Neutral Citation Number: [2020] EWCA Civ 1037

Case No: C1/2020/0677

IN THE COURT OF APPEAL (CIVIL DIVISION)
ON APPEAL FROM THE HIGH COURT OF JUSTICE
QUEEN'S BENCH DIVISION
ADMINISTRATIVE COURT
Mr Justice Cavanagh
[2020] EWHC 435 (Admin)

Royal Courts of Justice
Strand, London, WC2A 2LL

Date: 06/08/2020

Before:
LORD JUSTICE BEAN
LORD JUSTICE MALES
and
LORD JUSTICE PHILLIPS

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Between:

THE QUEEN ON THE APPLICATION OF CAIT COTTER (a child, by her mother and litigation friend, NATASHA COTTER)	**Appellant**
- and -	
THE NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE ("NICE")	**Respondent**
- and -	
THE SECRETARY OF STATE FOR HEALTH AND SOCIAL CARE	**Interested Party**

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Ian Wise QC & Michael Armitage (instructed by **Hodge, Jones and Allen Solicitors Ltd**) for the **Appellant**
Daniel Stilitz QC and Michael White (instructed by **DAC Beachcroft LLP**) for the **Respondent**
Julia Smyth (instructed by **Government Legal Department**) for the **Interested Party**

Hearing date: 22nd July 2020

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Approved Judgment

Covid-19 Protocol: This judgment was handed down remotely by circulation to the parties' representatives by email, release to BAILII and publication on the Courts and Tribunals Judiciary website. The date and time for hand-down is deemed to be on Thursday 6th August 2020 at 10.30 a.m.

Lord Justice Males:

Introduction

1. The defendant ("NICE") is responsible for deciding whether to recommend "health technologies", including drugs, for NHS use in England, and NHS bodies are obliged to fund treatments which it has recommended. In July 2018 NICE was asked by the Secretary of State for Health & Social Care to appraise a drug known as Kuvan and to make a recommendation whether it should be provided by the NHS. Kuvan is used to treat PKU, a rare metabolic condition which inhibits the body's ability to metabolise protein. Left untreated, and unless controlled by an extremely exacting diet, it causes irreversible brain damage.

2. In order to carry out an appraisal, NICE had to decide which of two procedures should be used. One of these is its standard procedure, the Health Technology Appraisal or "HTA" procedure. The other is its Highly Specialised Technology or "HST" procedure. This is reserved for highly specialised technologies which meet seven criteria set out in a document entitled "Interim Process and Methods of the Highly Specialised Technologies Programme" issued by NICE in April 2017 ("the 2017 Guidance").

3. By a decision recorded in a Topic Selection Outcome Report ("the TSOR") dated 30th April 2019, NICE determined that Kuvan did not satisfy three of the seven criteria for use of the HST procedure and, accordingly, that the standard HTA procedure should be used for its evaluation. It is that decision which is challenged in these proceedings. The claimant, an 11-year-old girl who suffers from PKU, does not challenge the lawfulness of the criteria which NICE has set for the use of the HST procedure. Rather, her case is that, on the facts, all of those criteria were satisfied in the case of Kuvan and, accordingly, that the decision to use the HTA procedure for its evaluation was unlawful.

4. Cavanagh J dismissed the claimant's claim for judicial review and the claimant now appeals with the permission of Carr LJ.

5. It follows that this case is not about whether Kuvan should be recommended for use on the NHS. No decision has yet been made, either that it should be or that it should not. The case is solely concerned with the procedure by which Kuvan should be appraised so that a decision one way or the other can be made. Moreover, it is not possible to say at this stage, either that Kuvan will be recommended if it is appraised under the HST process, or that it will not be if it is appraised under the HTA process.

6. Nevertheless it is reasonable to proceed on the basis that appraisal under the HST process would significantly enhance the prospect of a favourable recommendation. That is essentially for financial reasons. Because a positive recommendation for any treatment will have consequences for the NHS's budget, NICE needs to have some way of measuring the value for money of the treatments it is required to appraise, so as to ensure that the treatment in question represents an effective use of finite NHS resources and that there is a "level playing field" for the appraisal of widely differing treatments, all of which are of major importance to those whose lives may be transformed if the treatment is made available on the NHS.

7. For this purpose NICE makes use of two concepts, the "Quality Adjusted Life Year" ("QALY") and the "Incremental Cost Effectiveness Ratio" ("ICER"). A QALY is a

measure of the health benefits provided by a treatment in which a patient's expected increase in length of life is adjusted to reflect their expected quality of life. One QALY is equal to one extra year of life in perfect health. The ICER is a measure of the cost effectiveness of a health technology which is expressed as the cost of each QALY gained. There is no challenge to the use of these concepts or the way in which NICE uses them.

8. Under the standard HTA procedure, NICE will not generally recommend a health technology for use in the NHS if it will cost more than £30,000 for each QALY gained. Under the HST procedure, however, NICE will recommend a drug with an ICER of up to £100,000 per QALY gained. (A higher figure also applies to end of life treatments, but these are not relevant here). Thus, so far as cost effectiveness is concerned, the test for a favourable recommendation is considerably easier to satisfy under the HST procedure: a drug must be more cost-effective to be recommended under the HTA procedure than it need be under the HST procedure.

9. As the 2017 Guidance explains, this is a deliberate departure from the principle of a "level playing field" for the evaluation of all treatments. It is considered to be necessary because a simple utilitarian approach in which the greatest gain for the greatest number of patients was decisive would mean that expensive treatments which would benefit only a very small number of patients suffering from very rare conditions would be unlikely to be approved.

10. In practice the supplier of a drug with a high list price will often be prepared to negotiate a discount, sometimes a very substantial discount, from the list price in order to obtain a positive NICE recommendation. That is because the NHS is itself a major customer and also because a NICE recommendation carries weight in other markets. But, as is apparent from the scheme described above, a greater discount will be necessary to obtain NICE approval for a drug appraised under the HTA procedure than will be the case if the HST procedure is adopted. What level of discount the supplier of Kuvan may be prepared to offer is as yet unknown, but may be decisive in determining whether it will be recommended. It will be a matter for confidential commercial negotiations in due course.

11. Accordingly, while Mr Daniel Stilitz QC for NICE was right to describe the decision whether Kuvan should be appraised under the HTA or HST procedure as a "routeing decision", that decision is of considerable and potentially critical importance to the claimant and other sufferers from PKU. While NICE has a duty to ensure value for money in the treatments which it recommends, so that health care resources are used to deliver the greatest overall health benefit to NHS patients, it is obvious that any decision on financial grounds not to recommend (or which makes it less likely that NICE will recommend) a drug with life changing benefits will cause intense disappointment and frustration to sufferers from the condition in question and their families.

Factual background

12. The circumstances in which the issue arises are set out in detail in the judgment of Cavanagh J. For the purpose of this appeal, the following summary will suffice.

13. PKU (an abbreviation of phenylketonuria) is a rare metabolic condition which inhibits the body's ability to metabolise protein. Left untreated, it causes brain damage leading

to profound and irreversible intellectual disability, delayed speech, seizures and behavioural abnormalities. It can, in theory at any rate, be treated by sticking rigorously to an extremely limited low-protein, effectively synthetic, diet. Sufferers from PKU cannot eat 80% of all normal food and are limited to foods such as corn starch, tapioca starch and gums. That means eating unappetising meals which are difficult and time-consuming to prepare. They must in addition take protein substitutes three or four times a day, which have a poor smell and taste. This combination of a very low protein diet together with the administration of protein substitutes makes adherence to the diet extremely arduous for sufferers and, in the case of children, for their carers. Most adults with PKU do not succeed in adhering to the diet and suffer the resulting consequences. Long term outcomes are poor.

14. Kuvan, the brand name of a drug called sapropterin dihydrochloride, can be used to treat PKU. It is a synthetic form of tetrahydrobiopterin ("BH4"), which is naturally absent in sufferers from PKU. Not all individuals with PKU are responsive to Kuvan, but it is highly beneficial for those who are. It minimises (but does not eliminate completely) the need for the extreme dietary regime, reduces the risk of brain damage and enables them to live a more normal life.

15. The claimant has undertaken a trial of Kuvan and has been found to be responsive to it. But because it is expensive, it is unlikely to be available to her unless it is recommended by NICE for use on the NHS.

16. Kuvan is used in about 50 countries but is not currently available on the NHS in England. For many years it was provided in England, at a low cost, on a named-patient/compassionate basis, by Schircks Laboratories. In 1999, after it was found that a larger group of PKU patients responded to the drug than was previously thought, the rights to manufacture Kuvan in the UK were bought by a pharmaceutical company, BioMarin.

17. In July 2018 NICE was asked by the Secretary of State for Health & Social Care to appraise Kuvan and make a recommendation whether it should be provided by the NHS. In order to do so, NICE had to decide whether to use the HTA or HST procedure. As already indicated, NICE decided that Kuvan did not satisfy three of the seven criteria for use of the HST procedure and, accordingly that the HTA procedure should be used. Its decision and reasoning are set out in the TSOR dated 30th April 2019.

18. Following this decision the supplier, BioMarin, withdrew Kuvan from the appraisal process. As the participation of the supplier is essential, this meant that the appraisal could not proceed. We were told, however, that since the decision of the judge dismissing the claim for judicial review of the decision to use the HTA procedure, BioMarin has re-engaged with the procedure. There is a dispute between the parties, which we need not resolve, as to the likelihood of a favourable recommendation being made if the HTA procedure continues to be used. As I have explained, this is likely to depend to a considerable extent on whether BioMarin is prepared to discount its list price for Kuvan to an extent sufficient to achieve an ICER of no more than £30,000 per QALY gained from use of the drug. The claimant's witnesses say that this is, at best, highly unlikely, while NICE says that it would not devote resources to an appraisal unless it believed that there was a realistic prospect of a successful commercial negotiation with the supplier. Evidently, however, a lesser discount would be required if the HST procedure were to be used.

Legislative background

The Health and Social Care Act 2012

19. NICE was established by section 232 of the Health and Social Care Act 2012. Its general duties are set out in section 233:

> "(1) In exercising its functions NICE must have regard to—
>
> (a) the broad balance between the benefits and costs of the provision of health services or of social care in England,
>
> (b) the degree of need of persons for health services or social care in England, and
>
> (c) the desirability of promoting innovation in the provision of health services or of social care in England.
>
> (2) NICE must exercise its functions effectively, efficiently and economically."

20. Section 237(1) of the 2012 Act permits regulations to be made conferring functions on NICE "in relation to the … making of recommendations about any matter concerning or connected with the provision of … NHS services".

The 2013 Regulations

21. Regulations relating to the evaluation of health technologies, made under section 237(1), are set out in the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 (SI 2013 No. 259) ("the 2013 Regulations").

22. Regulation 5 of the 2013 Regulations provides (among other things) that:

> "(1) NICE has the function of giving advice or guidance, providing information or making recommendations about any matter concerning or connected with the provision of – (a) NHS services …
>
> (4) NICE must establish procedures for the giving of advice or guidance, the provision of information or the making of recommendations as NICE considers appropriate."

23. There are two kinds of recommendation which may be made.

24. Regulation 7 is concerned with "technology appraisal recommendations":

> "(1) NICE may make a technology appraisal recommendation –
>
> (a) in relation to a health technology identified in a direction given by the Secretary of State;

> (b) that recommends that relevant health bodies provide funding within a specified period to ensure that the health technology be made available for the purposes of treatment of patients. …
>
> (6) A relevant health body must comply with a technology appraisal recommendation. …
>
> (9) NICE must establish a procedure for the appraisal of health technologies, and must consult such persons as it considers appropriate in establishing the procedure.
>
> (10) The procedure must include arrangements – for NICE to consult such persons with an interest in the appraisal of a health technology that is the subject of a direction referred to in paragraph (1)(a) as it considers appropriate."

25. Regulation 8 is concerned with "highly specialised technology recommendations":

> "(1) NICE may make a highly specialised technology appraisal recommendation –
>
> (a) in relation to a highly specialised health technology identified in a direction given by the Secretary of State;
>
> (b) that recommends that the Board, in the exercise of the Board's function to arrange for the provision as part of the health service of services specified in regulations made under section 3B of the 2006 Act, provide funding within a specified period to ensure that the highly specialised health technology be made available for the purposes of treatment of patients. …
>
> (6) The Board must comply with a highly specialised technology recommendation. …
>
> (8) NICE must establish a procedure for the appraisal of highly specialised health technologies, and must consult such persons as it considers appropriate in establishing the procedure.
>
> (9) The procedure must include arrangements –
>
> (a) for NICE to consult such persons with an interest in the appraisal of a highly specialised health technology that is the subject of a direction referred to in paragraph (1)(a) as it considers appropriate; and
>
> (b) for the Board to be consulted as such a person."

26. As can be seen, a recommendation under Regulation 7 is directed to "relevant health bodies", an expression which is defined (in summary) to refer to (a) "the Board", that is to say the National Health Service Commissioning Board, (b) clinical commissioning groups and (c) local authorities (in the case of recommendations applicable to public

health services arranged by local authorities). In contrast, a recommendation under Regulation 8 is directed only to the Board. Consistently with this, when a technology is being appraised under Regulation 8, there is an express obligation to consult the Board which does not apply under Regulation 7 (although the Board may be consulted in such a case if NICE considers that appropriate).

27. The meaning of the terms used in the 2013 Regulations is explained in Regulation 2. "Health technology" is widely defined and includes a drug such as Kuvan. "Highly specialised health technology" and "highly specialised technology recommendation" are defined as follows:

> " … 'highly specialised health technology' means a health technology intended for use in the provision of services for rare and very rare conditions provided for in regulations under section 3B(1)(d) of the 2006 Act.
>
> 'highly specialised technology recommendation' means a recommendation made by NICE following an appraisal of the benefits and costs of a highly specialised health technology conducted by NICE in accordance with NICE's published methods and processes for appraisal of highly specialised health technologies that results in a positive assessment; …"

28. While "highly specialised health technologies" are a subset of the wider category of "health technologies", the two kinds of recommendation are mutually exclusive, as the definition of "technology appraisal recommendation" explains. This:

> "means a recommendation made by NICE following an appraisal of the benefits and costs of a health technology conducted by NICE in accordance with NICE's published methods and processes for appraisal of health technologies that results in a positive assessment (but does not include a highly specialised technology recommendation); …"

The 2012 Regulations

29. As appears from these definitions, in order to ascertain whether a health technology falls within the definition of "highly specialised health technology" it is necessary to refer to regulations made under section 3B(1)(d) of the National Health Service Act 2006 Act. These are the National Health Service Commissioning Board and Clinical Commissioning Groups (Responsibilities and Standing Rules) Regulations 2012 (SI 2012 No. 2996) ("the 2012 Regulations"), made under (among other provisions) section 3B(1) of the 2006 Act. Regulation 11, headed "Specified services for rare and very rare conditions", provides as follows:

> "The Board must arrange, such extent as it considers necessary to meet all reasonable requirements, for the provision as part of the health service of the services specified in Schedule 4."

30. Schedule 4 to the 2012 Regulations contains a list, under the heading "Services for rare and very rare conditions", of over 140 conditions. These are the services referred to in

the definition of "highly specialised health technology" in Regulation 2 of the 2013 Regulations. The list includes (at paragraph 63) "highly specialist metabolic disorder services" which, as is common ground, includes a service for the treatment of PKU. Some of the services in the list, of which paragraph 63 is an example, are expressly described as "highly specialist", while others are not. It is a puzzling feature of the list that, while some of the services listed are indeed services for rare or very rare conditions, many of them (despite the headings of Regulation 11 and Schedule 4) plainly are not.

31. Nevertheless, it is clear and is not disputed that, reading the 2012 and 2013 Regulations together, Kuvan falls within the definition of a "highly specialised health technology" in the 2013 Regulations.

The 2017 Guidance

32. Pursuant to regulation 8(8) of the 2013 Regulations, NICE issued a document in April 2017 setting out the procedure which it would adopt for the appraisal of highly specialised technologies. This was the 2017 Guidance. In addition the document set out the criteria which NICE would apply in order to decide whether a technology should be appraised under the HST procedure. Paragraph 28 set out seven criteria, all of which had to be satisfied for a technology to be appraised under the HST process (bold in original, numbering added in substitution for bullet points in the original):

> "Topics evaluated through the HST programme will be formally referred to NICE by Ministers. HSTs are selected using the following criteria, **all** of which have to apply:
>
> (1) The target patient group for the technology in its licensed indication is so small that treatment will usually be concentrated in very few centres in the NHS;
>
> (2) The target patient group is distinct for clinical reasons;
>
> (3) The condition is chronic and severely disabling;
>
> (4) The technology is expected to be used exclusively in the context of a highly specialised service;
>
> (5) The technology is likely to have a very high acquisition cost;
>
> (6) The technology has the potential for life long use;
>
> (7) The need for national commissioning of the technology is significant."

33. As already noted, there is no challenge to the lawfulness of these criteria. This is an important point. It means (as Mr Ian Wise QC for the claimant accepted) that not every health technology falling within the definition of a "highly specialised health technology" in the 2013 Regulations has to be appraised using the HST procedure, but only those highly specialised health technologies which also satisfy all of the seven criteria. Mr Wise was right to point out that there is no distinct requirement of

exceptionality in these criteria, but the nature of the criteria is such that it is only in exceptional cases that they will all be satisfied.

34. This was non-statutory guidance, but it is common ground that NICE is obliged to apply these criteria in deciding whether to use the HST procedure to appraise a health technology and that a failure to do so can be challenged on public law grounds by judicial review.

The TSOR

35. The NICE decision-making group accepted that criteria 3, 5, 6 and 7 were satisfied: (3) despite the availability of a very strict diet, PKU is chronic and severely disabling; (5) Kuvan is likely to have a very high acquisition cost; (6) it has the potential for lifelong use; and (7) the need for some form of national commissioning would be significant. However, criteria 1, 2 and 4 were not satisfied.

36. In relation to criterion 1 (target group so small that treatment will usually be concentrated in very few centres), the group noted that the marketing authorisation for Kuvan (i.e. the "licensed indication") was limited to patients "who have been shown to be responsive to such treatment" and that NHS England's commissioning policy of December 2018 had "identified the potentially eligible population for sapropterin [i.e. Kuvan] as approximately 500 individuals, with 300-330 patients to access treatment over time" and an estimated additional 28 patients per year who were expected to require treatment. Having made these observations, the group decided to postpone consideration of criterion 1 until it had considered criterion 4.

37. In relation to criterion 2 (target group distinct for clinical reasons), the group determined that this was not satisfied because, in order to identify patients who are responsive to Kuvan, it is first necessary to undertake a short trial using Kuvan:

> "To be clinically distinct the total population should be an entire population in its own right and not a subset of a larger group of patients. In the case of this population patients eligible for sapropterin are a subset of patients with PKU and only distinct from the wider PKU population because they can be identified by either a short trial using sapropterin, or through gene mutation analysis."

38. In relation to criterion 4 (expected to be used exclusively in the context of a highly specialised service), the group drew a distinction between "specialist" and "specialised" services:

> "The group was reminded of the fact that 'specialist' refers to the level of expertise delivered within a service (with 'highly specialist' meaning a very high level of expertise). And that the terms 'specialised' and 'highly specialised' referred to the commissioning models used by NHS England to commission and deliver specialised and highly specialised services respectively. Highly specialised commissioned services require national coordination for a distinct group of patients where it was agreed when the service was commissioned that national

> coordination would result in significantly improved outcomes that would be delivered in a more efficient set up. The group held it was this second use of the term that was the term used in the criterion: treatment must be used in a service that is commissioned as a highly specialised service model."

39. Understood in this way, criterion 4 was not satisfied. PKU is currently treated in 10 specialist metabolic services centres which were not commissioned as highly specialised services and this is not expected to change in the event that Kuvan is recommended.

40. Having reached this conclusion in relation to criterion 4, the group returned to criterion 1, concluding that it was not satisfied "because treatment of the target patient group is not expected to be concentrated in very few centres in the NHS".

The judgment

41. In a thorough and comprehensive judgment the judge considered first the approach to be adopted to the interpretation of a policy document such as the 2017 Guidance. Citing the well-known passage from Lord Reed's judgment in *Tesco Stores Ltd v Dundee City Council* [2012] UKSC 13, [2012] PTSR 983 at [18] and [19], he held that the meaning of the document was for determination by the court, interpreting the document objectively in accordance with the language used, and bearing in mind that a policy document is not to be read as if it were a statute or a contract. In this regard the judge noted that the primary readership for which the document was designed consisted of the expert decision-making group together with medical professionals and persons engaged in the pharmaceutical industry.

42. In contrast, the application of the guidance to particular facts was a matter for the judgment of NICE, and was susceptible to challenge only on irrationality grounds.

43. The judge turned next to consider the appropriate level of intensity which should be applied to a review on the ground of irrationality. Here he struck a middle ground between the submissions of the parties, accepting the very significant importance of the issue to the claimant and other PKU sufferers, but acknowledging that to some extent the criteria required the exercise of expert judgment and the use of expert knowledge and that there is always a high threshold for irrationality cases. Although the judge dealt with this topic in some detail, I need say no more about it as the arguments before us focused on the meaning of the criteria rather than their application.

44. Finally, the judge dealt with each of the criteria which NICE had held not to be satisfied.

45. In relation to criterion 2 (target group distinct for clinical reasons), which the judge dealt with first, he found that the target patient group could not be defined in advance because there was no clear bright-line cut off between PKU patients who would benefit from Kuvan and those who would not, their responsiveness being ultimately a matter for the subjective decision of the treating physician after the patient had first undergone a trial with Kuvan. On that basis, NICE was correct to hold that the target group was not clinically distinct and, accordingly, that this criterion was not satisfied:

> "83. … If you do not know which members of a group of patients with a particular disease will benefit from a treatment until you test the treatment on them, they are not 'clinically distinct'. The 'clinically distinct' criterion is intended to ensure that NICE can work out, in advance, which groups of patients will benefit from the treatment. This enables NICE to carry out the cost/benefit analysis. If this is not clear, NICE cannot do so."

46. In relation to criterion 4 (expected to be used exclusively in the context of a highly specialised service), the judge held that NICE was correct to hold that treatment "in the context of a highly specialised service" was a reference to the commissioning model for the treatment in question and did not have the broader meaning advanced by the claimant, that is to say a service provided by highly specialist practitioners. There was a recognised distinction between a highly specialist service (which the treatment of PKU was) and a highly specialised service (which it was not), the latter being a term of art used within the NHS:

> "104. However, in my judgment Mr Stilitz QC is right to submit that, in this context, 'highly specialised services' … is a reference to the commissioning model. Somewhat unhelpfully, the 2017 Guidance does not itself define 'highly specialised services'. However, in my judgment the Defendant is right that this is a term of art and is used within the NHS to refer to services that are commissioned as highly specialised services. In other words, it is the way that the services are commissioned that make them highly specialised, rather than the degree of expertise of those who provide the services. Just because something is recognised in Schedule 4 of the 2012 Regulations as being highly specialist, or because it is, in the common usage of the phrase, a highly specialist service, does not mean that it is a highly specialised service for the purposes of this criterion."

47. In relation to criterion 1 (target group so small that treatment will usually be concentrated in very few centres), the judge held that the question whether the treatment would usually be concentrated in "very few" centres was a matter of judgment which was dependent on context. The context here was that 47 out of the 60 services on the NHS's published list of highly specialised services were provided at four or fewer centres, 11 others were provided at five or six centres, and neither of the remaining two services was provided at more than eight centres. In contrast, PKU was treated at 19 centres, of which nine "hubs" provided a full service with the remaining ten "spokes" relying heavily on the support and direction provided by the "hubs". While nine (or 19) might be regarded as "very few centres" when compared with the total number of over 1,000 NHS hospitals in England, that was not the relevant test:

> "129. In my judgment, NICE was entitled to interpret this criterion in the way that it did. As I said earlier in this judgment, when reviewing the authorities on the correct approach to the interpretation of non-statutory guidance, the meaning of a passage in a policy document should be interpreted objectively in accordance with the language used, subject to the important caveat that the passage must be read in its proper context. In my

> view, the relevant context, for present purposes, is that the treatment must usually be concentrated in broadly the same number of centres as highly specialised services are normally provided in. This gives some content to the words 'very few', which are otherwise almost entirely a matter of opinion. Applying this approach, 'very few' means, normally, four or fewer, though there are some highly specialist [sc. specialised] services that are provided in a slightly higher number of centres."

48. Accordingly, it was not irrational for NICE to decide that a treatment provided at nine hub centres and (partially) at a further ten spoke centres will not usually be concentrated in very few centres.

The appeal

49. For the claimant Mr Wise advanced five grounds of appeal. The first two of these relate to the judge's overall approach and the remaining three challenge (in that order) the judge's decision relating to each of criteria 2, 4 and 1. I propose to take these grounds in turn, although in a slightly different order. Mr Wise accepted that because the criteria are cumulative, he needs to win on each of grounds three to five in order for the appeal to succeed.

Ground 1 – the statutory context

50. Mr Wise submitted that in construing the criteria in the 2017 Guidance, the judge failed to have proper regard to the statutory context. In particular, he ought to have approached the meaning of the Guidance on the basis that treatments for rare or very rare conditions such as PKU should be appraised under the HST procedure unless there are very good reasons for not doing so. This was because the "highly specialised health technologies" to which Regulation 8 refers are defined in Regulation 2 by reference to the "rare and very rare conditions" listed in Schedule 4 to the 2012 Regulations. Since Kuvan is a highly specialised health technology which is aimed at treating a rare or very rare condition, the presumption should be that it should be appraised under the HST procedure. This statutory context ought to have informed the judge's approach in relation to each of the three criteria.

51. I would accept that in determining the meaning of the 2017 Guidance it is necessary to have regard to the statutory context in which that Guidance was issued. If there are two possible meanings of a provision in the Guidance, one of which fits well with (or "goes with the grain of") the statutory provisions in question while the other does not, that is a powerful reason for adopting the former meaning. But once it is conceded (as it is) that not all technologies falling within the definition of "highly specialised health technologies" have to be appraised under the HST procedure, that NICE was entitled to establish criteria to determine which health technologies should be appraised under that procedure, and that the seven criteria set out in the 2017 Guidance were lawful, I see no scope for any rebuttable presumption in interpreting the Guidance that all the health technologies intended for use in the provision of a service listed in Schedule 4 to the 2012 Regulations should be appraised under that procedure.

52. There might – perhaps – have been scope for an argument that as a result of the definition of "highly specialised health technology" in Regulation 2 of the 2013

Regulations, NICE was obliged to appraise *any* technology intended for use in the provision of any of the Schedule 4 services under the procedure to be established under Regulation 8, or in other words that use in the provision of a Schedule 4 service was the *only* lawful criterion for determining which technologies should be appraised under the HST process. No such argument was advanced, however, either in this court or to the judge. It is in any event most unlikely that this was Parliament's intention in approving the 2013 Regulations. That is because many of the services in the Schedule 4 list cannot sensibly be regarded as "highly specialist" (or "highly specialised"), or even as services for "rare or very rare conditions".

53. It is apparent that the function of Regulation 11 and Schedule 4 in the 2012 Regulations was to ensure that the NHS Board was under a duty to ensure that the listed services were provided (not necessarily to provide them itself) as part of the NHS, rather than to define them as having any particular common characteristics. The reason for having two separate processes for evaluating health technologies was different. As is apparent from a comparison of Regulations 7 and 8 of the 2013 Regulations (see [26] above), the important distinction was between technologies which the Board itself would have a duty to provide (and thus an interest in being consulted in the course of an appraisal) and those which would be provided at local level.

54. Moreover, the argument for a presumption as a matter of interpretation of the Guidance that any health technology intended for use in the provision of any of the Schedule 4 services should be appraised under the HST procedure proves too much. It is accepted that the seven criteria in fact established by NICE were lawful, but many of the conditions listed in Schedule 4 are not "chronic and severely disabling" (criterion 3), and technologies for treating them would not necessarily have "a very high acquisition cost" or "the potential for lifelong use" (criteria 5 and 6). No doubt judgment must be exercised in determining such matters as whether any particular condition is "chronic and severely disabling" or whether an acquisition cost is "very high", but these criteria themselves are unambiguous, it is accepted that they are lawful, and the presumption for which Mr Wise contends has no part to play in their interpretation. I see no reason why the position should be different in interpreting the criteria with which we are concerned.

55. It follows necessarily in my judgment that not all technologies intended for use in the provision of the Schedule 4 services (and thus falling within the definition of "highly specialised technology") fall to be appraised under the HST procedure. That is a necessary condition for evaluation under the HST procedure as a technology will not otherwise fall within the definition of "highly specialised technology", but is not a sufficient condition and does not give rise to any presumption. The meaning of each of the criteria must be determined in accordance with the natural meaning of the words used, read in the light of the relevant context. This is not a surprising conclusion. As the existence of two distinct evaluation procedures presupposes a departure from the "level playing field" approach of evaluating health technologies, it is to be expected that the circumstances in which a technology will be evaluated under the HST procedure will be narrowly confined.

Ground 2 – objective interpretation

56. Mr Wise submitted that despite recognising the principle that interpretation of the Guidance was an objective matter to be determined by the court, the judge failed to

apply that approach when he came to determine the meaning of two of the criteria, holding that NICE was entitled to interpret them in the way that it did.

57. I can deal with this submission shortly because it is clear, in my judgment, that there is nothing in it.

58. In the course of argument it became clear, and as I understood it Mr Wise accepted, that his complaint about the judge's approach to criterion 4 was based on a mis-reading of what the judge had said at [112] and that in reality this ground of appeal was concerned only with the judge's approach to criterion 1. As to this, it is true that the judge said at [129] (set out at [47] above) that "NICE was entitled to interpret this criterion in the way that it did", but he went on immediately in the same paragraph to remind himself of the cases cited earlier in his judgment to the effect that the meaning of a passage in a policy document should be interpreted objectively by the court. Reading the judge's treatment of criterion 1 as a whole, it is clear that he did not lose sight of this principle. On the contrary, it is clear that his conclusion ("Applying this approach, 'very few' means, normally, four or fewer") was his own objective interpretation of the criterion read in what he found to be its proper context. Nowhere in the TSOR does the NICE decision-making group say that this is what "very few" means in the context of criterion 1. The group said no more than that "more than 10 specialist metabolic centres" or "the currently commissioned 10 specialist metabolic centres" could not be regarded as "very few".

Ground 4 – "used exclusively in the context of a highly specialised service"

59. Mr Wise submitted that the judge was wrong to interpret the reference to a "highly specialised service" in criterion 4 as referring to a service commissioned centrally by NHS England and appearing in NHS England's Highly Specialised Services List. He submitted first that on their ordinary meaning, these words refer to the nature of the service, not the way in which it is commissioned, and that there is no basis for drawing a distinction between the meaning of "highly specialist" and "highly specialised". On this ordinary meaning, the treatment of PKU with Kuvan is highly specialised. Second, he submitted that this interpretation is consistent with the same words used in the 2013 Regulations. The 2013 Regulations refer to "highly specialised health technologies" and there is no dispute that Kuvan is such a technology. Third, he submitted that even if the words do refer to the way in which the service is commissioned, services for PKU patients *are* commissioned by NHS England and not locally by clinical commissioning groups.

60. In my judgment there would be considerable force in these submissions if the wording of the Guidance had to be considered in isolation, without regard to the context as it would be understood by its intended readership. Viewing the Guidance in isolation from its context, I would accept that the natural and ordinary meaning of "highly specialised" has to do with the nature of the service and the expertise of those providing it, rather than the way in which it is commissioned, and that a critical distinction between "highly specialist" and "highly specialised" amounts to splitting hairs. Obviously, however, the Guidance must be considered in its context. As Mr Wise accepted, the judge was right to say that the primary readership for which the document was designed consisted of the expert decision-making group together with medical professionals and persons engaged in the pharmaceutical industry. It was, therefore, a readership which was

knowledgeable about NHS terminology and practices and which would read and understand the guidance in the light of that knowledge.

61. When criterion 4 is viewed in that context, it is apparent that there is a well understood distinction between "highly specialist" and "highly specialised" as a matter of NHS terminology, and that this must inform the true meaning of the criterion.

62. The technical meaning of "highly specialised services" in this context is explained in the Manual for Prescribed Specialised Services 2018/19 ("the Manual"), published by NHS England. This is the detailed technical document that describes which elements of specialised services are commissioned by NHS England and which by clinical commissioning groups. At page 12, the Manual states:

> "Definitions of 'specialist' and 'specialised'
>
> In this document, the term 'specialist' refers to a level of expertise delivered within a service (with 'highly' specialist meaning a very high level of expertise). The terms 'specialised' and 'highly specialised' refer to the commissioning models used by NHS England to commission highly specialised and specialised services respectively."

63. There was evidence before the judge, which he was entitled to accept, that "highly specialised" services are not merely those services commissioned by NHS England, but a recognised subset of such services which are commissioned through a national commissioning function, rather than through the regions, and that they are delivered at a very small number of centres of excellence. NHS England publishes a list of these highly specialised services known as the "Highly Specialised Services List", which explains the need for such a commissioning model:

> "Each highly specialised service is provided to a smaller number of patients compared to specialised services; usually no more than 500 patients per year.
>
> Due to the small number of patients accessing such services, they are most appropriately delivered and co-ordinated nationally through a very small number of expert centres. This model of delivery makes it easier to recruit appropriately qualified professionals and to ensure that they receive the level of training needed to maintain their expertise. It also permits the most effective use of resources by efficient management of patient care and ensuring access to the technology necessary to allow delivery of the services."

64. Against this background it is clear, in my judgment, that the judge was right to say that "highly specialised" means something different from "highly specialist", that the reference to a "highly specialised service" in criterion 4 is a reference to a service which is not only commissioned nationally by NHS England but is listed in the Highly Specialised Services List, and that this is a term of art within the NHS. Moreover, although services for PKU patients are commissioned by NHS England and not locally by clinical commissioning groups, they are not commissioned nationally as "highly

specialised services" and do not appear on the list of such services. NICE found that this would not change if Kuvan were recommended for use on the NHS.

65. Accordingly NICE and the judge were right to conclude that Kuvan did not satisfy criterion 4.

66. While I would not rest my judgment on this point, I note that there is some support in Regulation 8 itself for the view that the existence of a national commissioning model is relevant to the determination of what technologies should be appraised by means of the HST procedure for which that regulation provides. There is further support in paragraph 30 of the 2017 Guidance which states that:

> "Guidance published by the programme will be phrased as follows:
>
> "*<Technology x> is recommended as an option for the treatment of <disease y> in the context of national highly specialised commissioning by NHS England*.""

Ground 3 – target patient group distinct for clinical reasons

67. Because all of the seven criteria must be satisfied if a technology is to be evaluated under the HST process, my conclusions so far mean that (if Bean and Phillips LJJ agree) this appeal must be dismissed. As the point was fully argued, however, I will express some views about criterion 2.

68. Mr Wise submitted that the judge was wrong to interpret the words "clinically distinct" (although in fact the words are "distinct for clinical reasons") in this criterion as meaning that it must be necessary to know, in advance of the treatment in question, which group of patients with a particular condition will benefit from the treatment. He submitted that the ordinary meaning of these words is simply that the intended recipients of a treatment should be distinct from other patients for observable clinical reasons, even if this may require a trial treatment or tests for some patients, and that, on this basis, the target group of PKU patients who will respond to, and therefore benefit from, Kuvan, is clinically distinct.

69. Mr Stilitz for NICE supported the judge's approach, submitting that the target group who will benefit from treatment with Kuvan is not ascertainable without first being tested for their degree of response to the drug. Accordingly the target patient group is not clinically distinct because it is defined in a circular way (in short, the target group consists of those who are responsive to the drug) rather than being differentiated by some independent clinical criterion. He submitted that the purpose of this criterion was to avoid the risk that a drug with an ill-defined target group would be used more liberally than expected, making it hard to contain the costs associated with its deployment, an important factor in the case of a drug to be appraised under the HST procedure where a less demanding test for cost effectiveness is applied.

70. To put these submissions in context it is necessary to say something about which patients will benefit from Kuvan and how that is ascertained.

71. As already indicated, not all PKU sufferers are responsive to Kuvan. Identification of those who are responsive involves two stages. The first stage is a screening test undertaken by way of gene mutation analysis. This will determine whether the patient has a form of PKU which is responsive to BH4. If not, Kuvan will not be a successful form of treatment for that patient and may be deleterious. However, for patients who are responsive to BH4, Kuvan will potentially be beneficial. Whether it will in fact benefit any individual patient can only be determined by the patient undertaking a trial of Kuvan for a short period which will require careful monitoring and assessment by the treating physician. The standard criterion for a satisfactory response is stated in Kuvan's European Medical Agency Summary of Product Characteristics. It consists of "a ≥30 percent reduction in blood phenylalanine levels", although the summary goes on to give as an alternative the "attainment of the therapeutic blood phenylalanine goals defined for an individual patient by the treating physician". The ≥30 percent reduction represents a consensus among clinicians expert in this field.

72. In my judgment the first step in determining whether criterion 2 is satisfied must be to identify "the target patient group". When using the same words, criterion 1 refers to "the target patient group for the technology in its licensed indication" and it is clear, in my judgment, that this is also what is referred to by the more abbreviated term in criterion 2. The "licensed indication" refers to the use for which a drug receives an EMA licence which, in the case of Kuvan, consisted of "patients of all ages with phenylketonuria (PKU) who have been shown to be responsive to such treatment". (We were told, but I do not think it is in evidence, that it is unusual for a licence to define the patients for whom a drug should be prescribed by reference to those who are responsive to it: however, it seems obvious that a drug should only be prescribed for such patients).

73. Accordingly the target group referred to in criterion 2 consists of those PKU sufferers who have undertaken a trial of Kuvan and have been shown to be responsive to it. That will generally be because they have achieved a ≥30 percent reduction in blood phenylalanine levels, but in some cases it will be because they have achieved some other goal which the treating physician regarded as more suitable for the particular patient.

74. The next question is whether this target group can be regarded as "distinct for clinical reasons". There is, it seems to me, a danger of over-complicating this issue by insisting on a requirement that a group is only distinct for clinical reasons if it can be identified without a trial of the drug in question, at all events where what amounts to a satisfactory response is a clinically recognised measure, as is the case here (i.e. the ≥30 percent reduction referred to in the EMA Summary of Product Characteristics). I see no reason to doubt, in accordance with the evidence of Professor Anita Macdonald who was described by the judge as "probably the country's leading expert on PKU", that "individuals with some enzyme activity, i.e. Kuvan responders, are a clinically accepted subgroup".

75. Breaking the issue down, the group of PKU sufferers who are responsive to Kuvan are certainly distinct, as it seems to me, from PKU sufferers who are not responsive (as well as from those who do not suffer from PKU at all). It is hard to see why the reason for their distinctiveness should not be regarded as clinical. It is after all ascertained by clinical treatment and observation. I note that the NICE decision-making group had no difficulty in ascertaining the size of this group: the "potentially eligible population" was

stated to consist of approximately 500 individuals, with between 300 and 330 patients who would access treatment over time, and about 28 new patients each year.

76. In my judgment this view is not affected by the possibility that in some cases the treating physician may decide that the ≥30 percent reduction is an inappropriate measure of a particular patient's responsiveness to Kuvan. It will generally be necessary for a physician prescribing a new drug to monitor the patient's reaction to it and if necessary to modify the treatment in the light of the individual patient's particular characteristics. Not all patients will respond to treatment in a way that is expected. Patients who were expected to benefit may not do so or may even react adversely so that treatment has to be stopped. The fact that in the case of Kuvan the licensing application recognises (apparently unusually) this kind of possibility, allowing a degree of judgment to the treating physician, so that the drug should only be prescribed for patients who are responsive to it, does not seem to me to detract from the conclusion that patients who are responsive can be regarded as a group which is distinct for clinical reasons.

77. I acknowledge the need to ensure, in the case of an expensive drug, that the patients to whom it will be prescribed are well-defined, so that costs can be controlled. I accept that there is a risk (although not one which applies in this case) either that a target group may be loosely defined with the consequence that a drug is used more liberally than expected, or that a drug which has a narrowly defined licensed indication may prove to have other and much wider uses, and that in either case this may make it hard to contain costs in the event that it is recommended for use in the NHS after an appraisal under the HST procedure. However, it seems to me that criterion 1 (the target group in its licensed indication is so small that treatment will usually be concentrated in very few centres) and criterion 4 (expected to be used *exclusively* in a highly specialised service) should be sufficient to address these concerns. In any event, the concerns do not justify departing from the natural meaning of criterion 2.

78. Accordingly, while it is unnecessary to reach a final decision in view of my conclusion on criterion 4, in my judgment the better view is that criterion 2 was satisfied in this case.

Ground 5 – so small that treatment will usually be concentrated in very few centres

79. Mr Wise submitted that the words "very few" should be given their ordinary meaning and that, in the context of over 1,000 hospitals in the NHS, on any view nine treatment centres (or even nine hub centres plus ten spoke centres) satisfied criterion 1.

80. It is unnecessary to express any view about this submission and I would prefer not to do so. It is apparent that the conclusion of the NICE decision-making group, and indeed of the judge, depended upon their interpretation of the term "highly specialised service" in criterion 4. Because I have held that this interpretation was correct, and because all the criteria must be satisfied, criterion 1 need not be considered further. However, if some different meaning were to be given to criterion 4, the reasoning of the decision-making group and the judge would fall away. If that had been the case, and if criterion 1 had been decisive, it would probably have been necessary to remit this issue to NICE so that a decision could be made on the correct legal basis.

Disposal

81. NICE was right to decide that Kuvan did not meet all of the criteria set out in the 2017 Guidance for appraisal under the HST procedure. I would dismiss the appeal.

Postscript

82. I recognise that this will be extremely disappointing to the claimant and other sufferers from PKU, and that it will be of no comfort to them to know that this is because NICE has a statutory duty to have regard to the broad balance between the benefits and costs of any drug which it appraises for provision on the NHS. Nevertheless it remains to be seen whether NICE will be able to recommend Kuvan following an appraisal under the standard HTA procedure.

83. I would add one suggestion, which is that all of the criteria for appraisal of a "highly specialised health technology" under the HST procedure should be set out in plain language. In essence I have decided that the appeal must be dismissed because the term "highly specialised" in criterion 4 must be given what is on any view a technical meaning. While that may come as no surprise to those familiar with NHS concepts and terminology, it would be preferable, in my view, for all the criteria to be expressed in language which could readily be understood by patients and those caring for them.

Lord Justice Phillips:

84. I agree.

Lord Justice Bean:

85. I also agree.