UK COVID-19 PUBLIC INQUIRY

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

INTRODUCTION

1. NICE begins these submissions by again 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 particularly notes that not everyone was able to benefit equally from every treatment or vaccine developed. It is right to explore the reasons for that and identify whether there are any lessons to be learnt.

2. NICE would like to thank the Inquiry, the Core Participants and all who gave evidence in module 4 for the care and attention that they have devoted to the issues raised in that module.

PRELIMINARY REMARKS

3. As the Inquiry has heard, NICE's role, as relevant to this module, during the pandemic was predominantly focused on COVID-19 therapeutics. It cannot assist the Inquiry in relation to the development of vaccines. In particular, NICE's role was hosting and participating in Research to Access Pathway for Investigational Drugs in COVID-19 ["RAPID C-19"]. These submissions will similarly largely focus on RAPID C-19.

The Success of RAPID C-19

4. It seems to be generally accepted that the discovery of new therapeutics and new uses for existing therapeutics was a success and many lives were saved as a result. Counsel to the Inquiry noted in his opening remarks:

the view of the therapeutic expert instructed by the Inquiry, Professor White, who is a professor of tropical medicine at the University of Oxford and at Mahidol University in Bangkok, is that, in general terms, the speed of the clinical research response therapeutically in the United Kingdom in 2020 was at admirable. Transcript 14/1/2025 page 28 line 10

and

But again, like the vaccine programme, the evidence overwhelmingly suggests that the therapeutic programme was a success. Transcript 14/1/2025 page 37 line 15

5. RAPID C-19 contributed to the mobilisation of system partners to work collaboratively in an unprecedented way to bring effective treatments for COVID-19 to patients as quickly as possible. It monitored and translated emerging global research into usable evidence-based information to inform decisions on emergency access to COVID-19 therapeutics in the NHS. The witness statement of Helen Knight [INQ000474611] sets out an overview of RAPID C-19 activities beginning at paragraph 33. They were:

- 92 Oversight Group meetings held.
- 89 topics reviewed.
- >24,000 papers screened.
- >100 trial investigators contacted (see exhibit HK4-13 [INQ000316253] to the witness statement of Helen Knight).
- 551 completed actions

- 10 treatments had access (in the case of dexamethasone, due to the work of Rapid C-19 access was granted on the same day that trial results were published)
- <10 days from key trial readout to patient access (for repurposed therapeutics) (This timescale may be contrasted with a typical NICE single technology appraisal which would take on average 45-50 weeks, evidence of Helen Knight transcript 30/1/25, page 42 line 25)
- 20 reports to the Chief Medical Officer ["CMO"]
- Over 200,000 patients treated (by the end of October 2022). This number will include some of the most severely ill patients, for example dexamethasone is used in patients requiring ventilation or oxygen therapy and was rightly described as "lifesaving" by Counsel to the Inquiry (transcript 20 January 2025 page 42 line 21)

6. NICE respectfully disagrees with Professor White's possible characterisation of RAPID C-19 as "passive" (White report [INQ000474743] paragraph 6.16). That characterisation may stem from a misunderstanding that RAPID C-19 was a body that could commission its own research. RAPID C-19 was in fact highly active. It worked at pace, meeting on a weekly basis in the evening (with additional meetings as necessary). It actively sought out early access to emerging global information on new therapeutics or new uses of existing therapeutics and swiftly converted that information into a briefing and advice for the CMO. The scale of this exercise should not be underestimated. For example, by April 2021 there were 3,886 trials investigating 866 therapeutics, and by the end of June 2022, there were 5,980 trials investigating 1,194 therapeutics. That RAPID C-19 enabled access to dexamethasone on the same day that trial results were published was noted above, and Helen Knight's witness statement [INQ000474611] at tables 5 and 6 sets out comparably rapid access to a range of important therapeutics.

7. NICE does not wish to comment on whether the "right" research was commissioned or undertaken by others during the pandemic, precisely because the commissioning and funding of research is not within its remit, but it makes the following points:

    i. Given the general success noted above it would be difficult to be substantially critical either of research efforts or of the process for bringing therapeutics into use overall.

    ii. The medical research environment is highly complex. Trials are often international and require the co-operation of companies, regulators and clinicians.

    iii. Independently of whether there could or should have been greater central direction of trials by a UK[1] body, (and NICE observes that during business as usual at least, it is for the manufacturers of therapeutics to conduct the trials that will show their product's efficacy in a new area) there will always be a need for a function like RAPID C-19 in a pandemic, to manage the process of turning raw trial data into usable advice for decision makers.

    iv. It is important that the RAPID C-19 process is visible to research funders, (achieved in this case by National Institute of Health and Care Research ["NIHR"] membership of RAPID C-19) and Helen Knight describes at paragraphs 81-84 of her witness statement [INQ000474611] some of the interactions between RAPID C-19 and trial investigators. However, it may be questioned whether a process like RAPID C-19 should be involved in commissioning trials[2], for reasons of possible

[1] As to which Helen Knight says at paragraph 103 of her witness statement that the national co-ordinated approach that was shown in the UK was important

[2] As opposed to advising on trials, which NICE did, Helen Knight witness statement paragraph 27

perceived conflict, delay, and loss of focus. The key research need in RAPID C-19 was to identify a potentially clinically relevant evidential gap and report on it, which was done.

The differences between RAPID C-19 and Business as Usual

8. Part of NICE's core expertise is to identify, synthesize and analyse evidence relating to the use of therapeutics. Outside of a pandemic, this takes the form of an evaluation of the evidence of clinical and cost effectiveness for what is usually a new therapeutic, or a new use of an existing therapeutic. That evaluation culminates in a recommendation to use the therapeutic which is directly binding on NHS commissioners, (or a decision not to recommend the therapeutic[3]). NICE is itself directly accountable both for the evaluation of evidence and for the decision based on that evaluation, and NICE's decision will (usually) have a direct effect on the purchase and use of the therapeutic in England.

9. During the pandemic, a different approach in relation to COVID-19 therapeutics was applied. The differences included:

    i. RAPID C-19 was an emergency multi-agency initiative. That is significant because it brought to the table a wider range of perspectives and expertise than would be needed in a "normal" NICE process, with the Medicines and Healthcare Products Regulatory Authority ["MHRA"] having particular skills in therapeutic safety and pharmacovigilance, the NIHR having expertise in commissioning research, and NHS England having experience of commissioning healthcare.

    ii. RAPID C-19 surveyed, filtered, evaluated, and reported on the currently available evidence base for a particular use of an

[3] In this context NICE does not issue recommendations not to use, it declines to recommend use. The NHS may still use a medicine that has not been recommended, at its discretion.

identified therapeutic, including advice on whether that evidence base was likely to develop. But it did not have a role in deciding whether in light of that evidence a particular therapeutic should be used. Still less did it issue binding decisions that would require the purchase and use of a therapeutic. RAPID C-19 was a process that informed decision making but was not a decision maker.

iii. Cost effectiveness played no part in any discussion at RAPID C-19, or the advice sent to the CMO.

10. In one important respect RAPID C-19 did resemble a normal NICE process; in that it was entirely evidence driven. RAPID C-19's role was to ensure that whatever decisions were taken on the use of a therapeutic were taken in light of the available evidence on that therapeutic.

11. It might also be helpful to highlight what RAPID C-19 did not do and with respect, to correct some factual evidential inaccuracies. RAPID C-19 did not take decisions on what therapeutics to investigate or procure or make available. With respect, some of the evidence to the Inquiry has been inaccurate on these points. In particular this exchange on 17 January is factually incorrect:

Q. ...[RAPID C19] took, to a very large extent, the decision as to what particular therapeutics would be not just investigated and pursued, but ultimately made available?

A. That's correct. I said that most of the system did exactly as it did before the pandemic. NICE assesses drugs and makes a cost effectiveness judgement and asks the NHS to make them available. That was -- there was a different system so that was done faster in the pandemic, and that is chaired by NICE. RAPID C-19 did a very similar job to what NICE would have done, or does do, in the non-emergency time, and recommend

which therapeutics should be made available to the NHS. Transcript 17/1/25 Page 78 line 20 evidence of Clara Swinson, emphasis added

12. Similarly, Sir Sajid Javid was in error in saying that RAPID C-19 held trials of Evusheld (transcript 23/1/25 page 51 line 20). To repeat, RAPID C-19 only evaluated the evidence for clinical benefit of treatments generated by trials conducted by others, and it only provided advice relating to that issue[4] to decision makers. That does not amount to recommending which therapeutics should be made available.

13. Similarly, neither NICE nor RAPID C-19 fund research[5]. There are a range of bodies funding research in the UK, but NICE is not one of them. Should the Inquiry consider recommending further research, either now or in the context of a future pandemic, that recommendation should not be directed at NICE, which has neither the powers, the funding nor the experience to commission or manage research and in any event, it would be outside of the parameters in which NICE discharges its responsibilities, as set out in the Framework Agreement [INQ000252456].

Evusheld for pre-exposure prophylaxis

14. NICE cannot comment on any decisions made in relation to Evusheld outside of the RAPID C-19 process, including decisions on advance purchase or whether, given the nature of neutralising monoclonal antibodies ["Nmabs"], they are better assessed in a vaccine-like process (although it will point out that at present they are regulated as therapeutics and not as vaccines, and Professor Whitty's evidence was that the two are "fundamentally different"). Transcript 20/1/25, page 113 line 13

[4] And at the risk of repetition, not cost effectiveness

[5] Specifically NICE does not fund the 14 Health Protection Units, as suggested by UKHSA in their oral opening submissions. They are funded by the NIHR

15. The difficulty with advising on the use of Evusheld when the question came before RAPID C-19 is not in dispute: to what degree did the evidence of promising clinical benefit seen in the PROVENT trial during 2021 equate to evidence of likely clinical benefit during 2022 against new and emerging virus variants not present during the trial period? As Professor Whitty told the Inquiry:

there is a high -- there is a reasonable chance that by the time that we actually have this drug available we have clinical data, we know what the safety, is, and it's got licensing, that either it'll prove not to be as encouraging as we currently think, because it's going to be quite a long way in the future, or that the virus will have evolved to such an extent that this is no longer an effective treatment. Transcript 20/1/25 page 112 line 15

16. There seem to be two possible criticisms of RAPID C-19. The first is that RAPID C-19's analysis of the available evidence for Evusheld might have been incomplete. Professor White commented:

"Why pharmacometric testing was not encouraged or commissioned is not clear to me. Perhaps the group was not aware this could be done? I do not think the resistance risk was substantial. Overall, this was a cautious judgement that would have been strengthened substantially by pharmacometric evaluation" (Professor White report [INQ000474743] paragraph 6.11)

17. The second would be that the system-wide response to RAPID C-19's reports to the CMO were too cautious.

18. "Pharmacometric" means mathematically modelling an interaction between a drug and a patient. RAPID C-19 members acknowledged they were not experts in assessing non-clinical or in vitro data and sourced this expertise from the Prophylaxis Oversight Group. Much non-clinical/in

vitro data in relation to Evusheld was certainly provided and discussed by RAPID C-19. In May 2022, RAPID C-19 noted that further understanding was needed on how non-clinical trial data could be used to support decision making on clinical effectiveness for Nmabs with the evolving nature of the SARS-CoV-2 virus. Non-clinical trial data includes pharmacokinetic and pharmacodynamic data, although these terms were not explicitly stated by RAPID-C19 in a CMO report until August 2022. RAPID C-19 stated it would contribute as needed to system-wide work to consider what evidence is required to be confident that Nmabs work against emerging variants. None of the expert advice given to RAPID C-19 suggested that pharmacometric mathematical modelling would have solved this issue.

19. RAPID C-19 gave significant consideration to the data relating to Evusheld, as it was aware of the vulnerable people that either could not have or did not benefit from the vaccines. RAPID C-19 considered Evusheld for pre-exposure prophylactic use 10 times between February 2021 and August 2022 and submitted three reports to the CMO. The issue is clear. Evusheld showed promise against variants circulating during the PROVENT trial. But what was not known was to what extent Evusheld would effectively neutralise the virus and therefore protect vulnerable people in a clinical setting with changing variants. It was known to interact less promisingly with later variants in laboratory tests. In these tests it evidenced limited neutralising activity against omicron. NICE agrees that the science behind extrapolating from laboratory neutralisation data to possible clinical benefit in the case of Nmabs that have been shown to be clinically effective against earlier variants of a pathogen is challenging, and that it would be helpful to establish a clear and robust framework on this issue in the future. It would also require system partners to actively monitor the changing virus and provide the necessary information to inform the framework in a timely manner. Further scientific research would be helpful (generally for all Nmabs),

but whether any of it could have been available in time to inform a decision on Evusheld is doubtful.

20. In the absence of more knowledge or better tools in this area, it is difficult to see what different advice RAPID C-19 could have given. It is objectively correct that the protective effect of Evusheld against the variants circulating at the time the treatment could have been given was unknown, but, given its mechanism of action, likely to be less than that demonstrated in the PROVENT trial. That uncertainty becomes all the greater when it is considered that the treatment was expected to have a protective effect for 5-6 months after administration, and the variants that might be circulating at that time were unknown and unknowable, thereby putting vulnerable patients at potentially greater risk.

21. As to the second criticism, it is not for NICE to comment on the use made of RAPID C-19's work. RAPID C-19 itself was very mindful of the need for measures to protect those who could not directly benefit from vaccination.

LESSONS LEARNT

22. RAPID C-19 was a successful multi agency initiative. Its key to success was the expertise and commitment to collaborative work among the key partners.

23. Key enablers of the initiative were:

    i. The shared vision and perception of a common purpose, resulting in full commitment and engagement and a willingness to truly collaborate, which helped to ensure effective communication.

    ii. A consistent approach and unified delivery of agreed actions.

iii. The environment in which the RAPID C-19 Oversight Group conducted its business; it was a safe space for open dialogue, with all members being highly supportive and respectful as well as professional, focussed and responsive, which helped with the adaptive and flexible approach needed as the pandemic evolved.

iv. Early access to emerging information, a strong collaborative relationship with trial investigators (in particular the platform trials), open information sharing among members and companies, particularly around sensitive information, and strong independence enabled effective evidence based decision making.

v. The willingness and ability to bring in external expertise when required, for example the Prophylaxis Oversight Group.

24. NICE believes that any future pandemic is likely to bring about a similar surge in research as was seen during the COVID-19 pandemic. There is likely to be a need for a mechanism to translate the outputs of that research into actionable advice for the NHS at speed. NICE considers that the ability to stand up a function similar to RAPID C-19 at speed, very probably consisting of the same organisations, should be a part of future pandemic planning.

25. As noted in Helen Knight's evidence, there is a need for better understanding around pre-exposure prophylactic use of monoclonal antibodies and in particular how laboratory data translates into clinical outcomes. This fundamental research should be carried out well in advance of any future pandemic.

CONCLUSION

26. NICE would like to end these submissions by once again expressing its sympathies to those bereaved by COVID-19, to those still suffering from its effects and to their relatives and friends. It would like to pay tribute to the hard work and bravery of all that contributed to a successful vaccine and therapeutic programme. In particular, to all those that contributed to RAPID C-19. And finally, NICE would like to thank the Inquiry for its careful attention to its important work. NICE will welcome the recommendations of the Inquiry and looks forward to playing its part in implementing them.