itself on the risks of isolated thrombocytopaenia and isolated thrombosis which was significantly higher than after vaccination. For example, a paper published on a pre-print server on 14 April 2021 **(MP/190 – INQ000408458)**, and in a peer-reviewed journal on 15 July 2021 **(MP/180 – INQ000408372)**, highlighted that the incidence of cerebral venous thrombosis and portal vein thrombosis was 4.5-6 fold higher than after receiving a mRNA vaccine. Therefore, the possibility that some of the cases of thrombosis with thrombocytopaenia being due to an underlying COVID-19 infection could not be discounted.

e. The CHM was also informed that based on modelling data that a 10% reduction in vaccine rollout would be expected to increase COVID-19 related hospitalisations and deaths in the likely event of a third wave.

f. There were some early indications that the risk of TTS was higher in the younger age groups administered the AZ vaccine, but given the small numbers it was difficult to be sure that there was a distinct age cut-off.

g. On 1 April **(MP/173 – INQ000409499)**, the CHM acknowledged although the incidence of TTS remains very rare, the number of cases had risen, and the association appeared stronger as more data became available. The CHM concluded that "in older adults, the benefits of vaccination far outweigh the risk, however, in younger adult age groups the case numbers are closer to the estimated numbers of deaths prevented by vaccination, indicating a more finely balanced risk/benefit ratio". However, overall, the benefits of the AZ vaccine against COVID-19, and its attendant risks of hospitalisation and death, and possibly long COVID, outweighed the risks for the vast majority of people.

h. At the same meeting, the CHM advised the MHRA that (a) information on the risk should be communicated to healthcare professionals and the public; (b) a letter to healthcare professionals should be sent; (c) the product information for the AZ vaccine should be updated to include warnings around thromboembolic events with thrombocytopaenia. Contraindications were also added including not to administer a second dose if TTS had occurred with the first dose of the AZ vaccine. There was widespread dissemination of this advice to primary and secondary care, and to vaccine centres, and changes were made to the product information.

i. However, an age-based restriction in the product information for the AZ vaccine (in section 4.1 on therapeutic indications) was not recommended (apart from use in >18 years olds only which was introduced at the time of licensing based on the clinical trial data). Although there was evidence of a less favourable risk-benefit in those under the age of 40, it was initially difficult to be precise where the age cut-off should be, because of the small numbers of cases, difficulty in excluding underlying confounding factors, and the individual risk-benefit varied depending on the underlying co-morbidities. As far as I am aware, no other jurisdiction has introduced age-based restrictions in the therapeutic indication section of the product information.

156. Work with the Winton Centre was able to provide a better indication of the risk-benefit of the AZ vaccine at different ages **(MP/191 – INQ000408459)**. The risk-benefit analysis focused on prevention of ICU admissions due to COVID-19 by the AZ vaccine. The benefit-risk ratio was dependent not only on age but also on the local prevalence of the virus and how much an individual was exposed to other people who might be carrying it. Thus, for the 20-29 year age group, over 16 weeks, 0.8 ICU admissions would be prevented at low virus exposure risk, 2.2 at medium exposure risk and 6.9 at higher exposure at the cost of 1.1 case of TTS (see appendix 2 for figures).

157. Regarding the CHM meeting on 27 March 2021, I have been asked why risk/benefit evaluations were made without consideration of other vaccines, as stated in the minutes. The remit of the CHM is to assess the safety, efficacy and quality, and thereby the risk benefit, of individual products. For the AZ vaccine, we were becoming aware of the risk of the serious adverse drug reaction of TTS, but the case numbers were low at the time. Therefore, on a population basis, the benefits of the AZ vaccine far outweighed the risks of the serious adverse reaction. In the same minutes **(MP/172 – INQ000409498)** at 2.18, we state "*The Commission considered that the overall risk of thrombosis with thrombocytopenia remains low but there is concern of significant harm for individual patients. In younger age groups, the risk of COVID-19 and associated complications might not be as high and so the benefit risk from the vaccine in these groups may be different to older groups*." Furthermore, in 2.19 we highlighted that "*The Commission was not able to identify any specific risk factors but did note that cases with confounding factors should be further investigated to determine any populations at risk"*. Clearly, this was a rapidly changing situation with new information coming through all the time, and that is why the CHM and VBR EWG met frequently to review the situation, as demonstrated in Table 1.

158. I have been asked about a letter from Professor Wei Shen Lim of the JCVI to the Secretary of State for Health and Social Care, Matt Hancock, on 1 April 2021 (**INQ000416156**). The CHM was not aware of this letter to the Secretary of State. However, our advice on 1 April 2021 (point 2.18) was consistent

with this: "Discussed that information on the risk should be communicated to healthcare professionals and the public" **(MP/173 – INQ000409499)**. The majority of Commissioners are practicing doctors (including myself). In keeping with Good Medical Practice guidelines from the GMC, I believe in ensuring patients (and therefore members of the public) are given information on the benefits and risks of interventions in an open, transparent and timely manner. Clearly the situation here was more complicated than in an individual patient-doctor consultation as we were in a rapidly evolving pandemic, there was a huge amount of disinformation largely perpetrated through social media, and the benefit-risk evaluation was hugely complex (because of limited vaccine availability, the risks of catching COVID and its attendant complications, and the risks of a rare but serious adverse reaction). Despite this complexity, the CHM advised on the importance of communicating the benefit risk of the AZ vaccine to the public. I have been asked what lessons can be learned in relation to this. I would hope, that as part of this inquiry, lessons are learned from all the witness statements, and oral evidence sessions, to develop best practice guidelines in public communication for Government, press offices, regulators, advisers and clinicians.

159. These were two extraordinary meetings of the CHM on Sunday 4 April and Tuesday 6 April. We were receiving data from many different sources in relation to TTS. The minutes from the 4 April 2021 meeting **(MP/174 – INQ000409500)** state:

"The Commission advised that the balance of benefits and risk is less favourable for recipients less than 40 years, except where an individual has risk factors that increase their risk of COVID-19 mortality to a level comparable to the those for recipients aged 40 years and older, or if another vaccine is not suitable. ***The Commission recommended that the Regulation 174 authorisation should be amended to reflect this assessment of the benefit-risk balance****."* (Emphasis added.)

160. The minutes from the 6 April 2021 meeting **(MP/176 – INQ000409501)** state:

"2.8 Having considered the further data available, Commission advised

that the benefit-risk remained positive overall and that in light of the data presented to the Commission, ***an age cut-off for use of the AstraZeneca vaccine was no longer advised.***"

161. I have been asked why the CHM changed its advice between the two meetings. On 6 April, Astra Zeneca had presented data to the Vaccine Benefit Risk Expert Working group, which showed that there was a higher observed rate than expected in the younger age groups, but not in those over the age of 50 **(MP/175 – INQ000409521)**. However, the number of cases was small, and only 2 were outside of Europe. In the afternoon on 6 April, the same slides were presented to the CHM **(MP/176 – INQ000409501)**. The Commission was also informed of discussions taking place in other regions. At that point (and even until the recent withdrawal of the AZ vaccine), no regulator had introduced age-based restrictions on the use of the AZ vaccine. Based on these discussions, the CHM concluded that the overall risk-benefit profile was positive. The CHM also noted the value of consistency in the product information from international regulators in the context of a global pandemic.

162. Prof Wei Shen Lim was an observer at both of these meetings on 6 April, and we were made aware that JCVI was going to meet on 7 April following the discussions held at CHM.

163. There were several advantages to an advisory rather than a regulatory approach to age, including (a) it ensured consistency with international regulators; (b) the decision on the age cut-off could also be based on vaccine availability; and (c) it was consistent with what public health bodies had done in other European countries.

164. On 7 April 2021, a press conference **(MP/192 – INQ000408460)** was held with representation from DHSC (Prof Jonathan van Tam), MHRA (Dr June Raine), JCVI (Prof Wei Shen Lim) and CHM (myself). By 31 March 2021, 20.2 million doses of the AZ vaccine had been administered, and there were 79 reports of thrombosis together with thrombocytopaenia (19 people had died), meaning that the overall risk of TTS was approximately 4 per million people receiving the vaccine. It was

concluded that there was a possible link between the AZ vaccine and very rare adverse effect of TTS **(MP/177 – INQ000408453)**. JCVI, which is responsible for vaccine deployment, advised that "adults aged between 18-29 years of age who do not have an underlying health condition that puts them at higher risk of serious COVID-19 disease should be offered an alternative COVID-19 vaccine in preference to the AZ vaccine, where such an alternative vaccine is available" **(MP/192 – INQ000408460) (MP/178 - INQ000413051]**

165. On 7 May 2021, the JCVI changed the age-based advice so that individuals who were between 30-39 years old should also be offered an alternative vaccine to the AZ vaccine, "where available and only if this does not cause substantial delays in being vaccinated" **(MP/185 – INQ000408456)**. This considered data on the number of cases of TTS (up to 28 April 2021, there had been 242 reports of thrombosis in people with a low platelet count) and the availability of vaccines in the UK over the following months.

166. Between 7 April and 21 July 2021, the VBR EWG reviewed cases of thrombosis together with thrombocytopaenia every week, after which the frequency of updates decreased (as the number of cases of TTS came down). Up to 7 July 2021, there had been a total of 405 cases reported, and sadly, there were 74 deaths. The overall incidence rate was 14.8 cases per million after the first or unknown doses administered and 1.8 cases per million after the second dose. At that time, over 46 million doses of COVID-19 vaccine had been administered.

167. By 11 August, the number of fatal cases was revised down to 73 out of a total of 411 events, with an estimated overall case fatality rate of 18% **(MP/193 – INQ000408461)**. 24.8 million first doses and 23.9 million second doses of the AZ vaccine were administered across the UK from 4 January to 4 August 2021.

168. Although cases of TTS had been reported after the second dose of the AZ vaccine, it is likely that this was due to the background rate, and the advice was that people who had received the first dose of the AZ vaccine, and had not suffered any serious adverse effects, should receive the second dose **(MP/193 – INQ000408461)**.

169. We continued to review all cases of TTS including those reported for the mRNA vaccines. Up to 11 August 2021 **(MP/193 – INQ000408461)**, the MHRA had received 15 reports of TTS associated with the Pfizer/BioNTech vaccine, out of total of 20.46 million first doses and 13.8 million second doses administered. There were 2 reports of TTS following the Moderna vaccine. No signal of TTS was identified with these vaccines, and no change in the product information has been undertaken by the major regulatory agencies. These reports can be considered to represent background rates.

170. TTS has been reported with the Janssen vaccine, which is also an adenoviral vaccine, although the adenovirus is different from that used in the AZ vaccine. This vaccine has not been deployed in the UK. Data from the US show that there were 54 cases of TTS reported between 14 December 2020 to 31 August 2021 representing a reporting rate of 3.83 per million vaccine doses, with a 15% fatality rate **(MP/194 – INQ000408378)**.

171. The decision on which vaccine was deployed for the booster campaign was not within the remit of CHM, and I presume was made by JCVI. As outlined in paragraph 104, the CHM advised that the AZD1222 vaccine could be authorised for use as a (homologous) booster (i.e. third) dose only if the person had already received two previous doses of the vaccine.

172. All four strands of the COVID-19 vaccine vigilance strategy, as set out in paragraphs 118-121, were utilised by the MHRA in respect of the TTS safety signal. They were not evaluated in isolation, but in combination, to provide an assessment of the safety issues in real-world settings.

173. Are there any lessons to be learnt about detecting rare adverse events with medicines and vaccines in the future? In my personal opinion, yes. Accurate and detailed information on each case is critical for proper evaluation of the event. The Yellow Cards frequently do not contain all the information, and the MHRA team had to go back to the reporter for the additional information, which was resource intensive and time consuming, with a poor return rate. This needs to be improved for the future. Legal avenues which enable the MHRA to get rapid access to vital

individual patient level data in a public health emergency need to be explored. This could be done through either the ability to link data (as outlined below) or mandatory requirements on primary and secondary care settings to provide the information in a timely manner.

174. In relation to TTS, we not only needed data on vaccine administration, but also when the patient was admitted to a hospital or needed medical attention, what was the cause of the admission, and what radiological and laboratory data for that patient were available to either confirm or refute the diagnosis. This was not available to the MHRA or any Government department, and was only possible through manual evaluation of individual patient case records by haematologists and other healthcare professionals which was slow and not systematic (i.e. not all cases were identified). Therefore, another area which needs improving is the ability to link data between different parts of the healthcare system in the UK – this is particularly true for secondary care data because most patients with serious adverse events will end up being hospitalised. At present, most hospitals do not have the capability of linking data between the case records, laboratory data and imaging data unless this is done manually patient by patient. In an emergency, having the ability to link the vaccine administration data to admission data to imaging and laboratory data would have been transformational and would have allowed us to evaluate the signal of TTS more quickly.

175. An understanding of the mechanism of the adverse event helps in determining the biological plausibility and causality, and can also help in risk mitigation. As a clinical academic, and a researcher with expertise in drug safety, on my own volition, I set up a consortium of experts (including colleagues from MHRA and PHE) and applied for funding from DHSC to understand the mechanisms of TTS **(MP/195 – INQ000408462)**. This consortium has helped in furthering our understanding of the mechanisms of TTS and is currently completing work to ascertain whether there is a genetic susceptibility to TTS.

176. An additional factor which hampered the evaluation of the signal of TTS was the lack of data on the background incidence rates of TTS. A study published in late 2022 has shown that the background rates of TTS are extremely low ranging from

0.06 to 4.53 per 100,000 person-years for cerebral venous sinus thrombosis with thrombocytopaenia and mixed venous and arterial thrombosis with thrombocytopaenia, respectively **(MP/196 – INQ000408390)**. Furthermore, in November 2023, a study **(MP/197 – INQ000408463)** was able to show that rarely people can present with features of TTS (including the presence of special antibodies called anti-PF4 antibodies) in the absence of exposure to adenoviral vaccine or heparin, again providing evidence that this syndrome has a background frequency.

Myocarditis and pericarditis

177. These refer to inflammation of the heart muscle and the sac surrounding the heart (pericardium). These have been reported with vaccines in the past, and therefore were classified as adverse events of special interest at the time of vaccine authorisation (a noteworthy event which the marketing authorisation holder needs to monitor carefully).

178. The VBR EWG first discussed the issue of myocarditis and pericarditis on 4 February 2021 **(MP/198 – INQ000409513)**. At that time, numbers were small, and no conclusion could be reached. The EWG advised that monitoring of these adverse events should continue.

179. The diagnosis of myocarditis can be difficult, and assessment was made more difficult by the lack of adequate information in the Yellow Card reports. Furthermore, myocarditis can be caused by many other factors, including concomitant viral infections and COVID-19 itself. Between 1998 and 2017 (i.e., pre-pandemic), there were 12,927 admissions with myocarditis in England **(MP/199 – INQ000408471)**, an 88% increase in admissions over this period. Younger men were disproportionately affected by the myocarditis-related hospital admissions.

180. Subsequent reviews of Yellow Card reports of myopericarditis showed the numbers were slowly increasing but statistical analysis did not provide evidence of a signal, confirmed by similar analyses by the EMA and FDA. In late May 2021, a

signal of myocarditis was detected in Israel particularly in younger people. The numbers of reports also increased in the UK, US and EU, which led to the recommendation on 21 June 2021 by the VBR EWG **(MP/200 – INQ000409529)**, and agreed by CHM on 23 June 2021 **(MP/65 – INQ000409504)**, to add a warning to the product information that myocarditis and pericarditis had been reported with the mRNA vaccines, and highlight the symptoms people should be aware of.

181. Cases of myocarditis were more common in younger men, and also more common after the second dose of the vaccine. Most cases were mild typically occurring with a week of vaccine administration with symptoms abating after a few days.

182. By 23 November 2022, there had been 851 reports of myocarditis and 579 reports of pericarditis following the use of the Pfizer/BioNTech vaccine. The reporting rate across all age groups for myocarditis following vaccination with the monovalent Pfizer/BioNTech vaccine was 10 reports per million doses and 6 reports per million doses for pericarditis. There have been 251 reports of myocarditis and 149 reports of pericarditis following the use of the Moderna vaccine, with a reporting rate of myocarditis for the monovalent vaccine of 14 reports per million doses and 8 reports per million doses for pericarditis **(MP/201 – INQ000412954)**. The reporting rates for the bivalent vaccines which were introduced later have been similar. The reporting rates in those aged under 18 years has been lower than the reporting rates in young adults.

183. Although there have been reports of myocarditis with the AZ vaccine, these probably reflect the background incidence. Myocarditis and pericarditis have rarely also been reported with the Novavax vaccine, and product information for this vaccine has also been updated **(MP/202 – INQ000409568)**.

184. The VBR EWG continued to monitor the occurrence of myocarditis and pericarditis at its meetings (approximately 19 meetings covered this area) with input from expert cardiologists. Although the majority of individuals affected by myocarditis recovered, we monitored for the occurrence of long-term effects through the development of scar tissue which can occur after myocarditis. We also

asked the marketing authorisation holders to monitor for long-term effects from the myocarditis. Final study reports have not yet been returned. For Moderna, there are two ongoing observational cohort studies examining long-term outcomes from myocarditis and pericarditis. The final study reports are expected in June 2025 and October 2028 respectively. There have been no interim findings of note. For Pfizer-BioNTech there are two ongoing observational studies investigating myocarditis and pericarditis long-term outcomes. Final study reports are expected in September 2024 and November 2029 respectively. There have been no interim findings of note.

185. An article published on 1 February 2023 based on 7292 individuals aged more than 12 years from Denmark, Finland, Norway, and Sweden showed that the outcomes from myocarditis associated with the COVID-19 vaccines was better than the clinical outcomes of myocarditis caused by COVID-19 disease or conventional myocarditis **(MP/203 – INQ000408465)**. However, it will be important to continue monitoring patients who have had myocarditis after a COVID-19 vaccine over the long term as some show abnormalities on MRI imaging, but the consequences of this are unclear.

186. All four strands of the Covid-19 vaccine vigilance strategy set out in paras 118-121 were utilised in assessing the risk of myocarditis and pericarditis. However, the vaccine monitor may not have been adequately powered in a statistical sense to provide new information, but follow up is still on-going. Most of the information was obtained from passive surveillance, and through rapid cycle and ecological analyses. Epidemiological studies were conducted by academic investigators using the databases available in the UK. In addition, epidemiological studies from other countries, for example Israel, were also helpful in understanding how often these adverse events occurred, and whether there were particular groups at risk.

Neurological adverse events

187. Several neurological adverse events are classified as adverse events of special interest.

188. ***Facial paralysis***: There was an imbalance in the number of cases of paralysis of the facial nerves (also known as Bell's palsy) in the clinical trials for both the Pfizer and Moderna vaccines, and was therefore added to the product information. At a later stage, it was also added to the product information for the AZ vaccine following the US trial **(MP/51 – INQ000409509)**. A systematic review from October 2022 showed that Bell's palsy can be a rare non-serious adverse effect of COVID-19 vaccination and has a favourable outcome with treatment **(MP/204 – INQ000408388)**.

189. ***Guillain-Barre Syndrome (GBS):*** GBS is a rare condition characterised by muscle weakness and occasionally paralysis caused by attack on peripheral nerves by the body's immune system. It has been reported with other vaccines in the past and was therefore categorised as an adverse event of special interest. The VBR EWG reviewed Yellow Card reports of GBS associated with the AZ vaccine several times before recommending that it should be added to the product information on 23 July 2021 **(MP/205 – INQ000409532)**. A UK-based epidemiological study published in February 2023 has shown that the excess risk of GBS following the first dose of the AZ vaccine is 0.576 cases per 100,000 doses **(MP/206 – INQ000408391)**. No signal of GBS has been identified for the mRNA vaccines. The Janssen vaccine is also associated with GBS – a US-based analysis showed that the incidence rate of GBS per 100 000 person-years in the 1 to 21 days after the Janssen vaccine was 32.4, significantly higher than the background rate **(MP/207 – INQ000408466)**.

190. ***Transverse myelitis:*** There was one case of transverse myelitis (inflammation of the spinal cord which can lead to nerve damage and permanent scarring) reported in the original trial of the AZ vaccine **(MP/208 – INQ000408367)**. On 29 October 2021, the EWG heard that the overall reporting rate was about 4 reports per million vaccine participants. The EWG recommended that (a) a second dose of AZ vaccine should not be given if transverse myelitis was experienced after the first dose; and (b) the product information should be updated. Transverse myelitis was also included in the product information for the Janssen vaccine by the EMA, and the EWG considered that the product information for the Janssen vaccine in the UK should be aligned with EU product information.

191. ***Acute disseminated encephalomyelitis (ADEM)*:** The VBR EWG reviewed the issue of ADEM associated with the AZ vaccine on 25 August 2022 **(MP/209 – INQ000409543)**. There had been 14 suspected reports of ADEM associated with the AZ vaccine. The EMA had concluded the available evidence at that time did not support a causal association. The invited neurology experts felt that an association could not be excluded based on the limited available data. The EWG recommended that this possible adverse event should be kept under close monitoring. At its last meeting on 5 May 2023, the VBR EWG felt there was now adequate data on ADEM associated with the AZ vaccine to warrant its inclusion in the product label.

Diversity of clinical trials

192. I have been asked whether vaccine clinical trials were sufficiently diverse, in terms of age (including children), ethnic background and sex. The initial vaccine trials were large trials but were conducted in those above either 16 or 18 years of age. Both males and females were represented in these trials. They were multi-national trials and therefore the ethnic inclusion depended on the country in which the trial was conducted. It would have been impossible to include all ethnic groups in these trials, and trials seldom have an ideal mix of people, but the evidence that was presented in the ethnic groups provided supportive evidence that the effects in terms of efficacy would be similar. As with many new medicinal products, trials in children followed the trials in adults when the product is shown to have a positive benefit-risk ratio. This is covered in paragraph 115.

193. I have been asked if the clinical trials included testing on the immunosuppressed, or participants with co-morbidities. The CHM and EWGs were provided with data on comorbidities in the vaccine trial participants. The representation of immunosuppressed patients in the trials was small, and this was therefore included in the risk management plan as missing information. This would then require a post-authorisation commitment from the marketing authorisation holder to provide that information. For example, for the Moderna vaccine **(MP/210 – INQ000400239)**, there was a commitment to provide data

using a database from Kaiser Permanente. It is also important to note that there were many academically driven studies in immunosuppressed individuals which were launched in the UK following the authorisation of the vaccines which provided valuable information on the efficacy and safety of the vaccines, and further steps needed in these patients (for example booster doses). For example, a systematic review and meta-analysis of 82 studies **(MP/211 – INQ000502041)** showed that seroconversion rates in immunocompromised patients were significantly lower than in non-immunocompromised individuals, and although seroconversion improved with the second dose, it was still of lower magnitude. Such information was used by JCVI/UKHSA/NHS to make deployment decisions in terms of additional booster doses.

Use of COVID-19 vaccines in women

194. Two particular issues need to be considered here: the safety of the vaccines in pregnancy and breast feeding; and the effect on menstruation.

195. When the vaccines were first authorised, there was no information on the use of the vaccines in pregnancy and during lactation as pregnant women were excluded from the trials. We therefore had to take a precautionary approach and warn against the use of the vaccines in pregnancy and lactation. As more real-world evidence of the safety of the vaccines in pregnancy increased, and there was increasing evidence that COVID-19 infection can lead to worse outcomes in women, particularly if infection occurs in the third trimester, following a meeting with representatives from the Royal College of Obstetricians and Gynaecologists and the Royal College of Midwives **(MP/212 – INQ000409516)**, more permissive wording was introduced into the product information. The VBR EWG continued to monitor the safety of the COVID-19 vaccines in pregnancy, and we were reassured by the accumulating evidence that none of the original COVID-19 vaccines used in the UK, or any reactions to these vaccines, increased the risk of miscarriage, stillbirths, congenital anomalies or birth complications **(MP/213 – INQ000408467)**.

196. There is no evidence that COVID-19 vaccination while breastfeeding causes any harm to breastfed children or affects the ability to breastfeed **(MP/213 – INQ000408467)**.

197. The EWG continued to review the effect of COVID-19 vaccination on the menstrual cycle. There was a lot of media interest in this, with some anti-vaccination lobbies claiming that COVID-19 vaccines also led to infertility. Over the course of the vaccination campaign, evidence of a possible association between the mRNA vaccines and heavy menstrual bleeding increased (the menstrual bleeding was usually non-serious and temporary in nature), and the product information was therefore updated. There is no evidence to suggest that COVID-19 vaccines will affect fertility **(MP/213 – INQ000408467)**.

Yellow card reports with a fatal outcome

198. All Yellow Card reports with a fatal outcome are reviewed carefully by the MHRA, and the evidence that the vaccine may have caused the death is carefully assessed. This was reviewed by the VBR EWG on 22 January 2021 **(MP/214 – INQ000409512)**, 15 February 2021 **(MP/215 – INQ000409514)**, 18 March 2022 **(MP/216 – INQ000409539)**, 29 April 2022 **(MP/217 – INQ000409541)** and 22 July 2022 **(MP/202 – INQ000409568)**. The VBR EWG was reassured that there was no signal of excess mortality in any age group including the elderly. Most of the deaths had been reported in the elderly or in those who had pre-existing medical conditions. Given that we were vaccinating millions of people, and the priority was to vaccinate the elderly because of their increased risk of poor outcomes with COVID-19 infection, coincidental adverse events with a fatal outcome can occur in conjunction with vaccination, but that does not mean the vaccine was responsible for the death. The MHRA was able to look at the background death rates using ONS data and was able to show that several thousand deaths are expected to have occurred naturally, mostly in the elderly within 7 days of the many millions of vaccine doses administered **(MP/213 – INQ000408467)**.

199. The VBR EWG reviewed a study by the ONS which evaluated the risk of death in young people during the pandemic **(MP/216 – INQ000409539)**. No increased

risk of death from cardiac or other causes was identified in those aged 12-29 years in the six weeks following vaccination. The EWG were reassured by the data and agreed with the conclusion that COVID-19 vaccinations were not associated with an increased risk of death, from cardiac causes or otherwise in young people.

Other adverse events evaluated by the VBR EWG

200. Several other adverse events other than those discussed in the previous sections were evaluated by the VBR EWG. These are shown in table 2.

Table 2: Other adverse events evaluated by the Vaccine Benefit-Risk Expert Working Group

Date	Agenda Item	Outcome of the VBR EWG meeting
Thursday 18th March 2021 **(MP/216 – INQ000409539)**	Pfizer/BioNTech COVID-19 Vaccine – Risk of severe cutaneous adverse reactions (SCAR)	No update to the product information needed because of lack of evidence
Friday 14th May 2021 **(MP/218 – INQ000409526)**	COVID-19 Vaccine AstraZeneca and risk of Capillary Leak Syndrome	Keep issue under review.
Friday 4th June 2021 **(MP/219 – INQ000409527)**	Update on Capillary Leak Syndrome with COVID-19 vaccine AstraZeneca	Incorporate warnings into the product information for the AZ vaccine.
Monday 14th June 2021 **(MP/220 – INQ000409528)**	Update on Capillary Leak Syndrome with COVID-19 vaccine AstraZeneca	Advice unchanged from the meeting of 4 June 2021.
Monday 5th July 2021 **(MP/156 – INQ000409530)**	Moderna vaccine and delayed injection site reactions	Update the product information to incorporate the risk of delayed injection site reactions.
Monday 19th July 2021 **(MP/221 – INQ000409531)**	Capillary Leak Syndrome and COVID-19 vaccine Janssen	Amend product information to include this adverse event.
Tuesday 3rd August 2021 **(MP/222 – INQ000409533)**	Review of COVID-19 Vaccines and Herpes Zoster Review of COVID-19 vaccines and Vasculitis (SMQ)	Data were reassuring in showing no signal for herpes zoster. No signal of vasculitis identified.
Friday 10th September 2021 **(MP/223 – INQ000409534)**	Deafness and Tinnitus with COVID-19 Vaccines	No regulatory action required as no causal association had been identified.
Friday 17th September 2021 **(MP/157 – INQ000409535)**	Glomerulonephritis and nephrotic syndrome and COVID-19 vaccines	No regulatory action proposed.

Wednesday 6th October 2021 **(MP/224 – INQ000409555)**	COVID-19 vaccines and risk of dizziness, vestibular disorders and postural orthostatic tachycardia syndrome (POTS) Erythema Multiforme and mRNA COVID-19 vaccines	No evidence of a signal. Dermatological opinion requested.
Thursday 13th October 2021 **(MP/225 – INQ000409566)**	Corneal transplant rejection and COVID-19 vaccines	Further investigation of signal needed.
Tuesday 9th November 2021 **(MP/226 – INQ000409536)**	Update on Erythema Multiforme – expert opinion and PRAC feedback Capillary Leak Syndrome and Moderna & Pfizer COVID-19 Vaccines	Update the product information for the Pfizer and Moderna vaccines to include erythema multiforme as an adverse event. Further information requested from Moderna but no evidence of a signal with the Pfizer vaccine.
Friday 19th November 2021 **(MP/227 – INQ000409537)**	COVID-19 vaccines and risk of autoimmune haemolytic anaemia Corneal Transplant rejection with COVID-19 vaccines	No strong evidence of a potential signal. No signal of graft rejection but issue should be monitored closely.
Friday 18th March 2022 **(MP/216 – INQ000409539)**	Cardiomyopathy with mRNA vaccines	No safety concern identified.
Tuesday 29th March 2022 **(MP/127 – INQ000409540)**	Review of acute renal failure with Pfizer COVID-19 vaccine Capillary Leak Syndrome and COVID-19 mRNA vaccines	No regulatory action required but issue should be monitored. Warning on capillary leak syndrome to be added to the product information for the Moderna vaccine.
Friday 29th April 2022 **(MP/217 – INQ000409541)**	Autoimmune hepatitis and mRNA COVID-19 Vaccines	No causal association.
Friday 6th May 2022 **(MP/228 – INQ000409542)**	COVID-19 vaccines and Herpes Zoster in under 18-year-olds	No evidence of an association identified.
Thursday 23rd June 2022 **(MP/229 – INQ000409567)**	Risk of flare up of autoimmune disorders with the AZ, Pfizer & Moderna vaccines	No regulatory action necessary but issue should continue to be monitored.
Tuesday 20th September 2022 **(MP/230 – INQ000409544)**	Urticaria and extensive swelling of vaccinated limb in association with Moderna COVID-19 vaccine	Update product information.
Friday 18th November 2022 **(MP/231 – INQ000409545)**	Vaxzevria & addition of tinnitus to the product information following	Update product information.
Thursday 16th February 2023	CDC/FDA preliminary signal of ischaemic stroke in people aged 65 and older with bivalent Pfizer COVID-19 vaccine	Monitor signal and assess in UK date.

Friday 5th May 2023	Update on COVID-19 vaccine AstraZeneca and acute disseminated encephalomyelitis (ADEM). Updated analysis of COVID-19 vaccines and ischaemic stroke	Update product information about ADEM. No signal identified in UK data.

Communications

201. Communications on vaccine effectiveness and safety were critical during the pandemic. This was controlled by the Communications Offices at the MHRA and DHSC. Commissioners and members of the expert groups were asked not to communicate directly with the media about the content of meetings, and to refer any media enquiries to the MHRA Communications Office. As far as I know, no Commissioner or expert spoke to the media about the work and content of the committee meetings unless they were specifically asked to. Clearly this does not stop members from speaking with the media on their areas of expertise, but it was important that they made it clear that they were not speaking on behalf of the CHM or MHRA.

202. I was asked to speak at the press conferences that announced the authorisation of the Pfizer and AstraZeneca COVID-19 vaccines. I was also asked to take part in the press conference on 7 April 2021 which focused on the risks of thrombotic thrombocytopenia syndrome (see section 6.25). I was asked by the MHRA to speak to media outlets on certain vaccine-related items, but I think overall this was on about 3 other occasions.

203. During meetings, Commissioners and experts were able to provide advice to the MHRA on communications on matters related to the effectiveness and safety of vaccines, when appropriate. Our advice focused on the facts of the particular issues being discussed, and the need to be open and transparent about the benefits and risks of the vaccines, and to emphasise the overall risk-benefit balance. For some situations, we advised that the communications should be undertaken in collaboration with trusted organisations. For example, for vaccination during pregnancy, there was still hesitancy from pregnant women about being vaccinated, despite the accumulating data on the safety of the vaccines in pregnancy. Our advice was to work with Royal Colleges of Obstetrics

and Gynaecology and Royal College of Midwives to deliver the message on the benefit-risk balance of the vaccines **(MP/205 – INQ000409532)**.

204. There was a huge amount of information (and misinformation) available to the public during the pandemic. Information was provided to the public about reporting of side effects of vaccines and therapeutics but was probably drowned out by the "noise" in the system. Better, more expert use of social media, should be explored by the regulators in the future by employing individuals with the relevant experience of different social media platforms.

205. There is no *routine* process of updating people who have received a vaccine when side effects are subsequently discovered. The need to inform also depends on the nature of the side effect. Most side effects occur early after vaccination and are short lasting. Therefore, if an individual has received the vaccine earlier, and did not have any side effects soon after vaccination, it is unlikely that they will develop the side effect later. If the side effect is delayed, and serious, then the regulatory agency and public health bodies, should provide information to the recipients and to the public in a clear, open and transparent manner.

206. The information that was available on the benefits and risks of the vaccines was appropriately communicated during the pandemic. The nature of that messaging clearly had to be different at the time the vaccine was launched, compared to when almost the whole population had received at least two doses, when we knew more about the safety aspects. Unfortunately, it seemed that the information provided by the public health bodies was overwhelmed by the vaccine misinformation that was prevalent mainly on social media. Future strategies to overcome vaccine misinformation will be important.

207. When providing information to the public about vaccines, we should provide both relative and absolute risk estimates with the concepts explained.

Vaccine acceptance and hesitancy

208. The CHM largely stuck to its remit which focuses on the quality, safety and efficacy of medicinal products. The issue of vaccine acceptance and hesitancy was never discussed as a separate agenda item, but was discussed in conjunction with particular agenda items, for example, vaccinations in pregnant women as outlined above (section 7.2).

209. On 2 March 2021 **(MP/212 – INQ000409516)**, the VBR EWG had a presentation by experts from Imperial College who were leading the study on real-time assessment of community transmission 2 (REACT-2). The EWG heard that confidence in the vaccine program was high with 92% of people being vaccinated or agreed to accept the offer. However, confidence varied, being lower in younger age groups, and in those from certain ethnic minority groups (Black or Asian). The EWG were told that the survey had found that the main reasons for vaccine hesitancy were concerns about safety, pregnancy, fertility, and allergies. Such data (and data from many other studies) were used by Government and public health bodies to launch campaigns to increase confidence in vaccines and urge people to get vaccinated.

210. Overall, the vaccine campaign was hugely successful, particularly at the beginning when vaccine acceptance rates were high. This was critical in controlling the pandemic and opening up society. However, it is clear that as the vaccine campaign has continued, a degree of vaccine fatigue has crept in, leading to lower acceptance rates with booster campaigns, for example.

211. A huge amount of work has been undertaken by behavioural and social scientists, amongst others, on vaccine acceptance and vaccine hesitancy during the COVID-19 pandemic. We know that this is a hugely complex area and there is no simple single solution. In my opinion, this body of knowledge should be used in developing communication campaigns for future pandemics. Debunking myths (which are now mostly perpetrated through social media), highlighting the personal and societal benefits of vaccinations, and accurate information on the benefits and risks of vaccination, are all important messages that need to be prioritised, but it is also important to be aware that a one-size-fits-all approach will fail, and more

personalised messaging depending on the populations sectors being targeted will be important **(MP/232 – INQ000408382) (MP/233 – INQ000408392) (MP/234 – INQ000408468)**.

Other issues

Gene therapies and pro-drugs

212. I have been asked whether mRNA vaccines should have been characterised as "gene therapies" or "pro-drugs" as distinct from traditional vaccines. mRNA vaccines should not be regarded as gene therapies. A gene therapy is where a normal gene is introduced into cells to replace a missing or defective gene to treat a genetic disorder. A pro-drug is a biologically inactive compound which is converted in the body (usually through the action of enzymes) to an active compound. Therefore, mRNA vaccines can be classified as prodrug because they are converted to the S (spike) protein by the enzymatic action of intracellular structures called ribosomes (which are the site of protein synthesis in cells). A pro-drug will not work if it is not converted in the body to its active component. A pro-drug is usually inert but can in some instances also contribute directly to the safety of the drug. The overall assessment of the drug (i.e. the prodrug and its active component) is captured in the preclinical and clinical trials which are undertaken to assess the safety and efficacy of the drug. Thus, for the mRNA COVID vaccines, there were no other specific regulatory considerations needed because the data presented showed that the vaccines were effective, and the most common adverse reactions were short lasting reactogenic events (see paragraph 141).

Batch analysis and adverse events

213. I have been asked what, if any investigations or batch analysis was undertaken to determine whether certain batches were associated with higher rates of adverse events. Analysis of adverse reactions associated with different batches of the COVID-19 vaccines has been undertaken by the MHRA **(MP/235 – INQ000502038)**. This evaluation did not result in any safety concerns. There are however caveats to these types of analyses: (a) batch numbers are not available on all Yellow Card reports; (b) batches of the

COVID vaccines were of different sizes and there may have been differential distribution patterns and differential wastage rates; (c) different batches were used during different periods of the pandemic, and it is known that a vaccine-experienced person may have a different pattern of adverse reactions compared to a vaccine naïve individual; (d) a report on a Yellow Card is not proof of causality; and (e) not all adverse reactions are reported on Yellow Cards.

Long-term safety data and post-authorisation trials

214. I have been asked what obligations pharmaceutical companies have to proactively collect long-term safety data and/or conduct post-authorisation trials. The company obligations are outlined in the ABPI code of practice **(MP/236 – INQ000502031)**, and in more detail on the Government website **(MP/237 – INQ000502040)**. These include: (a) there is a mandatory legal obligation for the marketing authorisation holder to collect data about safety and adverse events reported with its products; (b) employees must be trained to ensure safety data are reported in a timely manner; (c) the company must collate and analyse individual and cumulative safety reports; (d) safety reports have to be submitted to the MHRA within defined timelines; and (e) companies can be inspected by the MHRA in relation to their pharmacovigilance systems.

215. A risk management plan (RMP) is required for every product being considered for a license. As part of the RMP, the MHRA can ask for a post-authorisation safety study as a specific obligation or a condition of the UK marketing authorisation. In these cases, a draft protocol needs to be submitted to the MHRA before starting the study, the MHRA then has 60 days to assess the PASS and request any amendments (if necessary). Voluntary PASS studies do not require protocol submissions. However final results of the PASS, irrespective of whether it is voluntary or imposed, need to be shared with the MHRA within 12 months of the end of the data collection. Interim reports may also be required for the imposed studies.

9. Lesson learning

216. The CHM held a meeting specifically to review the lessons that could be learnt from CHM's role during the COVID-19 pandemic. In order to capture all views, the CHM also invited members who were on the Commission during the pandemic but has since demitted. This included the following:

- Prof Stuart Ralston, Previous Chair of the CHM
- Prof Kein Taylor, Previous Chair of the Chemistry, Pharmacy and Standards Expert Advisory Group, ex-member of the CHM, and member of the COVID-19 vaccine benefit risk expert working group.
- Prof Jonathan Friedland, Previous Chair of the COVID-19 Therapeutics Expert Working and ex-member of the CHM.
- Prof Richard Gilson, ex-member of the CHM, and member of COVID-19 Therapeutics Expert Working.
- Dr Siraj Misbah, ex-member of the CHM, and Chair of the Covid-19 Vaccine Safety Surveillance Methodologies Expert Working Group.

217. The CHM pivoted to online working at the start of the pandemic, and this worked very well. Indeed, the CHM now meets online for all meetings apart from two every year.

218. The establishment of three Expert Working Groups (see section 28) early during the COVID-19 pandemic was successful and enabled members to take a deep dive into relevant issues, receive advice from a wider range of disciplines, and thereby provide input into the CHM. Despite the intensity of the work and the need to deal with urgent clinical issues during their regular work, experts were always available at short notice.

219. Commissioners agreed that all discussions at the expert working groups and at the CHM were held in a very open and constructive manner and members felt free to question one another outside their areas of expertise.

220. A wide range of organisations and individuals were invited to present to the committees. This was important as it enabled the CHM to hear from different parts of the UK health system. These meetings were organised to make sure that there was a clear distinction between the information gathering part of the meeting and

the decision-making part. It was appropriate that invited attendees could answer specific questions to provide information but could not be present for the decision-making part of meetings so that CHM maintained its independence. It was agreed that the MHRA should continue to build strong relationships with different parts of the health system in any future health emergencies., and that information should be shared with the CHM, but the CHM must remain independent and must be seen as being independent by all sectors of the UK health system.

221. Committee members were given access to the raw data during the vaccine submissions. Overall, this was felt to be useful. However, there was a huge amount of data, and it was not presented in the most user-friendly manner, and thus more signposting to the most relevant data would be helpful in the future.

222. The rolling submission of data from companies worked well and enabled the COVID-19 vaccines to be approved very soon after the final data set emerged. It gave Commissioners time to build up a picture of the vaccines' safety and efficacy. Rolling reviews should be used in the future when there is a particular need, for example, in a public health emergency, but they are highly resource-intensive, and the MHRA should be given the resource required to undertake rolling reviews, so that it is not at the expense of creating a backlog in other areas.

223. Because of the pressure on the system, there was a backlog in the publication of minutes from the CHM and expert working groups. Public assessment reports were also delayed. The Commission agreed that prompt publication of meeting minutes and public assessment reports is important for transparency and that additional resource should be made available in any future health emergency to enable assessors to continue their review work while other staff compiled meeting minutes.

224. The MHRA team and secretariat worked very efficiently throughout the pandemic period, and despite the pressure, the assessments and summaries produced were excellent. However, pivoting to COVID-related issues meant that other medicinal products (including clinical trials) not focusing on COVID-19 had to be deprioritised which led to a backlog in many aspects of the work required to be undertaken by

the MHRA. For future pandemics, it is important that "surge" resource is provided to the MHRA to prevent backlogs post-pandemic.

225. The difficulties of operating two different regulatory regimes, one for Great Britain and one for Northern Ireland, were acknowledged (and have been highlighted by the Nuffield Trust in its report of the effects of Brexit on the health system **(MP/238 – INQ000408459)**). For example, since 2021 more than 100 products had been approved in GB but not in NI, while 52 products had been granted marketing authorisation for NI but not in GB. During our deliberations, we were acutely aware of the fact that some of the decisions made by the MHRA, based on advice from the CHM, would be relevant only for GB but not for NI. Hopefully with the Windsor framework due to come into force in the near future, this should become less of an issue.

226. These difficulties were felt to be an issue that was a consequence of the coincidental timing of Brexit and COVID, rather than a pandemic issue *per se*. The Commission appreciated the interaction that occurred between the MHRA and other international regulators, but also felt that more interaction with the EMA would have been helpful. Irrespective of whether one is operating within or outside of a pandemic, it is important to ensure that there is on-going collaboration and information exchange (subject to issues of confidentiality) between international regulatory agencies. This would be mutually beneficial. It was felt by the CHM that there was more interaction with other non-EU regulatory agencies than there was with the EMA as a result of Brexit.

227. New data was being generated at a significant rate during the pandemic, which had to be dealt with during the regulatory process. In some cases, for example with the evolution of the virus and emergence of viral variants, this data was not mature, but despite this, decisions had to be made, with a view to modifying the decisions depending on the emergence of more data. While this was necessary, the Commission felt that it would have been helpful for basic science research to have been funded to ensure that the decisions could be validated or modified based on sound underpinning evidence.

228. The Commission discussed our responses to vaccine-related adverse reactions. Some of these reactions had been flagged as adverse events of special interest (AESI) before the COVID-19 vaccines were authorised and deployed. The AESIs included neurological adverse events, myocarditis, and anaphylaxis because these adverse reactions had been reported in the past with other vaccines. This helped in monitoring the occurrence of these events and taking appropriate regulatory action.

229. The Commission also discussed the emergence of thromboembolic events occurring together with low platelets (thrombotic thrombocytopenia syndrome) during the early part of the vaccination campaign with AstraZeneca vaccine. The timelines are provided in table 1 (section 137). This was a completely unexpected adverse event, and therefore had not been pre-specified as an AESI. The CHM also discussed whether we could have acted earlier. As the CHM is a scientific committee, it was felt appropriate to base advice on robust evidence of the benefits and risks. The committee felt that it promptly reviewed the data provided to it and advised timely and proportionate action once evidence of vaccine linked thrombosis and thrombocytopenia emerged.

230. It was noted that there were difficulties in getting specific detailed case-information on the cases as they were reported to the MHRA to inform decision making. It was agreed by all members that systems for gathering medical information from individual cases need to be improved and that improved collation and linkage of healthcare databases that would support the timely identification of adverse events was urgently needed. The differences in actions between different regulators/public health agencies in terms of use of the AstraZeneca vaccine was discussed and it was thought that this may have been driven by several factors such as the differences in the objectives/remit of the agencies, regional variations in the epidemiology of the pandemic, lack of availability of data on the background prevalence of the condition, availability of alternative vaccine options in the different constituencies, and the differences in the detailed information available for decision making.

231. The CHM also thanked the MHRA staff and secretariat for their excellent work during the pandemic, often responding at very short notice to provide the available information and arrange meetings.

Statement of Truth

I believe that the facts stated in this witness statement are true. I understand that proceedings may be brought against anyone who makes, or causes to be made, a false statement in a document verified by a statement of truth without an honest belief of its truth.

Signed: Personal Data

Dated: 5 September 2024

APPENDIX 1

LIST OF OBSERVERS INVITED TO CHM OR EXPERT WORKING GROUP MEETINGS

COMMISSION ON HUMAN MEDICINES*

Meeting	Date	Invited Experts
25	Saturday 27th March 2021	**Invited Experts** Professor Gordon Dougan Professor Neil French Professor Tom Solomon Professor David Goldblatt Professor Cheng-Hock Toh **Observers** Professor Jonathan Van-Tam Dr Nick Andrews Professor Wei Shen Lim Dr Mary Ramsay **NR**
26	Friday 1st April 2021	**Invited Experts** Prof Cheng-Hock Toh Ms Sara Payne **Observers** Prof Jonathan Van-Tam
27	Sunday 4th April 2021	**Invited Experts** Prof Cheng-Hock Toh **Observers** Prof Jonathan Van-Tam Dr Mary Ramsay **NR** Professor Wei Shen Lim Mr Luke Collet-Fenson Dr Andrew Earnshaw
28	Tuesday 6th April 2021	**Observers** Professor Jonathan Van-Tam Professor Wei Shen Lim Andrew Earnshaw
29	Thursday 8th & Friday 9th April 2021	**Experts from SPI-M - Modelling item only** Prof Dame Angela McLean Dr Tom Irving Prof Matt Keeling
37	Monday 6th September 2021	Prof Gordon Dougan Prof Neil French Prof David Goldblatt Sir Michael Jacobs

40	28th & 29th October 2021	Molnupiravir: Professor Judith Breuer Professor Deenan Pillay Professor David Dockrell
41	17th November 2021	Professor Kevin M G Taylor Mrs Madeleine Wang
42	29th November 2021	Professor Judith Breuer
45	30th December 2021	Professor Judith Breuer Sir Michael Jacobs Professor Deenan Pillay
46	14th January 2022	Professor Kevin M G Taylor Dr Robin Thorpe
47	27th & 28th January 2022	Professor Kevin Taylor Mr Robert Lowe Mr V'Iain Fenton-May Dr Robin Thorpe Professor Susannah Walsh
48	3rd & 4th March 2022	Professor David Dockrell
50	20th April 2022	Professor Judith Breuer Professor Gordon Dougan Professor David Dockrell
58	Thursday 27th October 2022	Robin Thorpe Shirley Price Kevin Taylor Judith Breuer

*Only meetings where experts or **Observers** were present are listed.

COVID-19 THERAPEUTICS EXPERT WORKING GROUP

Meeting	Date	Invited Experts/Observers
1	20th March 2020	**Observers:** Professor S Ralston – Chair of CHM Dr T Brooks - PHE Mr M Qualie - NHSIE Ms S McAleer - DHSC Dr J Bouvy - NICE Dr N Crabb - NICE

2	27th March 2020	**Observers:** Professor S Ralston – Chair of CHM Ms S Berry - DHSC Dr J Bouvy - NICE Dr T Brooks - PHE Mr M Qualie - NHSIE
3	3rd April 2020	**Observers:** Professor S Ralston - Chair of CHM **NR**
4	17th April 2020	**Observers:** Ms S Berry Dr J Bouvy - NICE Dr T Brooks - PHE Dr N Crabb - NICE Ms L Knowles Mr M Qualie - NHSIE Professor S Ralston - Chair of CHM **Invited Experts**: Professor T Spector Dr C Steves
5	24th April 2020	**Observers:** Dr J Bouvy - NICE Dr T Brooks - PHE Dr N Crabb - NICE Mr M Qualie - NHSIE Professor S Ralston - Chair of CHM
6	7th May 2020	**Observers:** Ms S Berry - DHSC Dr J Bouvy - NICE Dr N Crabb - NICE Mr M Qualie - NHSIE Professor S Ralston - Chair of CHM
7	15th May 2020	**Observers:** Ms S Berry - DHSC Dr J Bouvy - NICE Dr Tim Brooks- PHE Dr N Crabb - NICE Mr M Qualie - NHSIE Professor S Ralston - Chair of CHM
8	12th June 2020	**Observers**: Ms S Berry - DHSC Dr J Bouvy - NICE Dr Tim Brooks- PHE Mr M Qualie - NHSIE

		Professor S Ralston - Chair of CHM **Invited Experts**: Professor A Thomas (left after item 3.0) Professor S Devereux (left after item 3.0)
9	26th June 2020	**Observers**: Ms S Berry - DHSC Dr J Bouvy - NICE Dr Tim Brooks- PHE Mr M Qualie - NHSIE Professor S Ralston - Chair of CHM
10	24th July 2020	**Observers**: Mr David Wright - DHSC Dr Nick Crabb - NICE Professor S Ralston - Chair of CHM
11	7th August 2020	**Observers**: Dr J Bouvy - NICE Dr Tim Brooks- PHE Mr M Qualie - NHSIE Professor S Ralston - Chair of CHM Mr David Wright - DHSC
12	18th September 2020	**Observers**: Dr J Bouvy - NICE Dr Tim Brooks- PHE Mr M Qualie - NHSIE
13	16th October 2020	**Observers**: Dr J Bouvy - NICE Dr Tim Brooks- PHE Mr M Qualie - NHSIE Professor S Ralston - Chair of CHM Mr D Wright - DHSC
14	13th November 2020	**Observers**: Dr T Brooks Dr Jacoline Bouvy Mr D Wright Mr M Qualie Ms S Berry
15	11th December 2020	**Observers**: Dr T Brooks Mr D Wright Mr M Qualie Ms S Berry Professor S Ralston

16	Tuesday 12th January 2021	**Observers**: Dr Jacoline Bouvy Dr T Brooks Mr M Qualie Ms S Berry Professor S Ralston **Invited Experts**: Professor A Gordon Mr S Berry
17	Friday 29th January 2021	**Observers**: Dr D Dawoud Dr T Brooks Mr M Qualie Ms S Berry Professor S Ralston **Invited Experts**: Professor K Hyrich Professor H Lachmann
18	Friday 12th February 2021	**Observers**: Ms S Berry Dr T Brooks Dr D Dawoud Mr M Qualie
19	Tuesday 16th March 2021	**Observers**: Ms S Berry Dr T Brooks Dr N Crabb Dr D Dawoud Mr M Qualie
20	Friday 21st May 2021	**Invited Experts**: Professor J Breuer Professor G Dougan Professor T Golubchik **Observers**: Ms S Berry Dr T Brooks Dr D Dawoud
21	Friday 11th June 2021	**Observers**: Ms S Berry – DHSC Dr Tim Brooks- PHE Mr M Qualie – NHSIE Dr D Dawoud - NICE

22	Tuesday 27th July 2021	**Observers**: Ms S Berry Dr N Crabb Dr D Dawoud Mr M Qualie **Invited Expert**: Professor R Gupta
23	Tuesday 17th August 2021	**Observers** Ms S Berry Dr D Dawoud Mr M Qualie **Invited Expert** Professor Y Perrie
24	Monday 20th September 2021	**Observers** Ms S Berry Dr N Crabb Dr D Dawoud Mr M Qualie **Invited Expert** Professor Y Perrie
25	Friday 15th October 2021	**Observers**: Ms S Berry Dr T Brooks Dr D Dawoud Mr M Qualie **Invited Expert**: Professor Y Perrie Professor K Taylor
26	Tuesday 16th November 2021	**Observers**: Ms M Bartlett Dr D Dawoud Mr M Qualie
27	Thursday 9th December 2021	**Observers**: Ms S Berry Dr D Dawoud Mr M Qualie
28	Monday 20th December 2021	**Observers**: Ms S Berry Dr T Brooks Dr D Dawoud Mr M Qualie **Invited Expert**: Professor Y Perrie Professor K Taylor

29	Friday 14th January 2022	**Observers**: Ms S Berry Dr D Dawoud Mr M Qualie Ms M Mathews **Invited Expert**: Professor Y Perrie Professor K Taylor Dr R Thorpe
30	Monday 21st November 2022	**Observers**: Ms S Berry Dr D Dawoud **Co-Opted Expert:** Professor J Breuer
31	Monday 30th January 2023	**Observers**: Ms M Mathews **Co-Opted Expert**: Professor J Breuer
32	Tuesday 28th February 2023	**Invited Expert**: Professor Yvonne Perrie **Observers**: Dr Tim Brooks Dr Dalia Dawoud Ms Miranda Matthews

COVID SAFETY SURVEILLANCE METHODOLOGIES EXPERT WORKING GROUP

Meeting	Date	Invited Experts/Observers
1	28th May 2020	**Invited Experts**: Mr N Andrews Mr J Crofts Professor E Miller Professor A Scott Professor R Shattock **Observers**: Dr C Cameron Mr C Pile **NR** Professor L Smeeth

2	25th June 2020	**Invited Experts**: Mr N Andrews Dr J L Bernal Mr J Crofts Ms H McDonald Professor E Miller Ms H Pinches Professor A Scott Dr M Ramsay Ms J Stowe Ms J Walker Professor A Pollard Professor R Shattock **Observers**: Dr C Cameron Dr J Johnston Ms S Leeser Dr L Newport **NR** Professor J Van Tam
3	23rd July 2020	**Invited Experts**: Mr N Andrews Dr J L Bernal Ms H McDonald Professor E Miller Professor A Scott Ms J Walker Professor S McCormack Professor R Shattock **Observers**: Dr C Cameron Ms S Leeser **NR** Ms Claire Vittery
4	27th October 2020	Observers: Dr C Cameron Dr R Roberts Dr J Johnston Ms S Leeser Invited Experts: Professor A Pollard Mr N Andrews Dr J L Bernal Mr J Crofts Professor E Miller Ms H Pinches Professor A Scott Ms J Walker

COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Meeting	Date	Invited Experts
1	Tuesday 25th August 2020	
2	Friday 11th Sept 2020 (EWG attended CHM)	
3	Tuesday 29th September 2020	**Invited Experts** Prof Paul-Henri Lambert, Uni of Geneva Prof Linda Sharples
4	Wednesday 14th October 2020	**Invited Experts** Prof Linda Sharples
5	Wednesday 28th October 2020	Professor Linda Sharples PhD Professor of Medical Statistics, London School of Hygiene & Tropical Medicine (LSHTM) and Faculty of Epidemiology and Population Health
6	Tuesday 10th November 2020	Professor Linda Sharples PhD Professor of Medical Statistics, London School of Hygiene & Tropical Medicine (LSHTM) and Faculty of Epidemiology and Population Health
7	Wednesday 18th November 2020	**Observer** Professor Stuart Ralston
8	Friday 20th November 2020	Invited Experts Dr Alessandro Carabelli Research Lead, COG-UK, Cambridge Uni Dr Alexander Muik, Dr Annette Vogel & Dr Philip Dormitzer - BioNTech Mr Carbel Haber - Moderna

9	Saturday 21st November 2020	**Invited Experts** NHS: Keith Ridge – NHS England Alexander Williams – NHS England Justine Scanlan – NHS England Emily Lawson – NHS England Steve Powis – NHS England Alison Strath – NHS Scotland Andrew Evans & Lois Lloyd – NHS Wales **NR** - NHS Northern Ireland PHE: Mr Gareth Paul Thomas – Deputy Director at PHE **Observer** Prof Stuart Ralston
10	Tuesday 24th November 2020	**Invited Experts** Prof J Van Tam - Medical Officer **Observers** CHM members
11	Friday 27th November 2020	Mrs Helen Ward
12	Saturday 28th November 2020	**Observer** Professor Stuart Ralston
13	Monday 7th December 2020	
14	Wednesday 09th December (Hypersensitivity group)	
15	Thursday 10th December 2020	**Observer** Professor Stuart Ralston
16	Thursday 17th December 2020	**Observer** Professor Stuart Ralston

17	Tuesday 22nd December 2020	**Invited Experts attending for anaphylaxis item:** Professor Adam Fox, Allergy Consultant Paediatric Allergist Dr Shuaib Nasser, Consultant in Allergy and Asthma, Cambridge University Hospitals NHS Foundation Trust Dr Ravishankar Sargur Consultant Immunologist, Sheffield Teaching Hospitals; Dr Paul Turner Honorary Consultant in Paediatric Allergy and Immunology Imperial College London **AZ Reps:** Prof Andrew Pollard Dr Mary Plank Dr Tonya Villafana Dr Amanda Leach Dr Sam Lindgren Dr Beth Kelly Dr Elaine Jones Dr Ian Hirsch Dr Hugo Gomes da Silva Dr Gillian Traynor **Observer** Mary Ramsay - PHE Maureen O'Leary - PHS Prof Stuart Ralston
18	Thursday 24th December 2020	
19	Tuesday 29th December 2020	**Observer** Professor Stuart Ralston
20	Thursday 31st December 2020	**Observer** Professor Stuart Ralston
21	Sunday 3rd January 2021	
22	Wednesday 13th January 2021	**Observer** Andrew Earnshaw Professor Stuart Ralston Mary Ramsay

23	Monday 18th January 2021	Nick Andrews, Victoria Hall, Simon Funnell - PHE Dr A Carabelli & Sharon Peacock - COG-UK
24	Friday 22nd January 2021	
25	Friday 29th January 2021	Priya Mande, Human Challenge, Vaccines Taskforce Chris Charman, Human Challenge, Vaccines Taskforce Professor Rob Read, University of Southampton & Human Challenge Board Member Read R.C. Professor Chris Chiu, Imperial College (Study PI) Dr Charlie Weller Dr Debbie King Dr Shobana Balasingham - all from Wellcome Prof Paul Kellam - Imperial
26	Thursday 4th February 2021	Professor Tim Spector
27	Monday 15th February 2021	Professor Nick Andrews Mary Ramsay David Irwin Maureen O'Leary **NR**
28	Thursday 25th February 2021	**Invited Expert** Prof Nick Andrews, PHE Prof Stephen Devereux - item on Thrombocytopaenia

29	Tuesday 2nd March 2021	**NR** MBBS, PhD, FMedSci Chair in Epidemiology and Public Health Medicine Professor Helen Ward Professor of Public Health Professor Graham Cooke Professor Edward Morris, MD PRCOG President, Royal College of Obstetricians & Gynaecologists Professor Lucy Chappell, Lead for Vaccinations in Pregnancy, Royal College of Obstetricians & Gynaecologists Professor Marian Knight Professor of Maternal and Child Population Health Dr Kenneth Hodson MD MRCP(UK) MRCOG Head of UK Teratology Information Service Consultant in Obstetrics and Maternal Medicine Dr Mary Ross-Davie Director, RCM – Professional lead for RCM response to COVID-19 Ms Claire Livingstone RCM **Observers** Dr David Irwin Dr Jonathan Leach Dr Maureen O'leary Dr **NR** Dr Simon Stockley
30	Tuesday 9th March 2021	

31	Wednesday 17th March 2021	Professor Michael Murphy Professor of Transfusion Medicine, University of Oxford Dr Nichola Cooper PNS interest in Sanofi Imperial Healthcare College NHS Trust Dr Sue Pavord Consultant Haematologist at Oxford University Hospitals Dr Will Lester PNS interest in Pfizer and Sanofi Consultant Haematologist at University Hospital Birmingham Professor Marie Scully Consultant Haematologist, University College London Hospitals
32	Thursday 18th March 2021	Dr Jamie Lopez Bernal Consultant Epidemiologist, Public Health England Dr Laura Shallcross Institute of Health Informatics **NR** Public Health Registrar at UCL
33	Tuesday 23rd March 2021	Professor Michael Murphy Professor of Transfusion Medicine, University of Oxford Dr Nichola Cooper - Imperial Healthcare College NHS Trust Dr Sue Pavord - Consultant Haematologist at Oxford University Hospitals Dr Will Lester - Consultant Haematologist at University Hospital Birmingham Professor Marie Scully - Consultant Haematologist, University College London Hospitals Dr Josh Wright – Vice President of BSH Dr Keith Gomez - Chair, Haemostasis and Thrombosis Task Force of the BSH AstraZeneca Representatives
34	Wednesday 24th March 2021	

35	Wednesday 31st March 2021	Professor Aziz Sheikh Dr Nick Andrews **Observers** Dr Andrew Earnshaw - PHE Dr David Irwin - HSCNI Dr Jonathan Leach – NHS England Dr Maureen O'Leary - PHS Dr Mary Ramsay - PHE **NR** - PHW Dr Simon N. Stockley – NHS England Professor Elizabeth Miller – PHE **NR** – PHE Dr Paul Turner - PHE
36	Tuesday 6th April 2021	**Astrazeneca Representatives** Richard Marshall - SVP and Global Head of Late Respiratory & Immunology Kiran Nistala - VP and Head of Clinical Development, Immunology Johan Vekemans - Global Clinical lead Cathy Emmas - Head of Medical and Payer Evidence Strategy, Respiratory and Immunology Mike Laffan - (external expert) Professor of Haemostasis and Thrombosis, Imperial College Sam Lindgren - Senior Pharmacovigilance Medical Director Elaine Jones - Vice President - Regulatory Affairs Ann Taylor - Chief Medical Officer Gillian Traynor - Regulatory Affairs Director Mary Plank - Executive Regulatory Science Director, Inflammation Autoimmune, Infection and Vaccines Magnus Ysander - EU & UK Qualified Person for Pharmacovigilance (QPPV) **Observers** Magnus Nord - VP Global Patient Safety • Andrew Earnshaw - PHE • David Irwin - HSCNI • Jonathan Leach – NHS England • Maureen O'Leary - PHS • Mary Ramsay - PHE • **NR** - PHW • Simon N. Stockley – NHS England • Elizabeth Miller – PHE

		• NR PHE • Paul Turner – PHE • Nick Andrews – PHE • Wei Shen Lim – JCVI
37	Monday 12th April 2021	**Observers** Dr Nick Andrews - PHE Dr Andrew Earnshaw - PHE NR - JCVI Dr David Irwin - HSCNI Dr Jonathan Leach OBE – NHS England Dr Maureen O'Leary - PHS NR - HSCNI Dr Mary Ramsay- PHE NR - PHW Dr Simon N. Stockley – NHS England
39	Friday 23rd April 2021	
40	Monday 26th April 2021	
41	Tuesday 4th May 2021	**Observers** Dr Nick Andrews - PHE Dr Andrew Earnshaw - PHE NR - JCVI Dr David Irwin - HSCNI Dr Jonathan Leach OBE – NHS England Dr Maureen O'Leary - PHS NR HSCNI Dr Mary Ramsay- PHE NR - PHW Dr Simon N. Stockley – NHS England
42	Friday 7th May 2021	**Observers** Dr Nick Andrews - PHE Dr Andrew Earnshaw - PHE NR JCVI Dr David Irwin - HSCNI Dr Jonathan Leach OBE – NHS England Dr Maureen O'Leary - PHS NR - HSCNI Dr Mary Ramsay- PHE NR - PHW Dr Simon N. Stockley – NHS England
43	Monday 10th May 2021	
44	Friday 14th May 2021	

45	Monday 17th May 2021	
46	Friday 21st May 2021	**Observers** Dr Nick Andrews Dr Andrew Earnshaw – PHE **NR** - JCVI Dr Maureen O'Leary - PHS Dr Mary Ramsay- PHE Dr Jonathan Crofts – JCVI Professor Wei Shen Lim
47	Monday 24th May 2021	Dr Andrew Earnshaw - PHE Dr David Irwin - HSCNI Dr Jonathan Leach OBE – NHS England Dr Maureen O'Leary – PHS – Dr Simon N. Stockley – NHS England Dr Jonathan Crofts – JCVI
48	Tuesday 25th May 2021	Dr Andrew Earnshaw - PHE Dr Jonathan Leach OBE – NHS England Dr Maureen O'Leary – PHS Dr Mary Ramsay - PHE Dr Simon N. Stockley – NHS England Dr Jonathan Crofts – JCVI Professor Wei Shen Lim - JCVI
49	Tuesday 1st June 2021	
50	Friday 4th June 2021	
51	Monday 7th June 2021	
52	Monday 14th June 2021	
53	Monday 21st June 2021	Professor Matthew Snape Professor Andrew Grace Dr Guido Pieles **Observers** Dr Jonathan Crofts – JCVI Dr Andrew Earnshaw – PHE Dr David Irwin – HSCNI Dr Maureen O'Leary – PHS Dr Mary Ramsay – PHE Dr Simon N. Stockley – NHS England

54	Monday 28th June 2021	**Observers** NR – JCVI Dr David Irwin – HSCNI Professor Wei Shen Lim – JCVI Dr Jonathan Leach OBE – NHS England Dr Mary Ramsay – PHE NR – PHW Dr Simon N. Stockley – NHS England
55	Monday 5th July 2021	**Observers** Dr Nick Andrews – PHE Dr Jonathan Crofts – JCVI Dr Andrew Earnshaw – PHE NR – JCVI Dr David Irwin – HSCNI Professor Wei Shen Lim – JCVI Dr Jonathan Leach – NHS England Dr Maureen O'Leary – PHS Dr Mary Ramsay – PHE NR – PHW Dr Simon N. Stockley – NHS England
56	Monday 19th July 2021	**Observers** Dr Nick Andrews – PHE Dr Jonathan Crofts – JCVI Dr Andrew Earnshaw – PHE NR – JCVI Dr David Irwin – HSCNI Professor Wei Shen Lim – JCVI Dr Jonathan Leach – NHS England Dr Maureen O'Leary – PHS Dr Mary Ramsay – PHE NR – PHW Dr Simon N. Stockley – NHS England
57	Friday 23rd July 2021	**Observers** Dr Nick Andrews – PHE Dr Jonathan Crofts – JCVI Dr Andrew Earnshaw – PHE NR – JCVI Dr David Irwin – HSCNI Professor Wei Shen Lim – JCVI Dr Jonathan Leach – NHS England Dr Maureen O'Leary – PHS Dr Mary Ramsay – PHE NR – PHW Dr Simon N. Stockley – NHS England

58	Tuesday 3rd August 2021	**Observers** Dr Nick Andrews – PHE NR – JCVI Dr Andrew Earnshaw – PHE NR – JCVI Dr David Irwin – HSCNI Professor Wei Shen Lim – JCVI Dr Jonathan Leach – NHS England Dr Maureen O'Leary – PHS Dr Mary Ramsay – PHE NR PHW Dr Simon N. Stockley – NHS England
59	Thursday 19th August 2021	**Observers** Dr Nick Andrews – PHE NR – JCVI Dr Andrew Earnshaw – PHE NR – JCVI Dr David Irwin – HSCNI Professor Wei Shen Lim – JCVI Dr Jonathan Leach – NHS England Dr Maureen O'Leary – PHS Dr Mary Ramsay – PHE NR – PHW Dr Simon N. Stockley – NHS England
60	Tuesday 31st August 2021	**Observers from devolved nations and UKHSA/JCVI attend all meetings** NR Professor of Paediatric Immunology & Infectious Diseases
61	Friday 10th September 2021	Ms Emma Rourke Director, Health Analysis and Pandemic Insight, ONS Mr NR Deputy Director, Covid-19 Infection Surveillance Analysis Division, ONS Dr Vahe Nafilyan Statistician, Office for National Statistics Dr Koen Pouwels Senior Researcher at the University of Oxford's Nuffield Department of Population Health

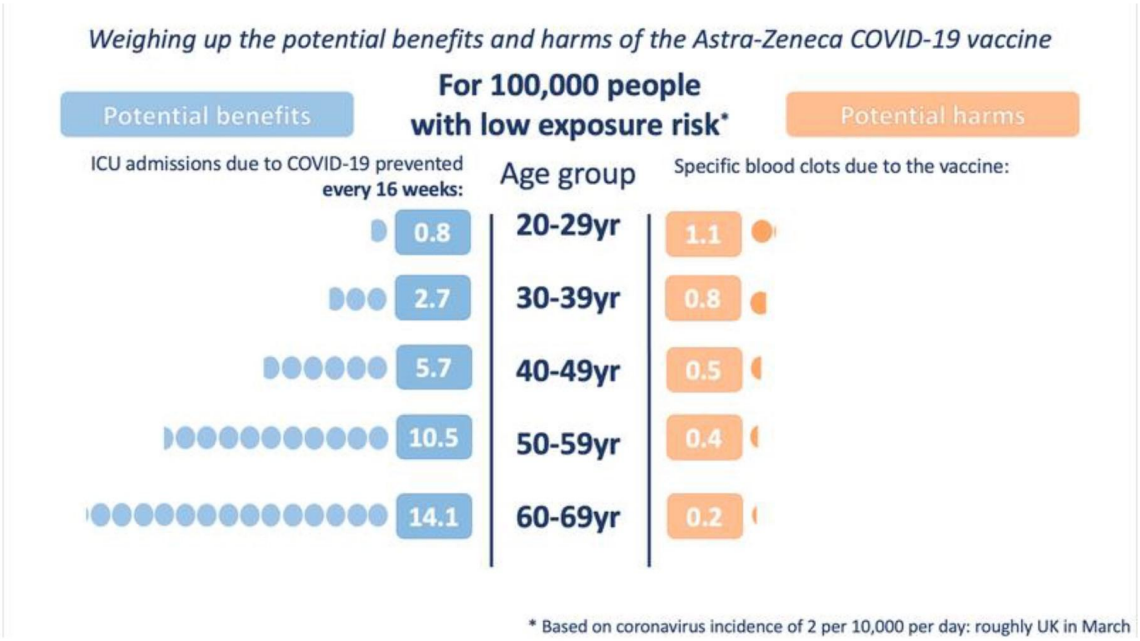
62	Friday 17th September 2021	Professor Michael Lunn Professor of Clinical Neurology and Consultant Neurologist Prof Andrew Grace Prof Guido Pieles
63	Friday 24th September 2021	
64	Wednesday 6th October 2021	
65	Thursday 13th October 2021	
66	Tuesday 19th October 2021	Andrew Grace Guido Pieles Professor Rickard Ljung Senior scientific expert Epidemiology, Swedish Medical Products Agency **NR** Swedish PRAC Delegate
67	Tuesday 9th November 2021	
68	Wednesday 17th November 2021	Moderna Representatives **NR** (item 6) Consultant Cardiologist, Lead cardiac MRI service at King's College Hospital **NR** (item 6) Consultant Cardiologist, Imperial College London Guido Pieles Rickard Ljung
69	Friday 19th November 2021	Professor Nigel Klein (for item 2 – Multi inflammatory syndrome) Consultant, Great Ormond Street Hospital for Children NHS Trust; Professor of Infectious Diseases and Microbiology, Institute of Child Health, UCL **NR** (for item 6 – Corneal transplant rejection) Department of Eye and Vision Science, Institute of Life Course and Medical Sciences, University of Liverpool

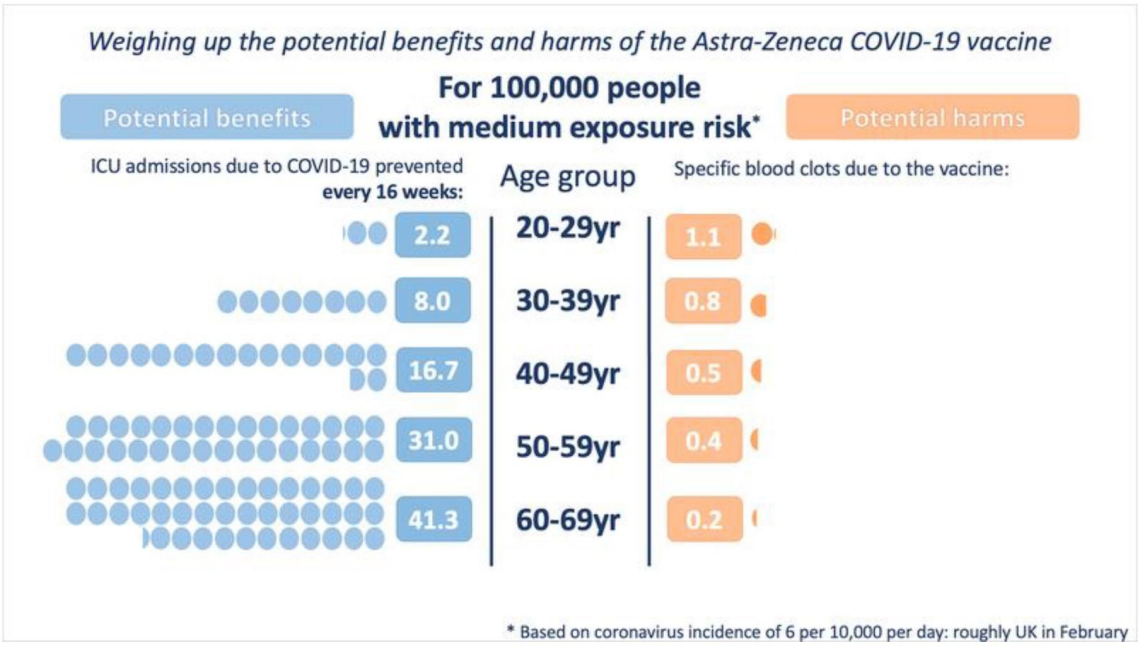
70	Friday 3rd December 2021	Professor Nigel Klein (for item 2 – General Safety Review) Consultant, Great Ormond Street Hospital for Children NHS Trust; Professor of Infectious Diseases and Microbiology, Institute of Child Health, UCL Professor Guido Pieles (for item 2 – General Safety Review) Consultant Congenital Cardiologist, Congenital Hear Unit, Bristol Heart Institute **NR** (for item 2 – General Safety Review) Consultant Paediatric Rheumatologist, Clinical Lead for Rheumatology Honorary Clinical Lecturer, University of Liverpool **NR** (for item 5 – ROC20 Observational study) University Medical Centre Utrecht
71	Friday 10th December 2021	Andrew Grace Guido Pieles Nick Andrews **NR**
72	Thursday 6th January 2022	
73	Thursday 13th January 2022	Prof Andrew Grace Prof Guido Pieles Nigel Klein **NR**
74	Wednesday 19th January 2022	**NR**
75	Friday 4th February 2022	Adam Fox NHSE/I Nick Andrews Paul Turner **NR**
76	Friday 18th February 2022	Prof Andrew Grace Prof Guido Pieles Beverley Hunt Sue Pavord
77	Friday 4th March 2022	Beverley Hunt Lance Turtle Sue Pavord

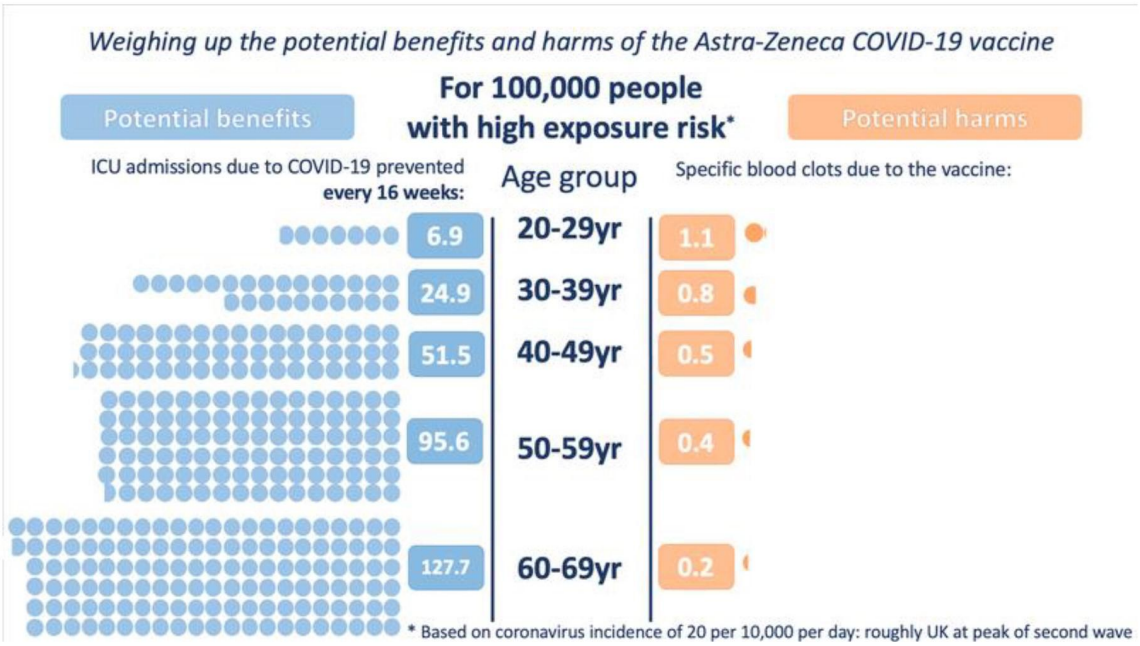
78	Friday 18th March 2022	Prof Andrew Grace Prof Guido Pieles Dr Vahe Nafilyan
79	Tuesday 29th March 2022	Maureen O'Leary
80	Wednesday 13th April 2022	Prof Andrew Grace Prof Guido Pieles
81	Friday 29th April 2022	
82	Friday 6th May 2022	Prof Andrew Grace Prof Guido Pieles
83	Wednesday 8th June 2022	Prof Andrew Grace Prof Guido Pieles
84	Thursday 23rd June 2022	Prof Andrew Grace Prof Guido Pieles David Hunt Waqar Rashid
85	Friday 22nd July 2022	
86	Friday 12th August 2022	
87	Thursday 25th August 2022	David Hunt Philip Smith Andrew Grace
88	Tuesday 20th September 2022	Vahe Nafilyan - ONS
89	Friday 18th November 2022	
90	Tuesday 13th December 2022	
91	Thursday 19th January 2023	
92	Thursday 16th February 2023	
93	Friday 5th May 2023	Prof David Hunt Prof Philip Smith

Appendix 2

Benefit risk analysis of the AZ COVID-19 vaccine undertaken by the Winton Centre following the occurrence of cases of thrombotic thrombocytopaenia syndrome (MP/239 – INQ000000 (RELC0000000081))






Weighing up the potential benefits and harms of the Astra-Zeneca COVID-19 vaccine
Potential benefits
For 100,000 people with high exposure risk*
Potential harms
ICU admissions due to COVID-19 prevented every 16 weeks:
Age group
Specific blood clots due to the vaccine:
6.9
20-29yr
1.1
24.9
30-39yr
0.8
51.5
40-49yr
0.5
95.6
50-59yr
0.4
127.7
60-69yr
0.2
* Based on coronavirus incidence of 20 per 10,000 per day: roughly UK at peak of second wave