Witness Name: Dr Justin Green
Statement No.: First
Exhibits: JG/1 – JG/95
Dated: 7 November 2024

UK COVID-19 INQUIRY

WITNESS STATEMENT OF DR JUSTIN GREEN

I, **DR JUSTIN GREEN**, will say as follows:

1. I am Global Product Lead for the Oxford/AstraZeneca Vaccine and work within AstraZeneca's Vaccines & Immune Therapies Unit. I provide this witness statement as part of AstraZeneca's response to the UK COVID-19 Inquiry's Request for Evidence dated 27 September 2023 made under Rule 9 of the Inquiry Rules 2006 (the ***Rule 9 Request***) and the Inquiry's further requests for information received on 7 August 2024.

2. The matters covered in the Rule 9 Request are wide-ranging and extend beyond the knowledge of any one individual. In giving this statement, I am speaking on behalf of AstraZeneca and, in some places, I will refer to information provided to me from various sources and individuals. Unless stated otherwise, the facts and matters to which I refer in this witness statement are within my own knowledge and are true. Where the facts and matters to which I refer in this witness statement are not within my own knowledge, they are true to the best of my knowledge, information and belief. Where information has been provided to me by third parties, I identify the source of that information and believe it to be true.

3. This witness statement was prepared in draft by AstraZeneca's legal representatives based on discussions with me. I then reviewed and amended the draft statement and ensured that it is expressed in my own words, before signing the statement of truth below.

4. The documents I refer to for the purposes of providing the evidence in this witness statement are listed in the attached Annex by the Unique Reference Number (***URN***) attached to these documents by the Inquiry. When referring to a document in the body of this witness statement, I also cite the URN. I have worked with

AstraZeneca's legal representatives to identify documents for inclusion in this way, having regard to the Inquiry's request only to disclose key documents at this stage.

5. Nothing in this witness statement is intended to waive any privilege of AstraZeneca or any member of its corporate group, or any associated individual, and I am not authorised to, and do not, make any such waiver.

Content and structure of this statement

6. I understand that Professor Sir Mene Pangalos is giving a statement to the Inquiry that provides an overview of the role played by AstraZeneca during the global pandemic and AstraZeneca's role in relation to the development, manufacture, supply and distribution of the Oxford AstraZeneca vaccine (the ***Oxford/AstraZeneca Vaccine***).[1] My statement addresses AstraZeneca's role in the clinical trials, regulatory approvals and pharmacovigilance (ongoing safety monitoring) processes for the Oxford/AstraZeneca Vaccine in the UK over the Inquiry's relevant period of 30 January 2020 to 28 June 2022.

7. The structure of my statement is as follows:

   (a) **Section A**: My background and role at AstraZeneca

   (b) **Section B**: Introduction to clinical, regulatory and safety-monitoring processes

   (c) **Section C**: Overview of the clinical trials of the Oxford/AstraZeneca Vaccine

   (d) **Section D**: Regulatory approval for the Oxford/AstraZeneca Vaccine in the UK – Regulation 174 authorisation

   (e) **Section E**: Post-authorisation monitoring – pharmacovigilance procedures in relation to the Oxford/AstraZeneca Vaccine

   (f) **Section F**: Updating the UK Product Information for the Oxford/AstraZeneca Vaccine

   (g) **Section G**: Real-world evidence for the Oxford/AstraZeneca Vaccine

[1] The Oxford/AstraZeneca Vaccine is also known as Vaxzevria (ChAdOx1 nCoV-19) or, formerly, as AZD1222 or the COVID-19 Vaccine AstraZeneca.

(h) **Section H**: Further UK regulatory approvals for the Oxford/AstraZeneca Vaccine following initial UK authorisation

(i) **Section I**: Future pandemic preparedness

SECTION A: MY BACKGROUND AND ROLE AT ASTRAZENECA

8. I am a UK qualified Infectious Diseases and General Internal Medicine physician. I hold an MA in Biological Anthropology from the University of Cambridge, a Bachelor of Medicine/Bachelor of Surgery (BM BCh) degree from the University of Oxford, a Fellowship of the Royal Colleges of Physicians of the United Kingdom (FRCP), diploma in Tropical Medicine and Hygiene (DTM&H) from the Royal College of Physicians of London (RCP) and a PhD from Imperial College London.

9. After various junior medical jobs, I passed the MRCP examination, then completed my Specialist Registrar training in the North Thames Deanery at various hospitals. As part of this training programme, I worked at Singapore's Tan Tock Seng hospital as a registrar in 2002 to 2003 and was responsible for the clinical care of over 200 individuals infected with Severe Acute Respiratory Syndrome Coronavirus 1 (SARS-CoV-1) during the first SARS outbreak. After completing my PhD, I worked in my final year as a Specialist Registrar at the Royal Free Hospital in London from 2008 to 2009, receiving a Certification of Completion of Training in Infectious Diseases & General Internal Medicine. In the 14 years since then, I have worked in clinical development for GSK, ViiV Healthcare and AstraZeneca.

10. I joined AstraZeneca in November 2020, by which time the company had been working on the Oxford/AstraZeneca Vaccine for some months. I joined as one of three Global Clinical Product Leads for the Oxford/AstraZeneca Vaccine and was later promoted to Global Clinical Head for the Oxford/AstraZeneca Vaccine. In these roles, I oversaw the continuation of the AstraZeneca-sponsored Phase III clinical trial for the Oxford/AstraZeneca Vaccine and was part of the core team working on AstraZeneca's regulatory submissions and responses to the UK's Medicines and Healthcare products Regulatory Agency (***MHRA***). In April 2022, I was promoted to Interim Vice President for Clinical Development in the Vaccine & Immune Therapy Unit. In this role I continued to have oversight of the ongoing development of the Oxford/AstraZeneca Vaccine. In October 2022, I became a Global Product Lead within AstraZeneca's Vaccines & Immune Therapies Unit. In this role, I work as the Global Product Lead with oversight and leadership of the Global Product Team for the Oxford/AstraZeneca Vaccine. This is a cross-functional team delivering the ongoing development, manufacturing and commercialisation of the Oxford/AstraZeneca Vaccine. My responsibilities, therefore, include oversight of

AstraZeneca-sponsored clinical trials, regulatory processes and labelling updates for the Oxford/AstraZeneca Vaccine.

SECTION B: INTRODUCTION TO CLINICAL, REGULATORY AND SAFETY MONITORING PROCESSES

11. My medical and clinical career has spanned both working as a physician in Singapore during the first SARS outbreak and working within the pharmaceutical industry during the COVID-19 global pandemic. I have seen first-hand in both cases the public health emergency posed by infectious disease epidemics and the loss of health, life and everyday freedoms associated with such outbreaks.

12. In this statement, I have endeavoured to address AstraZeneca's role in the clinical trials, regulatory authorisations and safety monitoring of the Oxford/AstraZeneca Vaccine. All of these are important processes that provide the scientific and evidence-based framework through which the vaccine's benefit/risk profile was investigated and evaluated. These robust processes are important, because vaccination programmes are rightly considered one of the most successful and cost-effective public health interventions for preventing the outbreak of infectious diseases. Vaccination programmes are a routine and essential part of paediatric and general public healthcare. They are estimated to have helped prevent approximately 25 million deaths in 2021 alone, from diseases such as diphtheria, tetanus, whooping cough, influenza and COVID-19.[2] They have also helped to eradicate smallpox and assist in reducing the circulation of polio and measles in many countries around the world.[3] Depending on the nature of disease, vaccination programmes will continue to be, in my opinion, a critical part of any future pandemic response in the UK.

13. Reflecting on AstraZeneca's contribution to protecting the UK public against COVID-19 during the pandemic, it is important to recognise that the Oxford/AstraZeneca Vaccine was one of the most studied COVID-19 vaccines. The positive interim efficacy, immunogenicity and safety results of the Oxford-sponsored global clinical trials programme that were used to support the UK regulatory authorisations, were consistently confirmed by subsequent clinical trials. A common misperception is that

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[2] See Exhibit JG/1 - INQ000506154, World Health Organization (WHO), 'Immunization' (*WHO*, 5 December 2019). See also Exhibit JG/2 - INQ000472219, Watson, Oliver J et al., 'Global Impact of the first year of COVID-19 vaccination: a mathematical modelling study' (2023) 22 The Lancet 1293.

[3] See Exhibit JG/3 - INQ000506151, U.S. Department of Health and Human Services (HHS), 'Goal 5: Increase Global Prevention of Death and Disease through Safe and Effective Vaccination' (*HHS*, 24 June 2016).

the announcement of clinical trial results marks the completion of these studies, which may have contributed to the idea that clinical trials for the COVID-19 vaccines were done particularly quickly. While the Oxford clinical trials did progress at pace, due to the urgent need for a vaccine against COVID-19, they followed standard clinical trial processes without compromise to safety monitoring. Furthermore, these trials did not end in 2020. Those volunteers who enrolled in the Oxford/AstraZeneca Vaccine clinical trials continued to be followed and assessed long after the announcement of initial results in November 2020.

14. Following authorisation, the Oxford/AstraZeneca Vaccine, like other COVID-19 vaccines, continued to be the subject of intensive safety monitoring (known as pharmacovigilance) by regulatory authorities and by AstraZeneca.

15. Post-authorisation pharmacovigilance has also included collection, investigation and reporting of Individual Case Safety Reports (***ICSRs***)[4] and their analysis by regulatory authorities, including the European Medicines Authority (***EMA***) and the MHRA, as well as by AstraZeneca. The analysis of information obtained through pharmacovigilance activities is used to keep the benefit/risk profile of the vaccine under continuous review and to update the Product Information available for healthcare providers and vaccine recipients in relation to the Oxford/AstraZeneca Vaccine to ensure that this reflects available medical and scientific knowledge.

16. Healthcare services, scientists and manufacturers also engage in the evaluation of real-world evidence for the ongoing and continued understanding of the Oxford/AstraZeneca Vaccine's effectiveness and safety profile. For example, the first set of real-world effectiveness data for the Oxford/AstraZeneca Vaccine came from a study by Public Health Scotland published in February 2021. As I explain below, the results reported showed the Oxford/AstraZeneca Vaccine was 94% effective in preventing hospitalisations (with further data published in April 2021 showing 88% effectiveness against hospitalisation in respect of a slightly different dataset), providing compelling evidence that the vaccine substantially reduced the risk of COVID-19 related hospital admissions.

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[4] AstraZeneca has a regulatory obligation to report to the MHRA all ICSRs that are received directly by AstraZeneca. Regulation 188 of the Human Medicines Regulations 2012 requires that all serious suspected adverse reactions (with "serious" defined in Regulation 8(1)) must be reported to the MHRA within 15 days of the marketing authorisation holder becoming aware of the reaction; all non-serious suspected adverse reactions must be reported within 90 days. The same obligations and timelines apply in relation to the reporting of ICSRs to the EMA.

17. The volume and robustness of the data and information generated from the above clinical, pharmacovigilance and real-world evidence processes is why regulatory authorities worldwide have consistently established the Oxford/AstraZeneca Vaccine's positive benefit/risk profile and explain why this vaccine was such an important medicine for preventing hospitalisations, severe outcomes and deaths in the UK from COVID-19 disease.

SECTION C: OVERVIEW OF THE CLINICAL TRIALS OF THE OXFORD/ASTRAZENECA VACCINE

Design of the registrational clinical trials for the Oxford/AstraZeneca Vaccine

18. In May 2020, AstraZeneca UK Limited and Oxford University Innovation Limited signed a licence agreement for the development and distribution of a potential vaccine against COVID-19. There was clearly an urgent need for such a vaccine. By the time the licence agreement was signed, more than 40,000 people in the UK alone had died from COVID-19[5] and the rates of hospitalisation and death from COVID-19 continued to increase.

19. To develop the vaccine, AstraZeneca agreed that Oxford would continue to lead its clinical trials and that AstraZeneca would provide support for these, including with the analysis and interpretation of results, and help obtain regulatory authorisations worldwide.

20. In summary, the Oxford-sponsored clinical trials that formed the basis of AstraZeneca's regulatory application to the MHRA for the Oxford/AstraZeneca Vaccine in the UK were:

- **COV001**, a single-blinded,[6] multi-centre, randomised,[7] controlled Phase I/II trial assessing the safety, immunogenicity [8] and efficacy of the Oxford/AstraZeneca Vaccine in over 1,000 healthy adults in five trial centres

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5 See Exhibit JG/4 - INQ000506144, *ONS*, 'Figure 2: The number of deaths due to COVID-19 decreased throughout June 2020' (*ONS*, 17 July 2020).

6 A "single-blinded" clinical trial of a vaccine is one in which the participants do not know if they are part of the "active arm" (the group of participants receiving the investigational vaccine) or instead part of the "control arm" (the group of participants receiving a placebo or comparator vaccine).

7 A "randomised" clinical trial is one in which the participants are randomly assigned to either the investigational arm of the study or the control arm of the study.

8 The extent to which a substance provokes an immune response.

in the UK. Participants aged 18-55 years were randomised to receive the Oxford/AstraZeneca Vaccine or (as a control) a comparator.

- **COV002**, a single-blinded, multi-centre, randomised, controlled Phase II/III trial assessing the safety, efficacy and immunogenicity of the Oxford/AstraZeneca Vaccine in over 12,000 participants in the UK. Trial participants were aged 18 years or over, who were healthy or had medically stable chronic diseases and were at increased risk for being exposed to the SARS-CoV-2 virus. Participants received the Oxford/AstraZeneca Vaccine or (as a control) a comparator.

- **COV003**, a single-blinded, multi-centre, randomised, controlled Phase III trial assessing the safety, efficacy, and immunogenicity of the Oxford/AstraZeneca Vaccine in over 10,000 participants in Brazil.[9] Trial participants were aged 18 years or over. Participants were healthy or had medically stable chronic diseases and were identified as being at increased risk for being exposed to the SARS-CoV-2 virus. Participants were randomised to receive the Oxford/AstraZeneca Vaccine or (as a control) a comparator.

- **COV005**,[10] a double-blinded,[11] multi-centre, randomised, controlled Phase I/II trial assessing the safety, efficacy, and immunogenicity of the Oxford/AstraZeneca Vaccine in over 2,000 participants in South Africa. Trial participants were aged 18-65 years, living with or without HIV, and were

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[9] COV003 and COV005 were led by Oxford in collaboration with its networks in Brazil and South Africa respectively. It is common for clinical trials to be conducted on a multinational basis, which allows for efficient recruitment of trial participants, and for products to be studied in larger and more geographically and ethnically diverse populations. I discuss the diversity of the clinical trials conducted for the Oxford/AstraZeneca Vaccine at paragraph 36 of this statement.

[10] A "COV004" study was also conducted: this was a single-blinded, randomised, controlled Phase I/II trial assessing the safety, efficacy and immunogenicity of the Oxford/AstraZeneca Vaccine conducted in 400 participants in coastal Kenya. The COV004 trial did not form part of the basis of AstraZeneca's regulatory application to the MHRA for the Oxford/AstraZeneca Vaccine, because the timing of the trial (conducted between 28 October 2020 and 19 August 2021) did not align with the timing of the pooled analysis of the other COV studies for the purpose of the regulatory application. The safety, immunogenicity and efficacy against asymptomatic infection of COVID-19 observed among the COV004 trial participants was similar to that observed in the other COV studies, but efficacy against symptomatic infection or severe disease could not be measured in this cohort (because, given the small size of the cohort, the study was underpowered to detect statistically significant differences in these measures of efficacy). The following paper on COV004 was published in November 2023 in the peer-reviewed journal National Library of Medicine: National Library of Medicine, 'Safety and immunogenicity of ChAdOx1 nCoV-19 (AZD1222) vaccine in adults in Kenya: a phase 1/2 single-blind, randomised controlled trial' (*NLM*, 24 April 2023) (see Exhibit JG/5 - INQ000506141).

[11] A "double-blinded" clinical trial of a vaccine is one in which neither the participants nor the investigators know if an individual is part of the "active arm" (the group of participants receiving the investigational vaccine) or is instead part of the "control arm" (the group of participants receiving a placebo or comparator vaccine).

randomised to receive the Oxford/AstraZeneca Vaccine or (as a control) a comparator.

Efficiency of Oxford-sponsored registrational clinical trials

21. The interim results of the pooled analysis of the Oxford-sponsored trials were announced on 23 November 2020, seven months after the trials started. I believe that an understanding of how the Oxford-sponsored trials were commenced and interim results analysed so efficiently may help inform the UK's future pandemic preparations. From AstraZeneca's perspective, four features were important to minimising delays in this process.

(1) Oxford's pre-existing "ChAdOx1" platform

22. The clinical development of the Oxford/AstraZeneca Vaccine was built on years of research led by Professor Dame Sarah Gilbert, with scientists and researchers at Oxford investigating the adenovirus-vectored [12] ChAdOx1 vaccine platform. This vaccine platform had been used to develop candidate vaccines for other pathogens including influenza, Zika, and another coronavirus, Middle East Respiratory Syndrome (***MERS***). This existing platform meant that the Oxford/AstraZeneca Vaccine could be developed for use in clinical trials soon after the Oxford team received the initial genetic sequencing for SARS-CoV-2.

(2) Availability of funding and efficient recruitment for clinical trials

23. Because of the global pandemic, there was a strong desire from governments and organisations worldwide to develop vaccines against COVID-19 disease. This meant that funding for research and development of these medicines was readily available. Oxford and AstraZeneca also found that the enrolment of clinical trials participants was faster as people were aware of, and wanted to help with, these scientific efforts. This meant that trials were able to start and complete without delay.

(3) Minimising delays between clinical trial phases

[12] "Adenoviruses" are ubiquitous viruses that, in humans, can cause infection that is usually asymptomatic or mild (symptoms are not dissimilar to a common cold). I understand that, in the ChAdOx1 platform, a weakened version of an adenovirus is used as a "vector" (i.e. carrier or delivery vehicle) to carry the genetic material that allows the production of the SARS-Cov-2 spike protein in the host.

24. An important aspect of the efficiency of the clinical trials process was the early engagement with regulators to achieve efficient transitions between different phases. And the way in which regulatory authorities worldwide prioritised the review of efforts to develop COVID-19 vaccines. For example, I understand that Oxford designed the clinical trial structure for the Phase II/III COV002 UK study before, and in anticipation of results from its Phase I/II COV001. This meant that as soon as the relevant data was available from Phase I/II COV001, Oxford was able to progress to large, late-stage trials with the COV001 Phase I trial running in parallel.

25. The use of this parallel structure is not new and can, with the engagement of regulators, be adopted for the development of any investigational medicine. However, this parallel structure is not often used because it requires investing in late-stage large clinical trials before the totality of the data for a medicine is available. Organisations and manufacturers are rarely prepared to take such significant financial risks before considering the early-stage data, but the global pandemic context meant this approach was needed and could be adopted.

(4) Prioritisation by all stakeholders

26. Oxford, AstraZeneca and regulatory authorities all prioritised engagement in the clinical trials process. Although this was before AstraZeneca's collaboration with Oxford and before I joined AstraZeneca, I believe that the backgrounds and reputation of the Oxford teams led by Professor Dame Sarah Gilbert and Professor Sir Andrew Pollard, and their wider networks within academia, government agencies and the healthcare services, all assisted in the rapid establishment of a clinical trials network in the UK for the vaccine, with the help of many people in the NHS and around the country.

27. The speed of progress of the Oxford-sponsored trials had no bearing on the safety procedures that were followed during the trials in accordance with regulatory requirements, and neither did it affect the quality or reliability of the resulting safety and efficacy data. The trials were carried out in compliance with the Good Clinical Practice (GCP) standard[13] and the safety monitoring and evaluation procedures that

[13] The EMA has said that compliance with this standard "provides public assurance that the rights, safety and wellbeing of trial subjects are protected and that clinical-trial data are credible". See Exhibit JG/6 - INQ000506088, EMA, 'Good clinical practice' (*EMA*, 23 April 2024). See also: MHRA, 'Good clinical practice for clinical trials' (*Medicines & Healthcare products Regulatory Agency*, 18 December 2014) (Exhibit JG/7 - INQ000506139), and International Council for Harmonisation of Technical Requirements for Registration of

they adopted were compliant with applicable regulatory requirements and rigorous at every stage (as I discuss further at paragraph 35 below). Further, as I outline below, the efficacy and safety data obtained in the trials were subject to robust assessment by the MHRA during the regulatory approval process, and further trials conducted in respect of the Oxford/AstraZeneca Vaccine have yielded data consistent with the results from the pre-authorisation Oxford-sponsored trials.

Interpreting the Oxford-sponsored clinical trial results

28. Results of clinical trials are analysed with reference to endpoints: targeted outcomes, defined in the trial protocol, that are statistically assessed. As was standard for all COVID-19 vaccines, the primary efficacy endpoint for the Oxford/AstraZeneca Vaccine was preventing symptomatic COVID-19; a key secondary efficacy point was early prevention of severe disease. The analysis of these clinical trial data is one of the many areas in which AstraZeneca supported Oxford with its sponsored clinical trials.

29. I understand from colleagues in AstraZeneca's Vaccines and Immune Therapies Data Science team that, prior to the unblinding of the clinical data (as noted above, each of the trials was "blinded", a measure taken to mitigate bias, alongside randomisation), [14] AstraZeneca designed and discussed the key principles and assumptions for pooling and statistically analysing these data with the MHRA. This is, in my view, another example of the constructive early engagement provided by the MHRA in the clinical trial process.

30. The pooling of clinical trial data meant that the individual clinical trials were combined into a larger dataset and statistically analysed. This in turn allowed the efficacy and safety of the vaccine to be assessed based on a larger dataset, for the purposes of

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Pharmaceuticals for Human Use (ICH), 'Guideline for good clinical practice E6(R2)' *(EMA*, 1 December 2016) (Exhibit JG/8 - INQ000506124).

[14] The "blinding" of a clinical trial is used to mitigate bias that could otherwise affect the outcome of the trial. In particular, the blinding of a trial promotes a balanced review and assessment of reported adverse events. As noted above, the COV001, COV002 and COV003 trials were "single-blinded" trials (i.e. the participants did not know whether they had been assigned to the active or the control arm, and for these studies the trial staff also had only limited information on allocation). The COV005 trial was "double-blinded" (i.e. neither the participants nor the trial staff (other than the study pharmacist who prepared the vaccines for administration) were aware of the arm of the study to which the participants had been assigned).
A further measure to mitigate the risk of bias in the Oxford-sponsored trials was that each trial was "randomised" (i.e. participants were randomly assigned to the investigational arm of the study or the control arm of the study), which introduced a deliberate element of chance in the assignment of participants between the active and control arms of the study. This assists with mitigating the risk of imbalances in demographic profiles (e.g. age and ethnicity) between the active and control arms of the study.

seeking regulatory authorisations. The pooling of clinical trial data is a standard practice though the exercise was more complex for the Oxford-sponsored trials because the COV002 and COV003 trial designs were not identical and some participants in the UK study incorrectly received a half dose[15] followed by a standard dose[16] instead of the standard dose-standard dose regime (which AstraZeneca understands resulted from differences in methods used to measure dosing concentration).[17] Yet taking the time to develop and establish these principles prior to the unblinding of the data was an important decision, because the analysis of a larger dataset allowed for the timely assessment of efficacy and safety results for the purpose of making the relevant regulatory applications.

Interim analysis of the Oxford-sponsored clinical trials published in The Lancet

31. The high-level pooled results from the interim efficacy and safety analysis of the Oxford-sponsored trials were announced by AstraZeneca and Oxford on 23 November 2020.[18] A more detailed description of this analysis was then published in The Lancet on 8 December 2020.[19]

32. These interim results demonstrated that the Oxford/AstraZeneca Vaccine was highly efficacious at preventing symptomatic COVID-19. The interim results provided a point estimate of the overall relative efficacy rate against prevention of symptomatic disease of 70.4% (30 [0·5%] cases out of 5807 participants in the active arm vs 101 [1·7%] cases out of 5829 participants in the control arm). This was the weighted average of a relative efficacy rate of 62.1% in participants who received the Oxford/AstraZeneca Vaccine as two standard doses (27 [0·6%] of 4440 in the active

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15 A dose including $2.5x10^{10}$ viral particles.

16 A dose including $5x10^{10}$ viral particles.

17 AstraZeneca's understanding from Oxford is that this issue arose as a result of differences between the spectrophotometry method of measuring dosing concentration adopted by Oxford and the qPCR method adopted by its partner in Italy, Advent. This resulted in certain COV002 trial participants receiving a lower dose than had been estimated. It was recorded which dosing regimen had been adopted for each trial participant and this was considered in the published analysis of the trial data discussed below. The reliability of the data obtained in the Oxford-sponsored trials was supported by the consistent efficacy and safety profile observed in the Phase III trial discussed at paragraphs 39-40 below.

18 See Exhibit JG/9 - INQ000413710, AstraZeneca, 'AZD1222 vaccine met primary efficacy endpoint in preventing COVID-19' (*AstraZeneca*, 23 November 2020).

19 See Exhibit JG/10 - INQ000408367, Merryn Voysey et al., 'Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK' (2021) 397 The Lancet. Further analysis of the Phase III clinical trials in the UK, Brazil and South Africa was published in The Lancet on 2 February 2021 and announced by AstraZeneca on 3 February 2021. These results confirmed that the Oxford/AstraZeneca Vaccine was highly efficacious at preventing severe cases of COVID-19 and hospitalisations and at preventing symptomatic COVID-19, see Exhibit JG/11 - INQ000485233, Merryn Voysey et al., 'Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials' (2021) 397 The Lancet 881.

arm vs 71 [1·6%] of 4455 in the control arm), and 90.0% relative efficacy in participants who received a half dose followed by a standard dose (three [0·2%] of 1367 in the active arm vs 30 [2·2%] of 1374 in the control arm). This interim analysis for efficacy was based on over 11,000 participants accruing 131 symptomatic infections in the COV002 and COV003 Oxford-sponsored trials.

33. Regarding the 90.0% relative efficacy result observed in the 1,367 participants included in the primary efficacy analysis who received a half dose followed by a standard dose: the interim analysis published on 8 December 2020 noted that this was "intriguingly high" compared with the efficacy of 62.1% in the 4,440 participants included in the primary efficacy analysis who received two standard doses. Further analysis published on 2 February 2021[20] indicated that, rather than the difference in efficacy rate having been driven by differences in dosing quantity, this result may have been "partly driven by the longer dosing interval that was a feature of this group" (since the interval between the first and second doses was longer on average for participants who received a half dose followed by a standard dose than the interval for those who received two standard doses). As to why approval of the Oxford/AstraZeneca Vaccine and its subsequent delivery was based on a regimen of two standard doses, this was because more safety data was available to support this dosing regimen (since more trial participants had received two standard doses in the Oxford-sponsored clinical trials and this half dose had not been used in the AstraZeneca-sponsored Phase III clinical trial discussed below, which was underway). The February 2021 further analysis also explained that this regimen was "preferred operationally because it is more straightforward to deliver the same vaccine for both doses and because there are more immunogenicity and efficacy data to support its use".

34. As to the secondary endpoint of early prevention of severe disease after the first dose: there were no hospitalisations or severe cases of COVID-19 more than 21 days after the first dose of the Oxford/AstraZeneca Vaccine. Ten participants in the control group (those who did not receive the Oxford/AstraZeneca Vaccine) were hospitalised due to COVID-19, among whom two were assessed as severe, including one fatal case.

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[20] See Exhibit JG/11 - INQ000485233, Merryn Voysey et al., 'Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials' (2021) 397 The Lancet 881.

35. The pooled safety data analysis was from more than 24,000 participants enrolled across all four of the Oxford-sponsored clinical trials, over 12,000 of whom received the Oxford/AstraZeneca Vaccine. As with all vaccine clinical trials, the clinical trial protocols included follow-up procedures in order to gather the relevant safety,[21] immunogenicity and efficacy information and ensure the safety of clinical trial participants. For the Oxford-sponsored clinical trials, Oxford's follow-up assessments for clinical trial participants included drawing of blood samples for safety and immunogenicity assays, clinical assessments for safety and COVID-19 PCR testing. Oxford also appointed a data safety monitoring board (***DSMB***) to review and monitor unblinded safety data on a regular basis, and to make associated recommendations concerning safety monitoring and procedures. For example, there was a pause of the clinical trials in September 2020 for the investigation of a serious unexpected suspected adverse reaction when a participant in the active arm of the COV002 trial exhibited symptoms consistent with transverse myelitis. Independent clinical review by the DSMB was conducted and did not conclude that there was likely to be any causal association between the symptoms and the Oxford/AstraZeneca Vaccine. The clinical trials resumed following assessment and agreement from the relevant regulatory authorities, including the MHRA. The pooled safety data analysis demonstrated the acceptable safety profile of the Oxford/AstraZeneca Vaccine and that it was well tolerated. There was only one serious adverse event confirmed in relation to the vaccine; namely one of a Grade 4 pyrexia (fever) which was treated with paracetamol, which did not require admission and which was resolved the same day.

36. The efficacy and safety data described above were obtained in respect of diverse trial populations that were generally well balanced in terms of demographic parameters between groups. The age of participants ranged from 18[22] to 88 years of

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21 As was summarised in the interim analysis published on 8 December 2020, all participants were given an emergency 24-hour telephone number to contact the on-call study physician for the duration of the study to report any illnesses. In accordance with regulatory requirements, serious adverse events were recorded throughout the trials and reviewed at each study visit, with causality assigned by the site investigator.

22 The participants in these trials did not include any children. For completeness, I note that in early 2021, a trial sponsored by the University of Oxford was conducted in children: COV006, a Phase II, single-blind, randomised, controlled trial at four trial sites in the UK in 374 participants aged 6-17 years who were randomly assigned to four groups (4:1:4:1). The results of this trial were published in The Lancet on 11 June 2022 (please see Exhibit JG/12 - INQ000413056, Li, Grace et al., 'Safety and immunogenicity of the ChAdOx1 nCoV-19 (AZD1222) vaccine in children aged 6-17 years: a preliminary report of COV006, a phase 2 single-blind, randomised, controlled trial.' (2022) 399 The Lancet 2212). The study showed that the Oxford/AstraZeneca Vaccine was well tolerated and immunogenic in children aged 6-17 years, and no additional safety concerns were raised in this trial. AstraZeneca did not conduct a clinical development programme (or seek regulatory approval) for use of the Oxford/AstraZeneca Vaccine in children.

age (the mean average age was around 42), with 9% of participants ≥65 years of age. 56% of participants were female. Participants were diverse in terms of ethnicity, with 76% of participants white, 10% black, 4% mixed ethnicity, 3% Asian and 7% "Other" ethnicity.[23]

37. The pooling of data between the different trial populations enrolled in the UK, Brazil and South Africa meant that the efficacy and safety data that formed the basis of the regulatory approval of the Oxford/AstraZeneca Vaccine (which I describe in detail in Section D below) was a diverse, large dataset. Indeed, the size of the dataset that was available at the time of the Regulation 174 authorisation (efficacy data based on more than 11,000 participants; safety data based on more than 24,000 participants) was consistent with the size of trials conducted for vaccines developed prior to the pandemic. By way of example, a Phase III trial for the Shingrix vaccine included around 15,000 participants enrolled between 2010 and 2011[24] and a Phase III trial carried out for the Trumemba MenB vaccine included around 5,000 participants enrolled between 2012 and 2014.[25] More recently, around 12,500 participants have been enrolled in an ongoing Phase III trial which commenced in 2022 for a Lyme disease vaccine (VLA15).[26]

38. The clinical trial efficacy and safety data analysis also informed the initial contents of the Product Information for healthcare professionals and vaccine recipients, as I describe further in Section F below.

Further clinical trials conducted for Oxford/AstraZeneca Vaccine

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[23] As to how this demographic data can be compared with the UK population, I note the England and Wales Census 2021 data published by the Office for National Statistics included the following:

- The median age in England and Wales was 40 years (see Exhibit JG/13 - INQ000506143, Office for National Statistics (ONS), 'Population and household estimates, England and Wales: Census 2021, unrounded data' (*ONS*, 2 November 2022));
- 51.0% identified as women (see Exhibit JG/13 - INQ000506143); and
- 81.7% identified their ethnic group as "White", 4.0% as "Black, Black British, Black Welsh, Caribbean or African", 2.9% as "Mixed or Multiple ethnic groups", 9.3% as "Asian, Asian British or Asian Welsh" and 2.1% as "Other ethnic group" (see Exhibit JG/14 - INQ000506142, Office for National Statistics (ONS), 'Ethnic group, England and Wales: Census 2021' (*ONS*, 29 November 2022)).

[24] See Exhibit JG/15 - INQ000506132, Lal, Cunningham et al., 'Efficacy of an Adjuvanted Herpes Zoster Vaccine in Older Adults' (2015) 372 NEJM 2087.

[25] See Exhibit JG/16 - INQ000506145, Ostergaard et al., 'A phase 3, randomized, active-controlled study to assess the safety and tolerability of meningococcal serogroup B vaccine bivalent rLP2086 in healthy adolescents and young adults' (2016) 34 Vaccine 1465.

[26] See Exhibit JG/17 - INQ000506146, Pfizer, 'An Efficacy, Safety, Tolerability, Immunogenicity, and Lot-Consistency Clinical Trial of a 6-Valent OspA-Based Lyme Disease Vaccine (VLA15) (VALOR)' (*Pfizer*, 26 July 2024).

39. In addition to the Oxford-sponsored trials, further clinical trials have continued to demonstrate the efficacy and safety profile of the Oxford/AstraZeneca Vaccine. The largest of these trials was a Phase III randomised, double-blind, placebo-controlled global trial that AstraZeneca sponsored involving more than 32,000 participants at 150 trial centres in the US, Peru and Chile.[27] This is the AstraZeneca-sponsored Phase III clinical trial that I oversaw in my initial role as a Global Clinical Product Lead for the vaccine.

40. Participants in this trial were randomised on a 2:1 basis so that around two-thirds of participants were in the active arm. Participants in the active arm all received two standard doses of the Oxford/AstraZeneca Vaccine, at an interval of ~4 weeks across all trial sites. The results demonstrated a point estimate of 74% vaccine efficacy against symptomatic COVID-19, 100% efficacy against severe or critical disease and 94.2% efficacy against hospitalisation.[28] The Oxford/AstraZeneca Vaccine was well tolerated, with no significant new safety concerns identified; the safety results were consistent with the safety profile of the Oxford/AstraZeneca Vaccine observed in the Oxford-sponsored trials, which formed the basis of the Regulation 174 authorisation discussed at Section D below and the initial Product Information discussed at Section F below.

41. Other studies to support local regulatory authorisations of the Oxford/AstraZeneca Vaccine were carried out in Japan, India, the United Arab Emirates, Russia, Belarus, Azerbaijan and Kenya. As of today, the efficacy and safety profile of the Oxford/AstraZeneca Vaccine has been studied in clinical trials involving 60,000 people, including two independent Phase III programmes. This makes the Oxford/AstraZeneca Vaccine one of the most studied vaccines for use in humans against COVID-19. In these trials, the Oxford/AstraZeneca Vaccine has consistently been shown to be effective at preventing symptomatic COVID-19 and preventing severe disease and hospitalisation with a positive benefit/risk profile.

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[27] This study started on 28 August 2020, with a Primary Completion Date of 5 March 2021, and a Study Completion Date of 10 February 2023, see Exhibit JG/18 - INQ000506080, AstraZeneca, 'Phase III Double-blind, Placebo-controlled Study of AZD1222 for the Prevention of COVID-19 in Adults' (*AstraZeneca*, 1 December 2023). The primary analysis of this trial was published in NEJM on 29 September 2021, see Exhibit JG/19 - INQ000506131, Falsey AR et al., 'Phase 3 Safety and Efficacy of AZD1222 (ChAdOx1 nCoV-19) Covid-19 Vaccine' (2021) 385 NEJM 2348.

[28] See Figure 3 of the primary analysis published in NEJM on 29 September 2021, Falsey AR et al., 'Phase 3 Safety and Efficacy of AZD1222 (ChAdOx1 nCoV-19) Covid-19 Vaccine' (2021) 385 NEJM (Exhibit JG/19 - INQ000506131).

SECTION D: REGULATORY APPROVAL FOR THE OXFORD/ASTRAZENECA VACCINE IN THE UK – REGULATION 174 AUTHORISATION

42. Under Regulation 46 of the Human Medicines Regulations 2012 (***HMR***), subject to limited exceptions, a person may not sell or supply an unauthorised medicinal product. In general, a new vaccine would be granted what is known as a "UK marketing authorisation", and the entity named on that authorisation would be known as the Marketing Authorisation Holder (***MAH***). However, under Regulation 174 of the same Regulations, the MHRA can grant a temporary authorisation for the supply of a medicine to combat the suspected or confirmed spread of a harmful disease (***R174 Authorisation***).

43. Several COVID-19 vaccines were authorised in the UK using the R174 Authorisation procedure. The use of the R174 Authorisation procedure was a decision made by the UK Licensing Authority, not the manufacturers of the vaccines. Under the R174 Authorisation procedure, the MHRA agreed that AstraZeneca could submit the information packages for the regulatory dossier on a rolling basis and that the MHRA would itself review and provide its questions on a similarly rolling basis. This process started with an initial pre-submission meeting with the MHRA in August 2020, followed by AstraZeneca making its regulatory submissions and responding to the MHRA's questions over the period September to December 2020. Engagement in the authorisation process was prioritised by AstraZeneca and the MHRA, which meant that the process was expedited. Data were reviewed by the MHRA, questions raised, and responses returned by AstraZeneca promptly.

44. On 29 December 2020, the UK Licensing Authority granted a R174 Authorisation for the Oxford/AstraZeneca Vaccine. A copy of the R174 Authorisation for the Oxford/AstraZeneca Vaccine is exhibited to this statement.[29] The R174 Authorisation outlined the conditions on which the MHRA had authorised the Oxford/AstraZeneca Vaccine, relating to matters including the provision of information to the MHRA, Product Information, quality assurance, manufacturing, [30] pharmacovigilance,

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[29] See Exhibit JG/20 - INQ000413711, MHRA, 'Conditions for authorisation for emergency supply under Regulation 174 for COVID-19 Vaccine AstraZeneca' (*MHRA*, 30 December 2020). This document was subsequently updated by the MHRA from time to time following the authorisation.

[30] The Oxford/AstraZeneca Vaccine was manufactured in accordance with the process outlined in the R174 dossier provided to the MHRA prior to authorisation. This dossier submitted to the MHRA included an overview of the manufacturing process that would be followed for scaled-up production, together with a comparability assessment outlining how this process compared with the one that had been used to manufacture the clinical trial product. The comparability assessment included process comparison as well as analytical

deployment, supply chain and distribution. A copy of the MHRA's Public Assessment Report (***PAR***) published in January 2021 is exhibited to this statement.[31] The PAR included the following explanation regarding the approval of the Oxford/AstraZeneca Vaccine:

> "***Why was COVID-19 Vaccine AstraZeneca approved?***
>
> *It was concluded that COVID-19 Vaccine AstraZeneca has been shown to be effective in the prevention of COVID-19. Furthermore, the side effects observed with the use of this product are considered to be similar to those seen for other vaccines. Therefore, the MHRA concluded that the benefits are greater than the risks and recommended that this medicine can be authorised for temporary supply during the COVID-19 pandemic".*

45. The Oxford/AstraZeneca Vaccine was the second COVID-19 vaccine to be authorised for use in the UK. The MHRA has publicly explained that the process it followed in relation to the R174 Authorisations for COVID-19 vaccines consisted of reviewing data submitted to the MHRA and also seeking input from the Commission on Human Medicines (***CHM***):[32]

> "*The temporary authorisations for use of the COVID-19 vaccines in the UK followed a rigorous scientific assessment of all the available evidence of quality, safety and effectiveness by the UK regulator, the Medicines and Healthcare products Regulatory Agency (MHRA). The MHRA expert scientists and clinicians reviewed data from the laboratory pre-clinical studies, clinical trials, manufacturing and quality controls, product sampling and testing of the final vaccine, and also considered the conditions for its safe*

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comparability studies. The processes adopted for manufacture of the clinical trial product and product for roll-out at scale were substantially the same as far as the inclusion of viral particles was concerned; the differences in manufacturing process were implemented to enable scaled-up production and were detailed to the MHRA prior to authorisation.
The manufactured product was subject to quality assurance processes (as detailed in the R174 Authorisation), which were the same in substance for product manufactured inside and outside the UK.
All manufacturing facilities were authorised for manufacturing by the relevant competent authorities and were detailed in the R174 Authorisation. AstraZeneca inspected sites in accordance with the Good Manufacturing Practice (GMP) standard, with inspections carried out by way of virtual inspections rather than on-site inspections given the pandemic setting. Such virtual inspections included the visual audit of quality management systems.

[31] See Exhibit JG/21 - INQ000413712, MHRA, 'Public Assessment Report Authorisation for Temporary Supply' (*MHRA*, January 2021).

[32] See Exhibit JG/22 - INQ000506081, Commission on Human Medicines, 'What we do' (*Commission on Human Medicines*, 31 January 2024). The CHM advises ministers on the safety, efficacy and quality of medicinal products. CHM is an advisory non-departmental public body, sponsored by the Department of Health and Social Care.

> *supply and distribution. The decision was made with advice from the Commission on Human Medicines (CHM), the government's independent expert scientific advisory body*".[33]

46. The relationship with the MHRA throughout the R174 Authorisation process was professional, robust and collaborative. I would hope that similar levels of work, dedication and prioritisation would be provided in any future pandemic response.

47. I understand that the Inquiry has sought confirmation of any financial relationship between AstraZeneca and the MHRA. AstraZeneca pays the required statutory fees to the MHRA, which include fees in relation to licensing applications. [34] Pharmaceutical companies may also pay subscription fees to the MHRA for other services, including in respect of information portals operated by the MHRA. Apart from the payment of such fees, I am not aware of any financial relationship between AstraZeneca and the MHRA.

48. I also understand that the Inquiry has asked about AstraZeneca's understanding of the procedures and safeguards in place that are relevant to the impartiality and independence of the MHRA, and AstraZeneca's view on the effectiveness of these procedures. AstraZeneca is aware that the MHRA has such policies. I understand that the details and content of these policies are decided by the MHRA. AstraZeneca's experience of engaging with the MHRA is that it is impartial, independent and objective. Prior to the Oxford/AstraZeneca Vaccine R174 Authorisation submissions, AstraZeneca's engagement with the MHRA regarding regulatory submissions was largely as part of the European centralised procedure overseen by the European Medicines Agency (***EMA***) and less frequently as a national regulatory authority in the context of National and Mutual Recognition licensing procedures as an individual Member State. In all instances, I understand from my regulatory colleagues that AstraZeneca has found that the MHRA's decision-making was independent and made within the iterative submissions, questions and responses processes forming part of the relevant regulatory framework within which AstraZeneca engages with the MHRA.

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[33] See Exhibit JG/23 - INQ000506137, MHRA, 'Freedom of Information request on the temporary authorisations for use of the COVID-19 vaccines in the UK followed a rigorous scientific assessment of all the available evidence of quality, safety and effectiveness (FOI 21/874)' (*MHRA*, 27 April 2022).

[34] The MHRA's guidance on these fees is available on the MHRA website, see Exhibit JG/24 - INQ000506138, MHRA, 'Current MHRA fees' (*MHRA*, 20 November 2023).

The role of the JCVI

49. I understand that the Inquiry has also asked about the role played by AstraZeneca, if any, in advising or otherwise liaising with the UK Government in relation to various matters relating to the use of the Oxford/AstraZeneca Vaccine after the R174 Authorisation. Advising the UK Government on the prioritisation and suitability of vaccines, selection of vaccines for subsequent boosters and related matters in the UK is, I believe, the responsibility of the Joint Committee on Vaccination and Immunisation (***JCVI***), which is an independent expert advisory committee.

50. I understand from my colleagues that during the COVID-19 pandemic, the JCVI established both a COVID-19 main committee and sub-committee. Representatives from the pharmaceutical industry are not members of the JCVI, but can be invited to present at a sub-committee meeting. During the COVID-19 pandemic, the JCVI COVID-19 sub-committee invited Professor Sir Andrew Pollard of Oxford and AstraZeneca to present data on the Oxford/AstraZeneca Vaccine from time to time. I did not attend any of these meetings, but I understand from my colleagues in Medical Affairs that these meetings would typically involve Professor Pollard presenting data, followed by questions from the sub-committee. Minutes of meetings were kept by the JCVI and are published on its website.

51. AstraZeneca's role was therefore to provide information to the JCVI COVID-19 sub-committee as requested. AstraZeneca had no role in the JCVI's decision-making and the recommendations made by the JCVI were made independently of AstraZeneca.

SECTION E: POST-AUTHORISATION MONITORING – PHARMACOVIGILANCE PROCEDURES IN RELATION TO THE OXFORD/ASTRAZENECA VACCINE

52. It is not possible to fully characterise the safety profile of any medicine or vaccine by, and through, pre-authorisation development alone. This is because all clinical trials, even large ones of the size conducted in relation to the Oxford/AstraZeneca Vaccine, are carried out in controlled conditions in a defined group of participants. Those investigations cannot identify every potential side effect, particularly those that are very rare.

53. Therefore, regulatory authorities and MAHs operate systems designed to monitor the ongoing safety data for an authorised medicine and share this information with each other. This scientific and evidence-based process of monitoring the safety of

medicines and taking actions to reduce the risks associated with their use is known collectively as ***Pharmacovigilance***.

AstraZeneca's Patient Safety Function

54. AstraZeneca's Pharmacovigilance processes adhere to the requirements of the European Union Good Pharmacovigilance Practice,[35] as required by the MHRA, and the International Conference on Harmonisation E2E Pharmacovigilance Planning Guideline.[36] Within AstraZeneca, post-authorisation Pharmacovigilance monitoring of a medicine's safety information is the responsibility of the Patient Safety function. This function is responsible for AstraZeneca's safety database, safety signal management processes and periodic safety reporting to regulatory authorities. I have described below how this operated for the Oxford/AstraZeneca Vaccine in the UK.

Risk Management Plan

55. As part of the regulatory approval process for any new medicinal product, AstraZeneca submits a draft risk management plan (***RMP***) to the MHRA. This was also done for the Oxford/AstraZeneca Vaccine as part of the process which resulted in the R174 Authorisation. The MHRA assessed and approved the draft RMP as part of the application process.[37] The approved RMP, which has been periodically updated, then forms part of the R174 Authorisation and outlines AstraZeneca's post-authorisation pharmacovigilance commitments for the Oxford/AstraZeneca Vaccine.

R174 Authorisation of the Oxford/AstraZeneca Vaccine

56. Although the R174 Authorisation was not a Marketing Authorisation, it was subject to conditions including that AstraZeneca "*must operate a comprehensive*

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35 See Exhibits JG/25 - INQ000506096 to JG/67 - INQ000506087 for the EMA Good Pharmacovigilance Practices (GVP) guidelines that were in force during the Inquiry's relevant period of 30 January 2020 to 28 June 2022.

36 See Exhibit JG/63 - INQ000506127, 'ICH Topic E2E' (*EMA*, June 2005).

37 The RMP approved by the MHRA in respect of the Oxford/AstraZeneca Vaccine included a UK-specific addendum to a European Union RMP. By way of further detail:

- On 21 December 2020, AstraZeneca submitted to the EMA the European Union RMP for the Oxford/AstraZeneca Vaccine (see Exhibit JG/68 - INQ000506071).
- On 28 December 2020, AstraZeneca submitted to the MHRA a copy of the European Union RMP (which was pending review by the EMA), together with an addendum that described how the EU RMP would be implemented in the UK (see Exhibit JG/69 - INQ000506077) (the ***UK Addendum***). This version of the UK Addendum was in place when the R174 Authorisation was granted by the UK Licensing Authority on 29 December 2020.
- On 6 January 2021, AstraZeneca submitted to the MHRA an update to the UK Addendum ("succession 2") (see Exhibit JG/70 - INQ000506078). This update was approved by the MHRA on 7 January 2021.

pharmacovigilance system for this product in accordance with UK legislation for licensed products, as if they were marketing authorisation holders for the product". This was done as described below.[38]

Individual Case Safety Reports

57. A core component of both regulatory authorities' and MAHs' Pharmacovigilance monitoring activities is the recording and analysis of individual reports that a person has experienced an untoward medical occurrence(s) following the use of a medicine. There is a lot of Pharmacovigilance terminology used in this area to refer to different categories and types of reports and different regulatory authorities prefer different terms. For clarity in this statement, I am going to refer to individual reports of an adverse event as Individual Case Safety Reports (***ICSR***). An "adverse event" can be defined as an "*unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product*".[39] An adverse event report does not mean that there is necessarily a causal association between the medicine and the reported adverse event. Where the adverse event report identifies the reporter, the patient, the adverse event and the medicine, this is known as an ICSR.

The MHRA's Yellow Card Scheme

58. The MHRA operates a dedicated COVID-19 Yellow Card reporting website for submitting ICSRs related to any medicine, vaccine, medical device or test kit used in the prevention or treatment of COVID-19 disease. This website was set-up before the supply of the Oxford/AstraZeneca Vaccine. Anyone may submit an ICSR about the Oxford/AstraZeneca Vaccine directly to the MHRA via its Yellow Card Scheme. This ICSR together with any follow-up information is shared with AstraZeneca by the MHRA. All such ICSRs shared by the MHRA with AstraZeneca are inputted into AstraZeneca's safety database and are subject to the signal management and Pharmacovigilance reporting processes described below. I understand from my Patient Safety colleagues in the UK that the MHRA actively raised awareness of this

[38] See Exhibit JG/20 - INQ000413711, MHRA, 'Conditions for authorisation for emergency supply under Regulation 174 for COVID-19 Vaccine AstraZeneca' (*MHRA*, 30 December 2020).
[39] See Exhibit JG/50 - INQ000506091, EMA, 'Guideline on good pharmacovigilance practices (GVP) Annex I – Definitions (Rev 4)' (*EMA*, 9 October 2017).

dedicated COVID-19 Yellow Card reporting website online and in MHRA publications.

ICSRs reported directly to AstraZeneca

59. An ICSR can also be made by anyone directly to AstraZeneca. An ICSR can be completed online with AstraZeneca, reported via telephone, or communicated to any AstraZeneca employee. For the Oxford/AstraZeneca Vaccine, most ICSRs were received directly by the regulatory authorities and shared with AstraZeneca's safety database electronically.

60. Before the start of supply of a new medicine, AstraZeneca forecasts the expected volume of ICSRs. This is in order to plan capacity and resources for analysing these data. As a result of the large-scale rollout of the Oxford/AstraZeneca Vaccine, increased awareness of the MHRA's COVID-19 online Yellow Card scheme (which provided a simple, accessible self-reporting route for those who received the vaccine), heightened public awareness of COVID-19 vaccination and related media reporting, the volume and rate of ICSRs of suspected adverse reactions received in relation to the Oxford/AstraZeneca Vaccine exceeded AstraZeneca's initial estimates,[40] with substantial variance in ICSR reporting rates between different regions.[41] Furthermore, the assessment and interpretation of such safety information is complex, and many of the ICSRs received by AstraZeneca were incomplete with variations in the quality and accuracy of reported information. This meant that, in many cases, it was necessary to follow up an initial report with the reporter to request additional information, sometimes on multiple occasions, to ensure the ICSR could be adequately assessed. Given the large number of ICSRs received, AstraZeneca agreed with the MHRA to prioritise the review of serious ICSRs before reviewing non-

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[40] Over the Inquiry's relevant period of 30 January 2020 to 28 June 2022, AstraZeneca received 811,111 ICSRs globally, 144% of the initial forecast of 563,805 ICSRs. 265,929 of the ICSRs that were received were serious ICSRs, within the meaning of Regulation 8(2) of the HMR and the ICH Harmonised Tripartite Guideline E2A (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting) (see Exhibit JG/58 – INQ000398114).
An adverse reaction is "serious" if it results in a person's death; threatens a person's life; results in a person being hospitalised as an inpatient or prolongs a person's existing stay in hospital; results in a person's persistent or significant disability or incapacity; or results in a congenital anomaly or birth defect.

[41] ICSR reporting rates were relatively higher in the UK and European countries, which were the focus of initial vaccine distribution and which generated the most intensive media attention. By contrast, reporting rates from low- and middle-income countries (where the safety reporting infrastructure was more limited) were generally lower. These regional differences in reporting rates were discussed in the peer-reviewed paper that was published by AstraZeneca's Patient Safety team in Nature Reviews Drug Discovery journal in October 2022, as discussed at paragraph 94 below (see Exhibits JG/94 - INQ000413709 and JG/95 - INQ000413708).

serious ICSRs. The EMA and MHRA also agreed that reports received directly by the MHRA would be reported directly to EMA's safety database, EudraVigilance.

Further sources of Pharmacovigilance data for the Oxford/AstraZeneca Vaccine

61. In addition to ICSRs notified to AstraZeneca, the other main sources of Pharmacovigilance information used for the purposes of signal management and evaluation of the Oxford/AstraZeneca Vaccine are:

(a) **pre-clinical studies**, such as relevant toxicology information;

(b) clinical trials for the Oxford/AstraZeneca Vaccine, including the collection of long-term follow-up data in accordance with the RMP;[42]

(c) published scientific and medical literature;

(d) external public safety databases, including, the EMA's EudraVigilance database and the World Health Organization's database VigiBase; and

(e) AstraZeneca's Post-Authorisation Safety Studies.[43] For the Oxford/AstraZeneca Vaccine, nine such studies have been conducted which are registered within HMA-EMA Catalogues of real-world data sources and studies.[44] To date, results are publicly available for eight of these nine studies (clinical study reports have been published for seven of the studies, with the publication of manuscripts and conference abstracts also planned or in submission for six of the studies).[45] These studies have consistently

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[42] See Exhibit JG/68 - INQ000506071, 'European Union Risk Management Plan (EU RMP) for COVID-19 Vaccine AstraZeneca (ChAd0x1-S [Recombinant])' (*AstraZeneca*, 21 December 2020) at III.2.2, Table III-3 and II.7.1.4.

[43] Marketing authorisation holders must undertake any Post-Authorisation Safety Studies that are outlined in the RMP (e.g. see Exhibit JG/68 - INQ000506071, 'European Union Risk Management Plan (EU RMP) for COVID-19 Vaccine AstraZeneca (ChAd0x1-S [Recombinant])' (*AstraZeneca*, 21 December 2020) at Table III-2 for the studies outlined in the RMP for the Oxford/AstraZeneca Vaccine as it applied at the time of the R174 Authorisation), and may also undertake studies voluntarily, including where this is considered appropriate based on ongoing safety and efficacy data collection through pharmacovigilance processes.

[44] The details of these studies, including regulatory timelines for reporting and publication status, are summarised in the overview provided at Exhibit JG/71 - INQ000506075, 'UK/EU Post-Authorisation Safety Studies' (*AstraZeneca*, 30 July 2024). For further background on the HMA-EMA Catalogues of real-world data sources and studies, please refer to the relevant EMA webpage, a copy of which is provided at Exhibit JG/72 - INQ000506130, EMA, 'HMA-EMA Catalogues of real-world data sources and studies' (*EMA*, 15 February 2024).

[45] The publication details of these studies are outlined in the column headed "Publications" in Exhibit JG/71 - INQ000506075. For the study for which results have not yet been published (EUPAS39096), analysis of the results is ongoing and the clinical study report is planned for July 2026. A decision on whether to publish the report in a peer-reviewed journal has not yet been made by the Principal Investigator.

supported the safety and effectiveness of the Oxford/AstraZeneca Vaccine, as outlined further in Section G below.

Signal Management

62. The processes for signal management followed by AstraZeneca are set out in Module IX of the EMA's Guideline on good pharmaceutical practices. These are also the same processes guideline followed by the MHRA for the purpose of its signal management processes. ***Signal Management*** is defined as "*a set of activities performed to determine whether, based on an examination of individual case safety reports (ICSRs), aggregated data from active surveillance systems or studies, scientific literature information or other data sources, there are new risks associated with an active substance or a medicinal product or whether known risks have changed, as well as any related recommendations, decisions, communications and tracking.*"[46]

63. Signal Management relating to any AstraZeneca medicine or vaccine, is undertaken in the UK by both the MHRA as the regulatory authority and AstraZeneca as the MAH. There are established methods for the conduct of quantitative and qualitative assessments of Pharmacovigilance information for these purposes. Signal management by AstraZeneca includes the undertaking of adverse event analysis for signal detection, evaluation of possible signals, signal confirmation and determination of a possible causal association. This process is ongoing as new information and data become available and AstraZeneca and the MHRA regularly communicate about their respective evaluations. I summarise the safety reporting communications below and in the following section I explain how new safety information is included in the Product Information (see Section F).[47]

Pharmacovigilance Reporting to the MHRA for the Oxford/AstraZeneca Vaccine

64. In addition to the reporting of ICSRs, AstraZeneca's Pharmacovigilance post-authorisation reporting obligations to the MHRA require the company to prepare and compile regular periodic safety reports. For all COVID-19 vaccines, including the

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[46] See Exhibit JG/41 - INQ000506107, EMA, 'Guideline on good pharmacovigilance practices (GVP) Module IX – Signal management (Rev 1)' (*EMA*, 9 October 2017).

[47] For completeness, AstraZeneca has systems in place for any product to detect cases where a particular batch is associated with higher rates of adverse events. Such systems were in place during the period of the pandemic. No such association was or has since been detected for any particular batch of the Oxford/AstraZeneca Vaccine.

Oxford/AstraZeneca Vaccine, these periodic safety reporting obligations to the MHRA were enhanced with more frequent contact and additional periodic reporting requirements.

65. Once the Oxford/AstraZeneca Vaccine was in use in the UK, AstraZeneca was in regular, frequent communication with the MHRA relating to the Pharmacovigilance monitoring of the Oxford/AstraZeneca Vaccine. AstraZeneca also met the MHRA on a twice weekly basis from January 2021 until February 2022 to discuss safety information. This then moved to monthly meetings and then to meetings as needed from May 2022.

66. In line with the enhanced periodic reporting requirements for COVID-19 vaccines, AstraZeneca submitted Monthly Summary Safety Reports (***MSSRs***) for the Oxford/AstraZeneca Vaccine to the MHRA every month from February 2021 until August 2021. This requirement then changed to bi-monthly safety reports until December 2021, after which no further MSSRs were requested. Each MSSR was substantial and together with its supporting appendices typically exceeded 10,000 pages and included detailed signal detection and evaluation information.

67. In addition to the MSSRs, AstraZeneca also prepared and submitted Periodic Safety Update Reports (***PSURs***), also known as Periodic Benefit Risk Evaluation Reports (***PBRERs***), following authorisation. These are typically submitted every six months for the first two years after authorisation; annually for the subsequent two years; and thereafter at three-yearly intervals. They are standardised in-depth Pharmacovigilance reports, which summarise all data relevant to the risks and benefits associated with the use of a medicinal product, including cumulative safety information and the more recent results of ongoing clinical studies and provide an evaluation of the risk-benefit balance of a product, taking into account new or emerging information.

The purpose of Pharmacovigilance processes

68. The main purposes of Pharmacovigilance processes are therefore:

    (a) to identify new safety information or changes in frequency of known safety information for a medicine after it is authorised for use in patients using defined Signal Management processes; and

(b) to use this new safety information to update a medicine's Product Information and, as appropriate, take related actions about a medicine's use or authorisation.

SECTION F: UPDATING THE UK PRODUCT INFORMATION FOR THE OXFORD/ASTRAZENECA VACCINE

69. ***Product Information*** refers to specific documents made available to healthcare professionals and patients about a medicine, which form part of the marketing authorisation for that product. For healthcare professionals, this information is in the form of the Summary of Product Characteristics (***SmPC***) and for patients it is in the form of the Patient Information Leaflet (***PIL***). For the Oxford/AstraZeneca Vaccine, during the period it was supplied under a R174 Authorisation, the equivalent documents were called the "Regulation 174 information for healthcare professionals" and the "Regulation 174 information for patients".

70. All Product Information must be approved by the MHRA as reflecting the current state of scientific and medical knowledge regarding the relevant medicinal product, before it is put into circulation. The initial Product Information is reviewed and approved by the MHRA as part of a medicine's authorisation and subsequent changes to the Product Information can only be made where and in the form approved by the MHRA. The Oxford/AstraZeneca Vaccine was supplied in accordance with a R174 Authorisation for temporary supply and not a marketing authorisation, with the result that AstraZeneca's ability to communicate information regarding the Oxford/AstraZeneca Vaccine was limited. In particular, AstraZeneca was initially not authorised to publish the Product Information. For a licensed product supplied in accordance with a marketing authorisation, the marketing authorisation holder may upload the SmPC and PIL for the product to the electronic medicines compendium (***emc***), an external hosting platform managed by Datapharm. However, since the Oxford/AstraZeneca Vaccine was initially supplied on the basis of a R174 Authorisation for temporary supply (rather than a marketing authorisation), AstraZeneca could not make the SmPC and PIL available on the emc, as the UK Government was required to approve this but had not done so. As a result, the MHRA website was for a period the only publicly available source for the Product Information (aside from copies of the Product Information provided to healthcare professionals and patients supplied with batches of the vaccine). On 1 April 2021, the MHRA confirmed to AstraZeneca that the upload of the Product Information to the

emc had been approved by the UK Government; the Product Information was thereafter made available on the emc. Once the CMA had been granted (which I discuss at paragraph 89 below), this restriction did not apply to the SmPC and PIL and these were published accordingly.

71. The MHRA accordingly published the Product Information and relevant updates, and made available such updates to healthcare professionals. A copy of the Product Information as it stood at the time of the initial R174 Authorisation of the Oxford/AstraZeneca Vaccine is exhibited to this statement.[48] A copy of the last Product Information for the Oxford/AstraZeneca Vaccine (last updated on 22 November 2023) is exhibited to this statement.[49]

72. The Product Information follows a standardised structure as required by and defined in UK legislation, according to which certain types of information are included in particular sections. The content of the Product Information is based on the available evidence, including the analysis of the relevant clinical trial data and additional information obtained post-authorisation. The Product Information identifies, for example, the following:

(a) The suitability of a medicine for particular individuals, for example, by reference to age and/or medical condition. This includes whether a medicine is authorised for use in a paediatric population (children).

(b) The dosing and recommended time between doses.

(c) Suitability for use in pregnant or breastfeeding women.

Oxford/AstraZeneca Vaccine Safety Information

73. The key safety information is set out in the following sections of the SmPC. The main requirements for the SmPC are set out in the EMA's Guideline on Summary of Product Characteristics (published in September 2009). That document runs to 29 pages, but in summary the main parts of the "Clinical Particulars" section (which

[48] See Exhibits JG/73 - INQ000413716, 'Reg 174 Information for UK Recipients' (*MHRA*, 29 December 2020), and JG/74 - INQ000413715, 'Reg 174 Information for UK Healthcare Professionals' (*MHRA*, 29 December 2020).

[49] See Exhibits JG/75 - INQ000413714, 'Package Leaflet: Information For The User' (*MHRA*, 21 November 2023), and JG/76 - INQ000413717, 'Summary of Product Characteristics' (*MHRA*, 21 November 2023).

describes the safety information that should be included in the SmPC) say the following:

(a) Section 4.3 concerns contraindications. This means situations where the medicine in question must not be given for safety reasons, for example, because the patient has a particular clinical diagnosis. The EMA Guideline says that these situations should be unambiguously, comprehensively and clearly outlined in the SmPC.

(b) Section 4.4 concerns special warnings and precautions for use. These may include, for example, information on special conditions that must be fulfilled before use; patient groups at increased risk; and serious adverse drug reactions and situations in which these may occur (also including serious adverse events that have been observed, but where a causal relationship has not been established).

(c) Section 4.8 concerns *"undesirable effects"*. The EMA Guideline says that this section of the SmPC should include confirmed adverse drug reactions for which "*a causal relationship between the medicine and the adverse event is at least a reasonable possibility"*. However, "*[a]dverse events, without at least a suspected causal relationship, should not be listed in the SmPC*".

74. Many of the adverse drug reactions included in the Product Information for the Oxford/AstraZeneca Vaccine were identified during the Oxford-sponsored clinical trials and were therefore included in the Product Information, approved by the MHRA during the initial authorisation process, and made available by the MHRA once the R174 Authorisation was granted in December 2020. Further safety information was added to sections 4.3 to 4.8 of the Product Information over time, following approval by the MHRA, as a result of Pharmacovigilance monitoring and in accordance with the EMA Guideline summarised above.

75. In most cases, AstraZeneca agreed with changes to the Product Information by the MHRA on the basis of further safety information that became available over time. In certain instances, an adverse drug reaction was later included in the Product Information by the MHRA, in circumstances where AstraZeneca either did not at the time or does not agree, based on the available evidence, that there was or is a reasonable possibility of a causal relationship. The MHRA exercising its authority in this way to require the inclusion of an adverse drug reaction in the Product

Information – which is not uncommon – is known as an imposition. In instances where the MHRA made an imposition, AstraZeneca and the MHRA would communicate about the appropriate terminology to be included in the Product Information and the MHRA would approve this prior to the updated Product Information being published. In the table at paragraph 77 below, I have set out details of the MHRA's impositions to the Product Information for the Oxford/AstraZeneca Vaccine. There were also instances where both AstraZeneca and the MHRA did not consider that, based on the available evidence, there was a reasonable possibility of a causal relationship, but decided in any event to add information about an adverse event into the Product Information while also noting that at the time of publication no causal relationship had been established. This is what is known as the exercise of the precautionary principle, where the Product Information is updated to warn of a possible safety issue even when the evidence is uncertain. The exercise of this precautionary decision-making remains grounded in the available Pharmacovigilance data and is and must be carefully applied. Such discussions between AstraZeneca and the MHRA relating to changes to the Product Information for the Oxford/AstraZeneca Vaccine were held in the context of AstraZeneca's frequent communication with the MHRA relating to Pharmacovigilance monitoring, which I have outlined above.

76. To indicate when each potential adverse drug reaction was established with a reasonable possibility of a causal relationship for inclusion in section 4.8 of the SmPC, I have set out below a summary table with four columns noting the following:

(a) The listed adverse drug reaction included in s.4.8 of the SmPC (identifying with asterisks those that either initially were, or remain, impositions by the MHRA).

(b) The frequency information, using the MHRA's defined terminology for frequency of occurrence as follows: "very common" (≥1/10); "common" (≥1/100 to <1/10); "uncommon" (≥1/1,000 to <1/100); "rare" (≥1/10,000 to <1/1000); "very rare" (<1/10,000); and "not known" (cannot be estimated from available data).

(c) The date on which the MHRA first included the adverse drug reaction in s.4.8 of the SmPC, whether in the tabulated list or otherwise. It is worth also noting that where an adverse drug reaction is identified and considered an emerging

safety issue,[50] the MHRA may take further steps to notify the public and healthcare professionals, as I explain below.

(d) Certain other information helpful for understanding the vaccine safety information in s.4.8 of the SmPC (under the heading "Notes").

77. The information in the table below lists all adverse drug reactions which appear in s.4.8 of the SmPC (last updated on 22 November 2023), listed in chronological order. The table does not attempt to capture all changes in the text of s.4.8 outside the tabulated list made after the particular adverse reaction was first included. Section 4.8 lists the "*most frequently reported*" adverse drug reactions for the Oxford/AstraZeneca Vaccine as injection site tenderness, injection site pain, headache, fatigue, myalgia (muscle aches and pains), malaise (overall weakness or discomfort), pyrexia (fever), chills, arthralgia (joint pain) and nausea. The Product Information notes that, for patients' first dose of the Oxford/AstraZeneca Vaccine, the "*majority of these adverse reactions were mild to moderate in severity and usually resolved within a few days of vaccination*"; for patients' second dose, adverse drug reactions reported were "*milder and reported less frequently*"; for patients' third dose, the "*majority of [the] adverse reactions were mild to moderate in severity and usually resolved within a few days of vaccination*".

[50] See Exhibit JG/41 - INQ000506107, EMA, 'Guideline on good pharmacovigilance practices (GVP) Module IX – Signal management (Rev 1)' (*EMA*, 9 October 2017).

Adverse effect (s.4.8)	Frequency	UK SmPC (s.4.8)	Notes
Lymphadenopathy	Uncommon	29 Dec 2020	
Decreased appetite	Uncommon	29 Dec 2020	
Headache	Very common	29 Dec 2020	
Dizziness	Common	29 Dec 2020	Frequency changed from *"uncommon"* to *"common"* on 21 November 2023.
Nausea	Very common	29 Dec 2020	
Vomiting, diarrhoea	Common	29 Dec 2020	Diarrhoea added on 22 February 2021.
Abdominal pain	Common	29 Dec 2020	Frequency changed from *"uncommon"* to *"common"* on 21 November 2023.
Hyperhidrosis, pruritus, rash, urticaria	Uncommon	29 Dec 2020	Urticaria added on 24 June 2021.
Myalgia, arthralgia	Very common	29 Dec 2020	
Injection site tenderness, ~~injection site~~ pain, ~~injection site~~ warmth, ~~injection site erythema, injection site~~	Very common	29 Dec 2020	- Injection site swelling and injection site erythema removed from this row and added to the row below (i.e. "*common*" rather than "*very common*") on 22

Adverse effect (s.4.8)	Frequency	UK SmPC (s.4.8)	Notes
pruritus, ~~injection site~~ ~~swelling,~~ ~~injection site~~ bruising, fatigue, malaise, feverishness, pyrexia, chills			February 2021. - Same change made for pyrexia on 24 June 2021, but pyrexia then moved back to "very common" on 21 November 2023. - Feverishness added on 24 June 2021. - Removal of the words "injection site" before "pain", "warmth", "pruritus" and "bruising" on 4 January 2022.
Injection site swelling, ~~injection site~~ erythema, ~~injection site~~ ~~induration~~, influenza-like illness, asthenia	Common	29 Dec 2020	- For additions of injection site swelling and injection site erythema on 22 February 2021: see above. - For addition and removal of pyrexia: see row above. - Asthenia added on 4 January 2022. - Injection site induration removed on 4 January 2022. - Removal of the words "injection site" before erythema on 4 January 2022.

Adverse effect (s.4.8)	Frequency	UK SmPC (s.4.8)	Notes
Neuroinflammatory disorders	Very rare	29 Dec 2020	Description at s.4.8 states that "*Very rare events of neuroinflammatory disorders have been reported following vaccination with Vaxzevria. A causal relationship has not been established*". (Note that neuroinflammatory disorders do not appear in the tabulated list within s.4.8 headed 'Adverse drug reactions'.)
Anaphylaxis, hypersensitivity	Not known	22 Feb 2021	Hypersensitivity added on 24 June 2021.
Thrombosis with thrombocytopenia syndrome	Very rare	7 Apr 2021	Description added to s.4.8 on 7 April 2021 of "*very rare events of major venous and arterial thrombosis with concurrent thrombocytopenia*", noting that "*a causal relationship has not been established*"; this note that "*a causal relationship has not been established*" was removed on 15 April 2021. (Note that "thrombosis with thrombocytopenia syndrome" was first added to the tabulated list and first used within s.4.8 on 24 June 2021.)
Angioedema, cutaneous vasculitis	Not known	24 June 2021	Cutaneous vasculitis added on 13 March 2023.

Adverse effect (s.4.8)	Frequency	UK SmPC (s.4.8)	Notes
Somnolence, lethargy, paraesthesia, hypoaesthesia	Uncommon	24 June 2021	- Lethargy added on 4 January 2022. - Paraesthesia and hypoaesthesia added on 13 March 2023.
Pain in extremity	Common	24 June 2021	
Thrombocytopenia	Common	24 June 2021	Frequency changed from *"not known"* to *"common"* on 24 June 2022, noting that in clinical trials *"transient mild thrombocytopenia was commonly reported"*.
Capillary leak syndrome*, Cerebrovascular venous and sinus thrombosis*	Not known	15 July 2021	Capillary leak syndrome (***CLS***) was accepted by AstraZeneca as an imposition made by the MHRA and was added to the Product Information on 15 July 2021. Very rare cases of CLS had been reported following vaccination with the Oxford/AstraZeneca Vaccine (cases observed among recipients of the Oxford/AstraZeneca Vaccine had usually become symptomatic within four days of vaccination, although in some cases symptoms have arisen more than 60 days later). AstraZeneca liaised closely with the MHRA and other regulators in order to investigate these reports and followed the signal

Adverse effect (s.4.8)	Frequency	UK SmPC (s.4.8)	Notes
			management processes described above. AstraZeneca's position was (and is) that there is insufficient evidence to suggest a causal relationship between the Oxford/AstraZeneca Vaccine and CLS.[51] I note that, at s.4.4 of the SmPC, the MHRA stated that a pre-existing history of CLS was apparent in some of the cases reported following vaccination. Cerebrovascular venous and sinus thrombosis (***CVST***) was accepted by AstraZeneca as an imposition made by the MHRA and was added to the Product Information on 4 January 2022. NB this refers to CVST <u>without</u> thrombocytopenia (updates to the Product Information regarding thromboembolic events including CVST <u>with concurrent</u> thrombocytopenia are addressed at paragraph 79 below). Cases of CVST without

[51] AstraZeneca had explained its position in this regard in response documents that were submitted to the EMA's Pharmacovigilance Risk Assessment Committee on 5 May 2021 and 2 July 2021 (which AstraZeneca shared with the MHRA in accordance with its request to be updated regarding EMA assessment reports and outcomes). See Exhibits JG/77 - INQ000506076, 'AZD1222 Response to Request from Pharmacovigilance Risk Assessment Committee – Capillary Leak Syndrome' (*AstraZeneca,* 5 May 2021) and JG/78 - INQ000506073, 'AZD1222 Response to Request from Pharmacovigilance Risk Assessment Committee – Capillary Leak Syndrome Signal Assessment Report' (*AstraZeneca*, 2 July 2021).

Adverse effect (s.4.8)	Frequency	UK SmPC (s.4.8)	Notes
			thrombocytopenia had been observed very rarely following vaccination with the Oxford/AstraZeneca Vaccine, typically within the first four weeks following vaccination. AstraZeneca liaised closely with the MHRA and other regulators in order to investigate such reports and followed the signal management processes described above. AstraZeneca's position was (and is) that there is insufficient evidence to suggest a causal relationship between the Oxford/AstraZeneca Vaccine and CVST in the absence of thrombocytopenia.
Guillain-Barré syndrome*	Very rare	14 Oct 2021	Guillain-Barré syndrome (***GBS***) was accepted by AstraZeneca as an imposition made by the MHRA and was added to s.4.8 of the Product Information on 14 October 2021 (having been included in s.4.4 from 20 August 2021 also as an imposition).[52] Very rare cases of

[52] On 11 August 2021, AstraZeneca had submitted a response document to the MHRA explaining why, on the basis of the totality of available information, AstraZeneca did not agree with including a specific warning for GBS in s.4.4; see Exhibit JG/79 - INQ000506070, 'Response to questions regarding the inclusion of Guillain Barré Syndrome in the label' (*AstraZeneca*, 11 August 2021).

Adverse effect (s.4.8)	Frequency	UK SmPC (s.4.8)	Notes
			GBS had been reported following vaccination with the Oxford/AstraZeneca Vaccine. AstraZeneca liaised closely with the MHRA and other regulators in order to investigate such reports and followed the signal management processes described above. AstraZeneca's position, including based on a review of cases by an expert neurology panel, was (and is) that any association between GBS and the Oxford/AstraZeneca Vaccine is uncertain. On 17 December 2021, the MHRA issued a further statement with additional information regarding the potential risk of GBS following administration of the Oxford/AstraZeneca Vaccine, including the fact that, while approximately an extra 5.6 cases of GBS per million doses had been reported within 6 weeks of an initial dose, the number of reports of GBS following a second dose was no higher than would be expected in accordance with the background rate of the condition.[53]

[53] See Exhibit JG/80 - INQ000506152, 'Information for healthcare professionals on Guillain-Barré Syndrome (GBS) following COVID-19 vaccination' (*UKHSA*, 17 December 2021).

Adverse effect (s.4.8)	Frequency	UK SmPC (s.4.8)	Notes
			I note for completeness that, on 11 March 2022, on the basis of additional information that had become available up to 28 December 2021, AstraZeneca took the decision to update the s.4.4 of the Core Data Sheet (***CDS***)[54] for the Oxford/AstraZeneca Vaccine to refer to very rare events of GBS having been reported, but advising that a causal relationship had not been established. S.4.4 of the CDS was accordingly updated on 11 May 2022.
Immune thrombocytopenia	Not known	4 Jan 2022	
Facial paralysis	Rare	4 Jan 2022	
Muscle spasms	Uncommon	4 Jan 2022	
Transverse myelitis*	Not known	24 Jan 2022	As noted at paragraph 35 above, there was a pause of the clinical trials in September 2020 when a participant in the active arm of the COV002 trial exhibited symptoms consistent with transverse myelitis (***TM***). Independent

[54] A CDS is a document prepared by the MAH containing, in addition to safety information, material related to indications, dosing, pharmacology and other information concerning the product. See GVP Annex IV, 'ICH guideline E2C (R2) on periodic benefit-risk evaluation report (PBRER)' (Exhibit JG/61 - INQ000506123).

Adverse effect (s.4.8)	Frequency	UK SmPC (s.4.8)	Notes
			review did not conclude that there was any likely causal association with the Oxford/AstraZeneca Vaccine, and the trials resumed following agreement by the MHRA. TM was accepted by AstraZeneca as an imposition made by the MHRA and was added to the Product Information on 24 January 2022. Extremely rare cases of TM had been reported following vaccination with the Oxford/AstraZeneca Vaccine. AstraZeneca liaised closely with the MHRA and other regulators in order to investigate such cases and followed the signal management processes described above. AstraZeneca's position was (and is) that there is insufficient evidence to suggest a causal relationship between the Oxford/AstraZeneca Vaccine and TM.[55] AstraZeneca's position as explained to the MHRA was therefore that no change to the Product Information was warranted, with

[55] AstraZeneca had also outlined this position to the MHRA on 1 December 2021 and 13 December 2021 in response to the MHRA's request for AstraZeneca to confirm its position on the MHRA's proposed updates to the Product Information regarding TM. See Exhibits JG/81 - INQ000506079 ('Response to MHRA request to update labelling with Transverse myelitis' (*AstraZeneca*, 1 December 2021)) and JG/82 - INQ000506072 ('Response to MHRA's further request to comment on the CT data of Transverse myelitis cases provided in previous response' (*AstraZeneca*, 13 December 2021)).

Adverse effect (s.4.8)	Frequency	UK SmPC (s.4.8)	Notes
			TM instead to be closely monitored as part of ongoing surveillance efforts for the adverse event of special interest of nervous system disorders.
Tinnitus	Uncommon	18 Jan 2023	

78. As to how, and to whom, changes to the Product Information are communicated: once the MHRA has approved updates to the Product Information, this information is made available, including on the MHRA's website, the electronic medicines compendium and through other sources such as press releases and public announcements. Safety issues may also be communicated directly to the NHS and to healthcare professionals by a "direct healthcare professional communication". Since a R174 Authorisation is not a marketing authorisation, AstraZeneca was substantially limited in its ability to communicate regarding the Vaccine, as outlined at paragraph 70 above. Instead, the MHRA prepared and circulated direct healthcare professional communications on occasion in relation to the Oxford/AstraZeneca Vaccine.

79. By way of illustration of the analysis and discussion with the MHRA that preceded changes to the Product Information, I summarise below the circumstances in which the Product Information was amended on 7 April 2021 and 15 April 2021 regarding very rare cases of serious thromboembolic events with concurrent thrombocytopenia (low levels of platelets).

(a) From early March 2021, concerns were expressed, initially in Austria and then subsequently in other EU countries, that the Oxford/AstraZeneca Vaccine might be associated with an increased risk of thromboembolic events in recipients (the first such case in Austria was notified to AstraZeneca on 3 March 2021). These initial reports related to cases of "ordinary" venous thromboembolism (VTE), i.e. the type of venous thrombosis (deep vein thrombosis or pulmonary embolus) that occurs frequently in the population in association with a number of risk factors.[56] There was at this stage no reference to thrombosis with thrombocytopenia syndrome (***TTS***), where thrombosis may occur at unusual sites, such as CVST.

(b) On 18 March 2021, the MHRA issued a statement regarding a small number of reports having been received of very rare cases of thromboembolic events with concurrent thrombocytopenia. In particular, the MHRA referred for the

[56] AstraZeneca liaised closely with the MHRA and the EMA in relation to their investigation of these reports. AstraZeneca's review of its safety database revealed no increased incidence of VTE events relative to the expected background rate in unvaccinated individuals. On 11 March 2021, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) concluded that the information available at that time did not indicate an increased incidence of thromboembolic events in people vaccinated with the Oxford/AstraZeneca Vaccine. The EMA issued a further statement on 15 March 2021 explaining that, while its investigations were ongoing, the EMA remained of the view that "the benefits of the [Oxford/AstraZeneca Vaccine] in preventing COVID-19, with its associated risk of hospitalisation and death, outweighed the risks of side effects".

first time to five reports of CVST ("*a very rare and specific type of blood clot*") with concurrent thrombocytopenia, which had been "*reported in less than 1 in a million people vaccinated so far in the UK, and can also occur naturally*". The MHRA stated that a causal association with the Oxford/AstraZeneca Vaccine had not been established and, further, that "*the MHRA's advice remains that the benefits of the vaccines against COVID-19 continue to outweigh any risks and that the public should continue to get their vaccine when invited to do so*".[57]

(c) AstraZeneca and the MHRA (and other regulators) liaised closely in relation to their ongoing investigation of these reports during March 2021 (and after), including on the analysis of the developing safety data.

(d) On 7 April 2021, the MHRA added information regarding very rare cases of serious thromboembolic events with concurrent thrombocytopenia in vaccine recipients to the Product Information. This information was first included using the precautionary principle, as mentioned above, noting at that time that the reasonable possibility of a causal relationship had not been established (the MHRA stated in its accompanying press release that the evidence of a link between "*extremely rare and unlikely to occur specific blood clots with lowered platelets*" and the Oxford/AstraZeneca Vaccine was "*stronger*" but that "*more work is still needed*").[58] The MHRA noted that, by 31 March 2021, it had received 79 UK reports of blood clotting cases alongside low levels of platelets following the use of the Oxford/AstraZeneca Vaccine, in the context of 20.2 million doses having been given in the UK ("*meaning the overall risk of these blood clots is approximately 4 people in a million who receive the vaccine*").

(e) The Product Information was later updated by the MHRA on 15 April 2021 when a reasonable possibility of causal association was established and further data and information on the very rare occurrence of thromboembolic events with concurrent thrombocytopenia had been collected and analysed.

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[57] See Exhibit JG/83 - INQ000408457, MHRA, 'UK regulator confirms that people should continue to receive the COVID-19 vaccine AstraZeneca' (*MHRA*, 18 March 2021).

[58] See Exhibit JG/84 - INQ000408453, MHRA, 'MHRA issues new advice, concluding a possible link between COVID-19 Vaccine AstraZeneca and extremely rare, unlikely to occur blood clots' (*MHRA*, 7 April 2021).

80. At AstraZeneca we make medicines to save lives and improve conditions for patients. As I hope I have explained in this statement, it is not possible to fully know the safety profile of a medicine from clinical trials. Even large trials like those for the Oxford/AstraZeneca Vaccine cannot identify all adverse drug reactions, particularly those that occur very rarely. This is why AstraZeneca and regulatory authorities worldwide, including the MHRA and EMA, carry out intensive ongoing Pharmacovigilance work after a medicine is authorised to be placed on the market.

81. These Pharmacovigilance processes and the consequent updating of vaccine safety information constitute an evidence-based scientific practice that requires the structure I set out above to identify new safety information for inclusion in a medicine's Product Information. The adverse drug reactions subsequently added to the Oxford/AstraZeneca Vaccine Product Information after the initial grant of its R174 Authorisation were primarily driven by these processes. Updates were made to the Product Information for patients and for healthcare professionals by the MHRA in accordance with the UK's regulatory regime and pursuant to the powers of the Licensing Authority. My opinion is that these Pharmacovigilance practices worked well and effectively for identifying new safety information and to ensure that the Product Information was kept updated. As I discuss further below, the MHRA and regulatory authorities worldwide have continued to monitor and review the positive benefit/risk profile of the Oxford/AstraZeneca Vaccine on this basis.

SECTION G: REAL-WORLD EVIDENCE FOR THE OXFORD/ASTRAZENECA VACCINE

82. AstraZeneca's post-authorisation activities also included monitoring the effectiveness of the Oxford/AstraZeneca Vaccine in the real world (i.e. outside the context of clinical trials). This analysis allows conclusions to be drawn regarding how the efficacy profile observed in controlled settings in clinical trials compares with real-world performance.

83. On 19 February 2021, the first set of real-world effectiveness data for the Oxford/AstraZeneca Vaccine was published,[59] following a study by Public Health Scotland (PHS) and the Universities of Edinburgh, Strathclyde, Aberdeen, Glasgow

[59] See Exhibit JG/85 - INQ000147534, Eleftheria Vasileiou et al., 'Effectiveness of First Dose of COVID-19 Vaccines Against Hospital Admissions in Scotland: National Prospective Cohort Study of 5.4 Million People' (2021) SSRN Electron.

and St Andrews.[60] The paper was based on data gathered between 8 December 2020 and 15 February 2021. The results reported showed the Oxford/AstraZeneca Vaccine to be 94% effective in preventing hospitalisation in the real world at 28-34 days post-vaccination with the first dose, and 81% effective at preventing hospitalisation for those aged 80 and over. On 23 April 2021, further results from this study were published in The Lancet for individuals who received a single dose of the Oxford/AstraZeneca Vaccine between 8 December 2020 and 22 February 2021.[61] A single dose of the Oxford/AstraZeneca Vaccine in these individuals was associated with a vaccine effect of 88% in preventing hospitalisation in the real world at 28-34 days post-vaccination. The paper concluded that the Oxford/AstraZeneca Vaccine was associated with "*substantial reductions in the risk of hospital admission due to COVID-19 in Scotland*".

84. Regulatory bodies have also monitored the effectiveness of the COVID-19 vaccines. Public Health England published a series of reports on this issue.[62] One of the first was published in March 2021 and considered data in relation to both the Pfizer/BioNTech vaccine and the Oxford/AstraZeneca Vaccine. This included the following summary in relation to hospitalisation risks:

> *"Hospitalisation rates were around 15% in unvaccinated individuals in both populations. Among those who had had their first dose at least 14 days previously, hospitalisation rates were 9% in those who had received the Pfizer vaccine and 8% in those who had received AstraZeneca. The survival analysis showed 42% (Pfizer) and 35% (AstraZeneca) reductions in the risk of hospitalisation among those who had been vaccinated but became symptomatic, compared with those who had not although confidence intervals around these estimates were broad and overlapping. Combined with the reduced risk of becoming a case (Section 3) this is consistent with vaccine effectiveness against hospitalisation of around 80%."*

85. The UKHSA has undertaken regular reporting on real-world effectiveness as part of the COVID-19 Vaccine Surveillance Strategy originally published by Public Health

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60 See Exhibit JG/86 - INQ000235195, Public Health Scotland, 'Vaccine linked to reduction in risk of COVID-19 admissions to hospitals' (*Public Health Scotland*, 22 February 2021).

61 See Exhibit JG/87 - INQ000147546, Eleftheria Vasileiou et al., 'Effectiveness of first dose of COVID-19 vaccines against hospital admissions in Scotland: a national prospective cohort study of 5.4 million people' (2021) 397 The Lancet 1646.

62 See Exhibit JG/88 - INQ000506147, Public Health England (PHE), 'PHE monitoring of the effectiveness of COVID-19 vaccination' (*PHE*, 22 February 2021).

England. The UKHSA's reports are available through the gov.uk website. From 2021 until May 2022 these were published weekly; since then, they have been published quarterly. The reports monitor the effectiveness of all vaccines being used in the UK against COVID-19 in relation to symptomatic disease, hospitalisation, death, infection (symptomatic or asymptomatic) and transmission.

86. AstraZeneca's also undertook its own monitoring of the real-world effectiveness of the Oxford/AstraZeneca Vaccine. This had three main parts:

(a) AstraZeneca sponsored a number of observational research studies in the UK (RAVEN), Europe (COVIDRIVE), Brazil (REFORCO) and other countries in Latin America (LIVE).[63]

(b) AstraZeneca supported external researchers to run observational studies in Eswatini, Indonesia and Nepal.

(c) AstraZeneca conducted regular reviews of the literature on the effectiveness of the Oxford/AstraZeneca Vaccine (including scientific publications, preprints, reports from Public Health Institutes, and the International Vaccine Access Center (IVAC) living systematic review).

87. The above is only a summary of some of the real-world evidence (***RWE***) available in relation to the Oxford/AstraZeneca Vaccine. Overall, the RWE studies have consistently demonstrated the effectiveness of a two-dose primary series of the Oxford/AstraZeneca Vaccine against severe COVID-19 for both ancestral strains of SARS-CoV-2, and also the Alpha, Delta, Gamma and Omicron variants.[64] Booster doses of the Oxford/AstraZeneca Vaccine have also been shown to offer high effectiveness against infection and severe disease due to Omicron variants of SARS-CoV-2.[65]

88. I have included this further information because it is an important body of information for understanding the Oxford/AstraZeneca Vaccine and the different ways in which it

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63 In broad terms, observational studies involve observation of individuals without manipulation or intervention - in contrast to experimental studies (such as randomised controlled trials) where investigators do intervene and look at the effects of the intervention on an outcome being studied.

64 See Exhibit JG/89 - INQ000506150, Sunate Chuenkitmongkol et al., 'Expert review on global real-world vaccine effectiveness against SARS-CoV-2' (2022) 21 Expert Review of Vaccines 1255.

65 See Exhibit JG/90 - INQ000506149, Rontgene Solante et al., 'Expert review of global real-world data on COVID-19 vaccine booster effectiveness and safety during the omicron-dominant phase of the pandemic' (2023) 22 Expert Review of Vaccines 1.

has been studied. For future pandemics, I would expect RWE to continue to be important and have therefore made some suggestions below about continued improvements for the gathering and communication of this information in the UK.

SECTION H: FURTHER UK REGULATORY APPROVALS FOR THE OXFORD/ASTRAZENECA VACCINE FOLLOWING INITIAL UK AUTHORISATION

89. On 22 March 2021, AstraZeneca made an application to the MHRA for a Conditional Marketing Authorisation (***CMA***) for the Oxford/AstraZeneca Vaccine. A CMA is "*intended for medicinal products that fulfil an unmet medical need*", such as "*serious and life-threatening diseases where no satisfactory treatment methods are available or where the product offers a major therapeutic advantage*" (MHRA guidance dated 31 December 2020). A CMA may be granted where comprehensive clinical data is not yet complete, but it is judged that such data will become available soon.[66] On 24 June 2021, the UK Licensing Authority granted a CMA for the Oxford/AstraZeneca Vaccine on advice of the MHRA.

90. The MHRA's decision to recommend to the UK Licensing Authority that a CMA should be granted meant that it had concluded that, based on all available evidence, the benefits of the Oxford/AstraZeneca Vaccine at that time continued to outweigh the risks. The PAR published in July 2021[67] provided the following information under the heading 'Why was Vaxzevria approved?':

> "*It was concluded that Vaxzevria has been shown to be effective in the prevention of COVID-19. Furthermore, the side effects generally observed with use of this product are considered to be similar to those seen for other vaccines. Therefore, the MHRA concluded that the benefits are greater than the risks and recommended that this medicine can be authorised for use*.
>
> *Vaxzevria has been authorised with a Conditional Marketing Authorisation (CMA). CMAs are intended for medicinal products that address an unmet medical need, such as a lack of alternative therapy for serious and life-threatening disease. CMAs may be granted where comprehensive clinical*

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66 See Exhibit JG/91 - INQ000506136, MHRA, 'Conditional Marketing Authorisations, exceptional circumstances Marketing Authorisations and national scientific advice' (*MHRA*, 31 December 2020).

67 See Exhibit JG/92 - INQ000413713, MHRA, 'Public Assessment Report National procedure' (*MHRA*, July 2021).

data are not yet complete, but it is judged that such data will become available soon."

91. In December 2021, AstraZeneca applied for the renewal of the CMA. The CMA for the Oxford/AstraZeneca Vaccine was renewed on 24 June 2022. A standard GB Marketing Authorisation was granted for the Oxford/AstraZeneca Vaccine on 19 June 2023. These authorisations represented continued confirmation by the MHRA that the benefit-risk profile of the Oxford/AstraZeneca Vaccine remained positive.

SECTION I: FUTURE PANDEMIC PREPAREDNESS

Clinical Trials

92. Professor Sir Andrew Pollard and the Oxford teams established funding for, designed and began the Oxford-sponsored clinical trials. In my opinion, they did this quickly and thoughtfully, with support of many people in the NHS. This approach relied heavily on Professor Pollard's existing network of academic, government agency and industry contacts. I think for future pandemics, learning from the clinical trial infrastructure and contacts that Professor Pollard established and ensuring that there is existing infectious disease clinical trial infrastructure in the UK and key individuals and sites are identified in advance of any outbreak would be a worthwhile investment. I was pleased to read in this regard the UK Government's announcement on 28 August 2024 that up to £400 million is due to be invested in "key health and life sciences projects", with 75% of this investment allocated to "expand the UK's capacity and capability for commercial clinical trials".[68] The announcement stated that up to 18 new clinical trial hubs (Commercial Research Delivery Centres) would be established to "enhance and build upon the UK's commercial clinical trials infrastructure and support patient recruitment into trials". I would encourage the UK Government to ensure that these trial hubs are pandemic-ready to support institutions with the rapid recruitment of trial participants, and efficient operation of trials, in a pandemic setting. This could usefully include (i) identifying suitable additional sites at which pandemic trials could be conducted and (ii) identifying (and providing appropriate training to) individuals who could support with the different

[68] See Exhibit JG/93 - INQ000506082, Department of Health and Social Care, Office for Life Sciences, Karin Smyth MP, The Rt Hon Wes Streeting MP and The Rt Hon Peter Kyle MP, 'UK secures £400 million investment to boost clinical trials' (*DHSC*, 28 August 2024).

phases of a large-scale trial programme, from recruitment through to long-term follow-up.

Regulatory approvals process

93. I understand from discussion with my regulatory colleagues that the R174 Authorisation process worked well. My colleagues have suggested that, as the MHRA continues to reflect on its own lessons learned from the pandemic, it could consider reviewing this process and developing an established structure for future submissions, while continuing to allow for the provision and evaluation of submissions on a rolling basis. I make this suggestion cautiously, as the pandemic demonstrated that ensuring frequent engagement, flexibility and a willingness to review information on a rolling basis was important to minimising delays while maintaining a robust process. However, it would be helpful to have a defined process set out which could serve as a starting point for future R174 Authorisations. It may, for example, be worthwhile for the MHRA to hold workshops to discuss the R174 Authorisation process, with a view to the MHRA then formalising the structure of future R174 Authorisations.

Pharmacovigilance monitoring

94. On 28 October 2022, AstraZeneca's Patient Safety team working on the Oxford/AstraZeneca Vaccine published a peer-reviewed paper in Nature Reviews Drug Discovery journal detailing the challenges of the forecasting and management of large volumes of ICSRs together with reflections on lessons learned for future pandemics.[69] I think their discussion and information should be helpful for future pandemic preparations.

95. The Inquiry has asked whether AstraZeneca has any suggestions for reform in relation to Pharmacovigilance monitoring procedures, the Yellow Card and Product Information procedures. However, these are not really matters for AstraZeneca to comment on. If in future the UK Government did decide that changes might be warranted, AstraZeneca would want to be part of that discussion, but it does not have any further suggestions on these topics at this time.

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[69] See Exhibits JG/94 - INQ000413709, Alexandre Kiazand et al., 'Pandemic vaccines: a formidable challenge for pharmacovigilance' (2023) 22 Nature Reviews Drug Discovery, and JG/95 - INQ000413708, Alexandre Kiazand et al., 'Pandemic vaccines: a formidable challenge for pharmacovigilance – Supplementary Information' (2023) 22 Nature Reviews Drug Discovery.

Real-world evidence

96. For all medicines, the collection and analysis of real-world data to generate RWE is important. My assessment is that in a pandemic context, this is even more the case. I would encourage a review and investment by the UK Government in the IT infrastructure necessary to consistently record and then extract this information from NHS services for the purpose of generating and analysing both effectiveness and safety information. In a pandemic, not only is the generation of RWE important, but the speed of that process is crucial to ensure that policy decisions can be made based on the latest and most recent evidence. For this reason, reducing barriers to accessing real-world data is crucial. By way of example, centralisation of data sources containing health records data (i.e. greater linkage between patients' GP medical records, hospital medicals records and laboratory diagnosis records) would assist with ensuring that data for each patient could be obtained from one single source, allowing RWE to be generated efficiently. In addition, granting industry researchers access to data sources that are presently only accessible by academia or government researchers (and at the same time) would be particularly valuable in a pandemic setting.

97. Further, making it possible to evaluate and generate evidence for specific populations including healthcare workers and vulnerable individuals (e.g. those who are immunocompromised, frail and/or living in long-term care facilities) is important as these are often the populations most impacted and in need of effective medical solutions. The sequencing and reporting of variant data were done well in the UK. However, ensuring these data are linked to NHS data would allow for better evidence on effectiveness and safety of medicines.

Conclusion

98. I am proud of how AstraZeneca and the Oxford teams worked together to produce an important and effective vaccine for the prevention of COVID-19 disease. I was part of a large team of people working extraordinarily hard for extended periods of time to develop the Oxford/AstraZeneca Vaccine, which was made available fairly and globally. AstraZeneca went on to supply 100 million doses in the UK, which was an

important part of ending the global pandemic. I hope this statement is of use in the UK's planning for future pandemics.

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
Justin Green (Nov 7, 2024 12:00 GMT)

Dated: 07-Nov-2024