UK COVID-19 INQUIRY

MODULE 4: WRITTEN OPENING SUBMISSIONS ON BEHALF OF THE NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE ["NICE"]

INTRODUCTION

1. NICE would like to begin these submissions by extending its sympathies to those bereaved by COVID-19, to those still suffering from its effects, and to their relatives and friends. It would also like to pay tribute to the remarkable work of the life sciences industry, academic, scientific and medical communities, and clinicians in developing treatments and vaccines for COVID-19 at pace during the pandemic. NICE especially notes that despite the successes in developing and delivering new treatments and vaccines, not everyone has been fully able to benefit from those advances, whether through contraindications or immunosuppression, and their perspective must not be forgotten.

2. NICE anticipates it will be best able to assist the Inquiry on the question of "*The development, trials and steps taken to enable the use of new therapeutics and repurposed medications during the pandemic*". NICE's remit was predominantly focused on pharmaceutical interventions, and it did not have a role in the development, approval or deployment of prophylactic vaccines.

3. As a Core Participant, NICE has had disclosed to it large numbers of documents from other organisations. Rather than responding to that evidence at this point, NICE will carefully consider all the evidence that the Inquiry will see and hear during the Module 4 hearings before reflecting further on its role and identifying any lessons that may come from that.

4. In relation to Module 4, NICE has provided witness statements and exhibits on behalf of the organisation from the Directors responsible for the main directorates involved in the response to the pandemic, as follows:

    i. Helen Knight – currently Director of Medicines Evaluation, Centre for Heath Technology Evaluation ["CHTE"] at NICE and during the pandemic was appointed to Deputy Director of CHTE and oversaw the Research to Access Pathway for Investigational Drugs in COVID-19 ["RAPID C-19"]. This was a multi-agency initiative aimed at ensuring safe and timely access to therapeutics that showed evidence of benefit in preventing and treating COVID-19, as part of temporary emergency pandemic arrangements.

    ii. Dr Paul Chrisp – retired from NICE in March 2024 and was the Director of the Centre for Guidelines ["CfG"] during the pandemic. The CfG produced rapid evidence reviews, which provided information on the evidence base for different medicines and delivered the COVID-19 rapid guideline programme. The programme then went on to make recommendations on COVID-19 medicines.

5. We will not seek to summarise that material here, but will set the scene for two areas where NICE is most likely to be able to assist the Inquiry. The Inquiry will also take oral evidence from Helen Knight during the Module 4 hearings.

BACKGROUND TO NICE

6. NICE is an arm's length body of the Department for Health and Social Care ["DHSC"]. A framework agreement exists between NICE and DHSC, which sets out the parameters in which NICE can operate and in which it discharges its responsibilities. This is a public document, and a copy of the framework agreement has additionally been disclosed to the Inquiry. NICE's role and responsibilities are defined by the Health and Social Care Act 2012 and its supporting regulations. In fulfilling these functions, NICE balances the best care with value for money across the NHS and social care, to deliver for both individuals and society as a whole.

7. In plain English; NICE's role is to issue guidance to the NHS and the wider health and social care system. (It does so directly in England, and by arrangements with the devolved governments in Wales and Northern Ireland.) The guidance is intended to improve the care that the NHS and others deliver. NICE's guidance is authoritative, and can only be departed from with good reason, (*R ota Rose v Thanet CCG* [2014] EWHC 1182 (Admin)), but with two exceptions it is not binding (the exceptions are that funding must be made available for technologies recommended by NICE through its technology appraisal programme or its highly specialised technology programme). NICE guidelines come with a standard rubric:

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

...

Local commissioners and providers of healthcare have a responsibility to enable the guideline to be applied when individual professionals and people using services wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with complying with those duties.

8. Other forms of NICE guidance have a broadly similar caveat.

9. It is important to understand the limitations of NICE's role. It does not consider affordability (which is, broadly, what can be bought with a finite budget), but it does consider cost effectiveness (which is, again broadly, whether the expected benefit of a treatment represents value for money for the NHS), although consideration of the cost effectiveness of treatments for and prevention of COVID-19 was largely suspended during the pandemic. It does not issue guidance on professional conduct, authorise medicines as acceptably safe for use, or have a role in their recall if they are found not to be safe (although consideration of safety may inform guidance on clinical effectiveness).

10. Even within its field of making recommendations on clinical and cost effectiveness of and the clinical uses of technologies and procedures for the NHS, NICE shares the space with other bodies, including the Royal Colleges and other professional associations, trusted producers of healthcare evidence such as the Cochrane collaboration, academic journals, and bodies with a similar remit to NICE in other health systems, including, importantly, NICE's equivalent bodies in Scotland and Wales, the Scottish Intercollegiate Guidelines Network ["SIGN"], the Scottish Medicines Consortium, the All Wales Therapeutic and Toxicology Centre; and, for non-medicine technologies the Scottish Health Technologies Group and Health Technology Wales.

11. For the most part, NICE can only act when requested to do so by the Secretary of State or NHS England ["NHSE"]. For example, it can only exercise its function of giving advice about NHS services if directed to do so by the Secretary of State or NHSE and it may only make a health technology appraisal ["TA"] or highly specialised technology recommendation if directed to do so by the Secretary of State. Although there is nothing in the statutory framework that governs NICE, which prevents it as a matter of law from appraising a vaccine or making recommendations in respect of a vaccination programme, in practice it has only ever been asked to do so for therapeutic rather than prophylactic vaccinations. NICE's published topic selection manual at paragraph 3.10 excludes prophylactic vaccinations from consideration as these fall within the remit of the Joint Committee on Vaccination and Immunisation. NICE was not asked to, nor did it undertake any work specifically on COVID-19 vaccines.

Research to Access Pathway for Investigational Drugs for COVID-19 [RAPID C-19]

12. RAPID C-19 was established on 29 April 2020 at the request of NHSE and was stood down at the end of March 2023. It was a multi-agency initiative to facilitate rapid patient access to medicines for COVID-19 when they were proven to be clinically beneficial and before more formal mechanisms of clinical and cost-effectiveness assessments were undertaken. It did so by monitoring the development of potential medicines (including new uses of existing medicines), assessing the evidence for them, and communicating RAPID C-19 Oversight group's consensus opinion to the Chief Medical Officer ["CMO"] and others, who could then use that opinion to inform their decision-making. Helen Knight's witness statement [INQ000474611] discusses the working of RAPID C-19 at paragraphs 33-109.

13. The scale of the exercise is given in paragraphs 43-45 of Helen Knight's statement, including 89 topics reviewed, more than 24,000 papers screened, access to 10 new treatments supported and the treatment of over 200,000 patients affected.

14. Helen Knight identifies that the purpose of RAPID C-19 was to support decision-making about temporary access arrangements in an emergency pandemic situation where the challenges were the availability of evidence and the quality of the data produced within a fast moving and ever-changing environment. Its role was to identify and monitor the development of potential medicines (including new uses of existing medicines) and their associated clinical evidence and licensing status/timelines; and rapidly to assess the emerging evidence to help support a route to patient access if the evidence of benefit was strong. Its processes were co-designed by the regulatory authority (Medicines and Healthcare products Regulatory Agency ["MHRA"]), evidence funders (National Institute for Health and Care Research ["NIHR"]), evidence assessors (NICE), and the organisation responsible for national clinical commissioning (NHSE). NICE's role was to provide the secretariat function and to enhance horizon scanning information. This was a novel and innovative way of working for all concerned. The processes followed were not based on any pre-existing NICE process and the outputs did not have the status of NICE guidance/guidelines. Those outputs were not guidance to the NHS, clinicians, or information for patients, but advice to the CMO and DHSC, whose decision it would be whether or not to deploy the medicine. The outputs were not for public or clinical use.

15. RAPID C-19 provided advice to the CMO, where:
    i. evidence of clinical benefit was sufficient to support consideration for rapid interim patient access. 10 treatments were made available during the pandemic, to which RAPID C-19's work and advice contributed, for example, Tocilizumab; or

ii. the evidence was not sufficient to support consideration for rapid interim access, but where there was high interest (this included Evusheld).

16. It should be noted that a report that the evidence of clinical benefit was sufficient to warrant consideration for rapid interim patient access is not the same as a recommendation for use. RAPID C-19 reports were one source of information concerning interim therapeutic access, but there were others. It was for the CMO and DHSC to synthesise all of that information and make a decision in light of the priorities at that time.

17. The work of RAPID C-19 was subject to an oversight group, which included representatives from a range of bodies including NICE, NHSE, MHRA, NIHR, DHSC, and representatives of devolved governments.

18. RAPID C-19 was a part of the UK's emergency pandemic arrangements. During that time, COVID-19 medicines were centrally funded by the DHSC and rapid deployment was in place without more formal clinical and (especially) cost effectiveness assessments being undertaken. Those emergency arrangements were unsuitable for routine commissioning (not least, as assessment of cost effectiveness is relevant to routine commissioning) and so RAPID C-19 was stood down in March 2023.

Evusheld

19. The Inquiry's attention has been drawn to Evusheld (tixagevimab and cilgavimab in combination, sometimes: "tix-cil" or AZD7442) and in particular, questions around whether it should have been considered earlier in the pandemic and/or made available for either pre-exposure prophylactic use, for post-exposure prophylactic use, or for therapeutic use, particularly for those who are immunocompromised and/or clinically unsuitable for vaccination.

20. As Helen Knight's witness statement details in paragraphs 114 to 133, Evusheld in all of its possible settings was considered by RAPID C-19, (which had its own processes and did not use NICE's normal methods).

21. Post-exposure prophylactic use was considered and discounted by the RAPID C-19 oversight group on 13 October 2021: a key clinical trial had failed to demonstrate that Evusheld was clinically effective in that setting.

22. Therapeutic use in non-hospitalised patients was considered by the RAPID C-19 oversight group on 15 June 2022. The trial results relevant to that use were considered not directly relevant to the situation at the time of the report, because the study population were unvaccinated and enrolled when different variants of the virus were dominant. Progress towards patient access was not advised.

23. The evidence for the therapeutic use in hospitalised patients was shared with the RAPID C-19 oversight group on 17 August 2022. Once again, the key clinical trial did not suggest any benefit from treatment, so this was not considered further.

24. RAPID C-19's consideration of Evusheld was therefore primarily focused on pre-exposure prophylactic use. Helen Knight's witness statement sets out at table 7 and paragraphs 119-133 the substantial consideration given to this use and gives the references to the briefing papers prepared. In total, RAPID C-19 considered Evusheld for pre-exposure prophylactic use 10 times between February 2021 and August 2022. It submitted reports to the CMO in December 2021, May 2022 and September 2022.

25. In December 2021, RAPID C-19 advised that there was a potential signal of efficacy for pre-exposure prophylaxis, but cautioned that this was based on data generated at a time when the Alpha variant of the SARS-CoV-2 virus was dominant and that at the time of the report the Omicron

variant was dominant. Consequently, it advised that any consideration for rapid access needed to be subject to MHRA marketing authorisation (as with all new treatments) and confirmation of activity against the Omicron variant. Subsequent consideration of the emerging data, both non—clinical (in-vitro) and clinical did not provide sufficient confidence that Evusheld would be clinically effective against Omicron. RAPID C-19 therefore advised that the uncertainties in the evidence base for Evusheld for pre-exposure prophylaxis use were too substantial to warrant consideration for rapid access.

26. At paragraphs 134-135, Helen Knight describes two TA's concerning Evusheld, (referred to NICE by the DHSC in July and August 2022) neither of which recommended its use. The July referral related to the use of Evusheld for the treatment of COVID-19 and the August referral to its use as a prophylaxis. These referrals reflected a return to routine commissioning arrangements under the government's return to living with COVID-19. (One significance of a TA referral is that, unlike the work of RAPID C-19, it will follow NICE's usual published processes which include consideration of cost effectiveness as well as clinical effectiveness. The Inquiry will also recall that NICE can only start a TA when the topic is referred to it by DHSC.)

27. Treatments such as Evusheld will always present a dilemma: at the time when they may be at the peak of whatever their clinical efficacy will be, there will be little robust trial data to support use. At the time that trial data has been generated, their efficacy is likely to be in decline. However, it cannot simply be assumed in any evidence based decision-making process that a treatment such as Evusheld will have clinically significant benefits in vivo, simply because it has a plausible mechanism of action.

28. Helen Knight concludes at paragraph 136 of her statement:

> *"NICE considers that, with the benefit of hindsight, the UK public health and regulatory system could have looked more intensively at whether or not Evusheld was effective against SARS-CoV-2 variants. This in itself would have been challenging however as the virus was constantly mutating and would require intensive tracking. Inevitably, there would always be a delay before any therapeutic was licensed and administered as a treatment and by that point, variants would likely have progressed and the therapeutic may no longer be as effective. This would cause a substantial concern and uncertainty for those patients who had received the therapeutic, which was given every 6 months, and believed they were protected from the virus, when in fact that may not be the case if the therapeutic was now less effective."*

Lessons learned

29. Helen Knight summarises the lessons learned from RAPID C-19 at paragraphs 165-182 of her witness statement and exhibits the RAPID C-19 lessons learned review.

30. Helen Knight highlights the success in horizon scanning and prioritisation, the need for flexibility and collaborative working between agencies, and the experience gained in deviation from standard processes where speed or a reduced evidence base requires it. The initiative demonstrated flexibility and a capacity to evolve. External communications were highlighted as an area for improvement, particularly around ineffective treatments.

31. Broadly, Helen Knight thinks that a similar (and similarly successful) initiative could be quickly established in future pandemics, (subject to funding and the participation of other agencies), but the challenge of extrapolating in vitro or trial data into in vivo in practice decisions for any therapeutic whose effectiveness will vary or decline over time remains. There is also a judgement to make (albeit not by NICE) as to when to switch from a "pandemic" approach to making recommendations on the availability of medicines back to a "business as usual" approach (and specifically in the case of NICE, when it should be directed to return to appraising medicines with its normal processes and methods, which include consideration of cost effectiveness).

Conclusion

32. NICE welcomes the opportunity to provide evidence and explanation to the Inquiry. It recognises the ongoing importance of identifying prophylaxis treatments for those who to date have not benefited from the COVID-19 vaccines. It also welcomes the Inquiry's scrutiny and any recommendations, suggestions or criticisms the Inquiry may have. NICE has a long-standing commitment to transparency and accountability and approaches its engagement with the Inquiry in that spirit.