Neutral Citation Number: [2017] EWHC 2000 (Admin)

Case No: CO/5243/2016

**IN THE HIGH COURT OF JUSTICE**
**QUEEN'S BENCH DIVISION**
**ADMINISTRATIVE COURT**

Royal Courts of Justice
Strand, London, WC2A 2LL

Date: 8/08/2017

**Before** :

**THE HONOURABLE MRS JUSTICE ANDREWS DBE**

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**Between :**

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| **THE QUEEN (on the application of SB) (by his father and litigation friend PB)** | **Claimant** |
| **- and –** | |
| **NHS ENGLAND** | **Defendant** |

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**Ian Wise QC and Stephen Broach** (instructed by **Hodge Jones & Allen LLP**) for the **Claimant**
**Jenni Richards QC** (instructed by **Blake Morgan LLP**) for the **Defendant**

Hearing dates: 18 and 19 July 2017

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# Approved Judgment

**Mrs Justice Andrews:**

## Introduction

1. The Claimant ("S") is a severely autistic 7½ year old child, with an associated severe learning disability, whose autism was first diagnosed when he was 3. He attends a specialist school. He is non-verbal, and does not socialise with other children. He displays violent and challenging behaviour, and is difficult to manage. S also suffers from Phenylketonuria ("PKU"). PKU is a rare inherited metabolic condition, present from birth, which inhibits the ability to digest protein. The condition prevents the body from breaking down an amino acid called phenylalanine, which consequently builds up in the blood.

2. Professor Anita MacDonald is a consultant dietician in Inherited Metabolic Disorders at Birmingham Children's Hospital, and part of the team there that has been treating S since July 2015. She was also the clinical lead for the clinical reference group that advised the Defendant in respect of the formulation of its Clinical Commissioning Policy: "The use of Sapropterin in children with Phenylketonuria" ("the CCP"). It is her evidence that increasing blood phenylalanine is clearly associated with decreased cognitive function, especially in children under 12 years old (when the brain is continuing to develop). There is a probability of an IQ less than 85 at blood phenylalanine over 400 μmol/L. Poorly controlled blood phenylalanine levels are also associated with the occurrence of white matter abnormalities in the brain. Even well-controlled patients have IQs that are 5 to 7 points lower than their unaffected siblings, although generally within the normal range of 92 to 102.

3. The higher the concentration of phenylalanine in the blood, the worse the impairment is likely to be. This is not simply a logical deduction, but the subject of scientific consensus. In a study published in 2007 by Waisbren and others ("Phenylalanine blood levels and clinical outcomes in phenylketonuria: a systematic literature review and meta-analysis") a meta-analysis was carried out examining the correlation between IQ and phenylalanine levels reported in 40 different publications. Among the conclusions drawn was that a difference of 100 μmol/L between birth and 6-12 years predicted a difference in IQ between 1.3 to 3.1 points in patients whose phenylalanine levels ranged from 423-750 μmol/L. That study was among the evidence presented to the Defendant by the clinical reference group and used when formulating the CCP.

4. Without treatment, most children with PKU develop profound and irreversible intellectual disability, delayed speech, seizures and behavioural abnormalities. Other adverse outcomes include impaired executive function, reduced processing speed, attention problems, and impaired fine motor skills.

5. The objective of any treatment is to ensure that blood phenylalanine levels are maintained consistently within a safe range. If levels are consistently above that range, there is a risk of long term cognitive impairment. For children under 12 the upper limit of the range is 360 μmol/L (although in England the slightly lower figure of 350 μmol/L has been used, the difference is immaterial for the purposes of the present claim). The link between cognitive impairment, and phenylalanine levels above the upper limit of the range is well documented. By way of example, in another of the studies referred to by Professor MacDonald (which again was among those considered when the CCP was formulated) Huijbredts and others: "Sustained attention

and inhibition of cognitive interference in treated phenylketonuria" (2002), the authors found that 38 children with PKU with concurrent blood phenylalanine levels in excess of 360 μmol/L performed significantly worse in several tests targeting executive function than matched controls, whereas children with PKU whose phenylalanine was 360 μmol/L or less performed as well as the control group and better than the children whose phenylalanine level exceeded that figure.

6. There is a consensus that, for an optimal outcome, treatment should start as early as possible and that strict control of blood phenylalanine levels is of primary importance, particularly during the first years of life. Patients with PKU are diagnosed by newborn screening, and treatment will commence by the age of 14 days when blood phenylalanine levels are consistently above 360 μmol/L.

7. The standard treatment for PKU is dietary management. This involves restricting the amount of natural protein consumed, often to only 10%-20% of the amount contained in a normal diet, coupled with the taking of a supplement (a protein substitute) to promote normal growth and development. With the exception of fruit and some vegetables, there are few foods that can be eaten without severe limitation. The carefully supervised dietary management of a child with PKU aims to provide enough protein and phenylalanine for adequate growth, but not too much that the levels go too high. Regular blood tests are used to monitor the levels of blood phenylalanine. Dietary adherence is essential, but problematic, and provides a huge burden to families. It can be difficult to achieve, especially as the child gets older. It is recommended that the diet is continued for life.

8. S has two siblings who also suffer from PKU, but they are not autistic. In their case, it has been possible to implement a dietary regime that successfully manages the condition. However, the extreme severity of S's autism and the way in which it affects his behaviour has made it increasingly difficult to control his consumption of protein and to ensure that he takes his supplements as he should. S dislikes low protein foods and refuses to eat them; he becomes obsessed with certain foods, and when he is unable to eat the things he wants, he becomes very distressed. Attempts to restrict his consumption of foods that he does like which are too rich in protein, such as custard, will result in severe emotional outbursts, sometimes accompanied by violence towards himself or others.

9. S has tried and rejected almost all types of protein substitute, and although he currently takes one in the form of a dry powder, the amount he will consume from day to day is inconsistent, and much of it goes to waste. He does not understand why he is not allowed to eat the same food as his parents or other children, or why he needs to take the supplement. He is highly unpredictable in what he will and will not accept. His parents, specialist teachers and treating clinicians have done their best to manage his condition in highly challenging circumstances, and the tireless dedication of his parents is something to which the Court must pay tribute: but despite their efforts his levels of phenylalanine are regularly above the levels that are considered safe. Even when kept inside the target range, they are usually only just inside the upper limit.

10. In S's case, higher levels of phenylalanine in the blood appear to correlate with increased emotional volatility, though it is not possible to definitively attribute certain behaviour to the amount of phenylalanine in his blood rather than to his autism. Both may be contributing factors and one may exacerbate the other. However, when his

phenylalanine levels are high he has severe temper tantrums, and exhibits unacceptable disruptive behaviour, described in detail by Professor MacDonald, by one of S's former teachers, Mrs Leaf, and by S's father in their witness statements. He also becomes restless at night and has poor sleeping patterns. Because of the severity of S's autism, he is intolerant of invasive medical procedures, so intubation is not a practical option. Even if it were, it would cause him unacceptable psychological harm.

11. By this claim for judicial review S, by his father and litigation friend, seeks to challenge a series of decisions made by the Defendant refusing an application made on S's behalf by one of his treating consultants, Dr Santra, through the individual funding request ("IFR") process, for funding to treat S with sapropterin dihydrochloride. For ease of reference, I shall refer to that drug by its trademarked brand name, "Kuvan". In simple terms, for patients who are responsive, Kuvan reduces the level of phenylalanine in the blood, thus making the patient more protein tolerant and enabling them to eat more "normal" foods. In those who respond to Kuvan, the diet is likely to be relaxed and the dietary supplement reduced by 50%. The use of special low protein foods will be decreased or even stopped altogether. Kuvan significantly ameliorates the effects of PKU: however, even in a responsive patient there still has to be some dietary management, and the patient will still have to take supplements (albeit a smaller amount). The European Commission granted a marketing authorisation for Kuvan, valid throughout the European Union, on 2 December 2008.

12. The group of patients who are responsive to Kuvan are those with "mild to moderate" PKU; around 20% of children with the condition aged 4 and above. S's treating clinicians believe that S falls within that group, although the question whether he will be responsive to Kuvan can only be answered definitively if he undergoes a clinical trial. The manufacturers offer a free trial of the drug, but quite understandably the treating clinicians consider that it would be unethical to allow S to undergo the trial if funding would not be available for the longer term were he to prove receptive.

13. In summary, the case that was put forward on S's behalf is that the successful management of his PKU to within acceptable levels of blood phenylalanine is untenable with dietary treatment alone, due to the severity of his co-existent autism. If S proves to be responsive to it, as appears likely, Kuvan would provide a significantly greater clinical benefit for S than for other child patients who can maintain their phenylalanine levels through dietary control alone, because it would enable the levels of phenylalanine in his blood to be brought consistently within the target range beyond which he runs the risk of suffering long term brain damage.

14. Thus far, there have been four relevant decisions, although the first two decisions have been superseded and Ms Richards QC, on behalf of the Defendant, has sensibly indicated that if one or both of the later decisions were to be quashed, it would not be her client's intention to rely on the earlier ones. For that reason, I propose to focus on the more recent decisions, comprising a substantive decision by the IFR Panel not to provide the requested funding, which was made on 14 December 2016 and communicated in a letter to Dr Santra dated 21 December 2016; and a subsequent decision by the IFR Screening Group, after further information was provided by Dr Santra, not to recommend that the case be presented to the IFR Panel for reconsideration. The latter decision was communicated by letter dated 20 February 2017.

## THE RELEVANT LEGAL FRAMEWORK

15. The Defendant, NHS England, is a body established by section 1H(1) of the National Health Service Act 2006 ("the NHS Act"), as amended by the Health and Social Care Act 2012. It has concurrent responsibility with the Secretary of State for Health for the discharge of the overarching duty to continue to promote a comprehensive health service in England. To that end, NHS England is responsible for arranging the provision of services for the health service in England.

16. Clinical commissioning groups are responsible for the planning and commissioning of health services for their local area. However the Secretary of State has a power under section 3B(1) of the NHS Act to require NHS England to arrange for the provision of certain services, to such extent as it considers necessary to meet all reasonable requirements, if the Secretary of State considers that it would be more appropriate for NHS England to make those arrangements.

17. By regulation 11 of the National Health Service Commissioning Board and Clinical Commissioning Groups (Responsibilities and Standing Rules) Regulations 2012 ("the 2012 Regulations") NHS England is responsible for arranging "*to such extent as it considers necessary to meet all reasonable requirements"* for the provision as part of the health service of the 144 services listed in Schedule 4 to the 2012 Regulations. These include services for the treatment of approximately 600 highly specialist metabolic disorders, of which PKU is but one. Although the Schedule does not draw a distinction between children and adults with metabolic disorders, many of the services listed in the Schedule are specialist services for children.

18. The duty imposed on NHS England by the 2012 Regulations is of a general nature. The obligation is limited to providing the services identified to the extent that NHS England considers that they are necessary to meet all reasonable requirements. This necessarily places a considerable amount of discretion (or judgment) in the hands of NHS England, not only as to the scope of the reasonable requirements and as to the services that it considers necessary to meet them, but as to how it goes about its task: see Hickinbottom J's succinct exposition of the principles derived from earlier authorities in *R (Dyer) v The Welsh Ministers and others* [2015] EWHC 3712 (Admin) at [105] – [107].

19. As Hickinbottom J observed earlier in his judgment at [17]:

> "*There is no enforceable individual entitlement to a particular level or location of care from the NHS… That is consistent with article 8 of the European Convention on Human Rights (ECHR), which does not give a patient a right to any particular type of medical treatment from the State, given the fair balance that has to be struck between the competing interests of the individual and society as a whole and the wide margin of appreciation enjoyed by States especially in the assessment of the priorities in the context of allocation of limited state resources."*

20. The reference to the allocation of limited state resources is an important one. The NHS is subject to financial constraints and it cannot possibly fund every healthcare treatment for every patient. It has an express statutory duty to balance its budget. A decision to spend even what, in isolation, may appear a relatively small sum on one patient will mean that that sum is not available to fund the treatment of others who

may be just as deserving. As Sir Thomas Bingham MR pointed out in *R v Cambridge Health Authority, ex parte B* [1995] 1 WLR 898 at 906:

*"It is common knowledge that health authorities of all kinds are constantly pressed to make ends meet… Difficult and agonising judgments have to be made as to how a limited budget is best allocated to the maximum advantage of the maximum number of patients."*

21. The NHS Commissioning Policy: "Ethical framework for priority setting and resource allocation" ("the Ethical Framework") published in April 2013, underpins and is applied to priority setting processes, including the making of decisions regarding the management of individual funding requests. It explains that the NHS Commissioning Board ("NHS CB") receives a fixed budget from Central Government and has specific areas in which it is required to directly commission healthcare for specified groups of NHS patients. A guidance note explains that the NHS CB seeks to take decisions about which services to commission through a systematic approach which is centred around the needs of patients, but which fairly distributes services across different patient groups. It can only do so if all decision-making is based on clearly defined evaluation criteria and follows clear ethical principles. The NHS CB may take a decision not to commission a service to meet a specific healthcare need due to resource constraints. A decision taken on those grounds will not amount to a breach by the NHS CB of its statutory obligations.

22. The Ethical Framework sets out a number of core principles that should guide all decision-making by the NHS CB. The important themes emerging from those core principles are identified as including the following:

    i) a requirement to ensure that all decisions are framed and considered in such a way that all options or investments are considered. This means that there should not be a parallel system operating which allows individual treatments or patients to bypass prioritisation (e.g. by lobbying).

    ii) If funding for a treatment cannot be justified as an investment for all patients in a particular cohort, the treatment should not be offered to only some of the patients, unless it is possible to differentiate between groups of patients on clinical grounds. This is because a decision to treat some patients but not others has the potential to be unfair, arbitrary, and possibly discriminatory. A treatment policy approved by the NHS CB should therefore not be approved unless the NHS CB has made funds available to allow all patients within the clinical group identified in the policy to have equal access to treatment. Individual patients may be considered for funding through the individual funding request process if their clinician can demonstrate that the patient is clinically exceptional.

    iii) the need to demonstrate clinical effectiveness and value for money is only the first stage in assessing priority. Effectiveness and value for money are minimum requirements to enable prioritisation for funding, but are not the sole criteria that must be met for funding to be agreed.

## THE RELEVANT POLICIES

23. Regulation 34 of the 2012 Regulations requires NHS England to have in place arrangements for making decisions and adopting policies on whether a particular health care intervention is to be made available to persons for whom the relevant body has responsibility, and that such arrangements must include arrangements for the determination of any request for funding of a health care intervention for the person where (as in the present case) there is no relevant NICE recommendation and the general policy is not to fund that intervention.

24. Pursuant to those provisions, NHS England has established an Individual Funding Request ("IFR") Policy pursuant to which applications on grounds of exceptional clinical circumstances may be made by an individual clinician and considered by a specialised panel comprising both clinical and non-clinical members. The IFR Panel have a discretion to approve funding if the patient has "exceptional clinical circumstances" as defined in the IFR Policy:

> "*To meet the test of "exceptional clinical circumstances" there must be an NHS [Clinical Commissioning] policy in place that describes the availability of the requested intervention and your patient must demonstrate that they are both*
>
> *Significantly different clinically to the group of patients with the condition in question and at the same stage of progression of the condition*
>
> *AND*
>
> *Likely to gain significantly more <u>clinical</u> benefit than others in the group of patients with the condition in question and at the same stage of progression of the condition" (*emphasis in the original*).*

The reference to the "same stage of progression" is irrelevant in the current case, as PKU is not a progressive condition.

25. The IFR Policy explains in paragraph 1.9 how an IFR Panel will go about the assessment of exceptional clinical circumstances. They will use the information provided by the requesting clinician to compare the patient to other patients with the same presenting medical condition at the same stage of progression:

> *"… Specifically the panel may consider, based upon the evidence provided to it, whether or not the patient has demonstrated exceptional clinical circumstances <u>which lead the panel to believe that the patient would benefit significantly more from the treatment than the other patients not meeting funding criteria.</u>*
>
> *When making their decision, the IFR Panel is required to restrict itself to considering <u>only</u> the patient's <u>presenting medical condition</u> and t<u>he likely benefits which have been demonstrated by the evidence to be likely to accrue to the patient from the proposed treatment</u>."* [Emphasis added].

26. An assessment based exclusively on clinical factors does nothing more than to apply the resources for the purposes for which they are provided (i.e. medical treatment) without giving preferential treatment to one patient over another on non-medical

grounds: *R(Condliff) v North Staffordshire Primary Care Trust* [2011] EWCA Civ 910, especially at [36]. The application of such a Policy will not infringe Art 8 of the European Convention on Human Rights ("ECHR"). Nor is its application inconsistent with the duty imposed on NHS England by s.11(2) of the Children Act 2004 to make arrangements for ensuring that its functions are discharged having regard to the need to safeguard and promote the welfare of children.

27. In terms of further guidance as to what is meant by "exceptional circumstances" the IFR Policy specifically states that the fact that a patient failed to respond to or is unable to be provided with one or more treatments usually provided to a patient with his or her medical condition *may* be a basis upon which the Panel may find that a patient is exceptional. However, the Panel must be satisfied that the patient's inability to respond to the usual treatment is genuinely an exceptional circumstance.

28. Paragraph 1.20 goes on to state that the IFR Panel is entitled to approve an individual funding request when, among other conditions, "*exceptional circumstances apply and there is sufficient evidence to show that, for the individual patient, the proposed treatment is likely to be clinically and cost-effective"*. Thus establishing "exceptional circumstances" is only the first stage of the assessment; it is the threshold that must be crossed to qualify for consideration for funding. Paragraph 1.21 makes it clear that the Panel members are not obliged to accept the views of the patient's treating clinician concerning the likely clinical outcomes for the individual patient. They can reach their own views both on the likely clinical outcomes for the patient and on the sufficiency and quality of the evidence presented to them. That gives the Panel a wide ambit of discretion; and the Court cannot interfere with a decision that is properly taken, and for which adequate reasons are given, especially where matters of expert clinical judgment are concerned, on which there is scope for different views.

29. The distinction between interpretation and application of a policy is well established in public law. The correct *interpretation* of a policy is a matter for the Court. Its *application*, however, is a matter of judgment for the decision maker. However, that judgment must be formed on the basis of a proper understanding of the evidence available to him, taking into account all relevant factors: a material mistake of fact or law, or a material misunderstanding can lead to an invalid conclusion. Even if the decision is fatally flawed, then irrespective of its own views of the merits the Court is not entitled to substitute its own judgment for that of the body charged with making the decision save in those very rare circumstances in which there is only one rational outcome. If there is any material public law error in a decision of this nature, the proper course would usually be to quash the decision and send the matter back for reconsideration.

30. As I have already mentioned, NHS England does have a CCP in respect of the use of Kuvan to treat children over the age of 4 with PKU. The policy is not to routinely commission the treatment. In the plain language summary, the CCP states as follows:

"*Sapropterin (Kuvan) is a drug licensed for patients aged 4 years and over. Up to 20% of children with PKU (mainly mild/moderate) are likely to gain benefit from it if used in combination with a more relaxed diet. There is good evidence to indicate that Sapropterin is effective in the short term and that it enables children to eat significant amounts of "normal" foods which has many social and nutritional benefits. It also*

*allows children to adhere to their treatment regimen as well as lessen the treatment burden on families*."

31. The introduction to the CCP goes on to discuss PKU, its effects and standard dietary treatment, by reference to the many clinical studies that were considered by the NHS clinical reference group (which are listed later in the CCP). Of some relevance to the present claim is a passage which states as follows:

"*Associations between the quality of blood phenylalanine control and behavioural problems, sustained attention and lower IQ are well documented [Hooda et al 2014; Jahja et al, 2014; Clancy et al, 2014; Anjema 2011, Huijbregts et al 2002]. A meta-analysis of all published literature including both phenylalanine levels and IQ measurements has documented an inverse relationship between IQ and mean blood phenylalanine levels when either the critical period of birth to 12 years or the lifetime of the individual is considered [Waisbren et al 2007]*."

32. In its epidemiology and needs assessment, the CCP reiterated that around 20% of children (mild/moderate phenotype) with PKU may benefit from Kuvan. Given the incidence of PKU in England, if children under 4 and over 16 were excluded, it was likely that the drug would be beneficial and used for fewer than 130 children. It was estimated that at least 50% of the costs of special low protein foods and the dietary supplements would be saved with Kuvan use, but it was unlikely that Kuvan would completely replace diet in most (receptive) children.

33. The clinical case put by the clinical reference group to NHS England is summarised in Appendix A to the CCP. This states:

"*In BH4-responsive patients with PKU the strength of the evidence demonstrates that [Kuvan] is effective for reducing blood phenylalanine and improving dietary phenylalanine tolerance (increased by at least 2 to 4 fold) in the short term (level A evidence) but there is less evidence for longer term effects on cognition (Level C evidence) and for all other outcomes (C and D evidence).*"

The 10 longer term studies that are summarised in the appendix indicated that in 147 patients out of 214 taking Kuvan for more than 12 years, reported median phenylalanine tolerance increased 3.9 times compared with dietary treatment; and median phenylalanine blood concentrations were within the therapeutic range <u>in all patients</u>. Compared with diet alone, improvement in adherence to treatment was reported in 63.3% of patients. No severe adverse events were reported.

34. However, the clinical reference group stated that there was much less data in respect of [positive] cognitive improvement and nutritional status. The summary in the appendix to the CCP stated that although early results of the treatment of PKU patients with [Kuvan] indicated possible improvements in cognition/behaviour, further studies were needed. There is limited nutritional status data reported with [Kuvan] but growth is reported to improve (in this regard, reference is made to a single study carried out by Singh and others in 2010).

35. On reviewing the available clinical evidence relating to the treatment, NHS England concluded that there was insufficient evidence to support the routine commissioning of the drug for children because "*the evidence review provided an assessment of*

*effectiveness and safety of [Kuvan] in the short term (up to 10 weeks) and could not demonstrate the benefits of treatment on nutritional status and cognitive development".* It is not suggested that this conclusion was irrational, and the legality of the CCP is not challenged. The CCP is currently under review, but the process commenced after the decisions under challenge were made, and I was told that the results of the review are unlikely to be forthcoming for some time.

## THE IFR APPLICATION

36. Any IFR request for Kuvan treatment for a child with PKU would fall to be considered in the light of the CCP. It is for the clinician making the application to demonstrate "exceptional circumstances" in accordance with the two limbs of the test. When such applications are made, they are initially considered by an IFR Screening Group in accordance with the Interim Standard Operating Procedure on the Management of Individual Funding Requests. It is only if the Screening Group decides there is a reasonable prospect of an IFR Panel reaching the view that the threshold test of "exceptional clinical circumstances" is made out on the evidence supplied, that the matter will go forward for consideration by the Panel.

37. In May 2016 Dr Santra submitted an IFR prompted by recent worsening of S's phenylalanine control. It was stated in the request that in 2016, 60% of his phenylalanine levels had been higher than the target range. When S had been compliant with dietary treatment, his phenylalanine control had been acceptable, with levels within the target range. However due to his autism he is prone to unpredictable behavioural changes which are not easily amenable to behaviour management strategies. This had manifested itself as a refusal to take prescribed low protein foods and/or protein substitutes and had led to higher levels outside of this range (›600 µmol/L) which had now been maintained for nearly 6 months.

38. In the section of the application form dealing with exceptionality, Dr Santra stated that whereas other children with PKU should be able to maintain good control of blood phenylalanine levels with dietary treatment alone, due to his autism, his clinicians anticipated that S would not be able to comply with dietary treatment as required "*and will continue to run blood phenylalanine levels outside of the target range. This will put him at risk of ongoing brain damage from phenylalanine toxicity which could be prevented if phenylalanine control could be better.*" That risk was referred to again in a later passage, which spelled out what might be regarded as obvious, namely, that ongoing brain damage from phenylalanine toxicity may prevent S from reaching his maximum potential level of functioning.

39. Thus the sole clinical justification for the treatment that was put forward by Dr Santra was to eliminate the risk of S suffering ongoing brain damage due to his blood phenylalanine levels being maintained consistently above the range that is generally accepted to be safe. It was not to improve his behaviour, or his nutritional intake and associated growth and physical development, though of course an improvement in his tolerance of protein might achieve some improvement in those matters also. As Dr Santra put it in one of his letters to the Defendant "*it was never the intention that the use of [Kuvan] should improve this patient's behaviour or that his behaviour should be a measured outcome of treatment. Whilst there may be some improvement noted in behaviour if the phenylalanine levels are more consistent, we are not expecting this*

*patient's behaviour to change much, as this is predominantly a reflection of his unusually severe autism which will continue.*"

40. By the time of the substantive decision in December 2016, Dr Santra had supplied further information including an update on S's blood phenylalanine levels which were shown both in graphic and non-graphic form. In September 2016, he stated in a letter to the Defendant that whilst at the time of the application, S had been running phenylalanine levels of around 600 μmol/L, in the last few weeks his levels had improved. He supplied S's blood phenylalanine levels from July to September 2016 which were respectively 460, 370, 370, 300, 320, 340, 320, 380 and 410 μmol/L. He said that he and the treating team "*believe there is a strong chance that S would respond in a meaningful way to [Kuvan] and that this would improve his phenylalanine control into the target range.*" In a later passage he added: "*in my experience I have not managed a child with PKU and autism in whom the behavioural disturbance has been so severe as to affect their ability to comply with dietary therapy in the way it does with S.*"

41. In October 2016, in response to a request from the IFR Screening Group for information on a long-term trend, Dr Santra provided a chart illustrating S's blood phenylalanine levels since July 2015. He explained that he did not have ready access to information about S's blood phenylalanine levels prior to July 2015 (which of course is when S started treatment at Birmingham Children's Hospital). He provided a comparative chart for one of S's siblings from January 2016 onwards, which is when that sibling began to be treated by the same specialist team. The charts showed that S's levels were above 360μmol/L on many occasions, whereas his sibling's levels only rarely exceeded the range. Given that the children are members of the same family with the same parents trying their best to manage their PKU with a strict dietary regime, that is probably the best evidence that could ever be obtained of the practical impact that S's autism is having on the management of his blood phenylalanine levels to within acceptable limits. Dr Santra commented on S's chart "*it should be readily apparent that the majority of blood levels are higher than the upper limit of the desired range.*" He did not reiterate what the consequences of this were likely to be.

42. Whilst it *is* immediately apparent that the majority of blood levels are higher than the upper limit of the range, Ms Richards submitted that the further information indicated that what the doctor had said in the original application was inaccurate. S's phenylalanine levels had not exceeded 600 μmol/L even once in the 5/6 months prior to the application in May 2016, let alone throughout that period. Whilst that is correct (the highest recorded level prior to the application appears to have been 570) the figures during that period were almost all in excess of 400 μmol/L. The statement that higher levels outside the desired range had been maintained for almost six months was true, even though only one of the readings came close to 600 μmol/L. The fact remains that whether one looks at the matter over the short term or the longer term, for around 56%-60% of the time S's levels have been higher than the upper limit, and even when inside the range, they have generally been close to that upper limit. Dietary control is not bringing the levels within the desired range all, or even most of the time.

## THE 14 DECEMBER 2016 DECISION

43. In the two earlier decisions under challenge, the application fell at the first hurdle because it was decided, first by a Screening Group and then by an IFR Panel, that there was insufficient evidence of "exceptional clinical circumstances". In response to a request by the Screening Group for further information about the rarity of autism of this severity in children, Dr Santra provided evidence in support of an estimated prevalence of a child with autism of S's severity of 0.2%. The prevalence of a Kuvan responsive child with PKU who is as severely affected by autism as S was of 0.03 per million population: a total of 1 or 2 individuals in the whole of the UK, including S. In the light of this and other information supplied by Dr Santra, it has now been accepted by the Defendant that the severity of S's autism and its impact on his ability to comply with the dietary regime does make him exceptional to the cohort.

44. Ms Richards nevertheless submitted that the IFR Panel which made the substantive decision to refuse funding (on 14 December 2016) were not persuaded that S met the second limb of the test for "exceptional clinical circumstances". That was not an easy argument to advance in the light of the express statement in the letter to Dr Santra conveying the decision, which said in terms that "*the Panel agreed that the patient did demonstrate exceptional clinical circumstances due to the co-existence of both very severe autism and the condition of PKU"*.

45. Ms Richards' argument depended on reading the decision framework document by which the Panel was guided, as addressing the second limb of the threshold test only at a much later stage of the decision-making process. That would necessarily involve the framework document being interpreted in a manner which is inconsistent with the IFR Policy, by asking the appropriate questions in the wrong order.

46. I cannot accept that interpretation. The questions that the Panel must ask under Stage 1 of the decision framework are directly concerned with the complete threshold test of exceptionality, and not with just one facet of it. That is what the document itself envisages. First, the Panel must ask whether NHS England has a policy to cover the treatment which is made available to patients with the medical condition of this patient. If so, and the policy is not to fund treatment for all patients, the next question is "*did the Panel reach the view that the requester has provided enough evidence that this patient has exceptional clinical circumstances*"? In the column where the answers are to be recorded, the framework document states "*NB, if NHS England has a policy for the condition in question and the patient has not demonstrated exceptional clinical circumstances, the IFR panel are required to turn down the application and the process stops here*." Whoever drafted the framework document therefore plainly intended the Panel to address <u>both</u> limbs of the threshold test at Stage 1.

47. The answer to the Stage 1 question whether the patient has demonstrated exceptional clinical circumstances recorded in the decision framework document for this decision is "yes." The record of the discussions of the Panel indicates that at Stage 1 they turned their minds to "how the interdependency between the conditions (PKU with severe Autism) impact on the day to day management of the patient and *therefore the capacity to benefit/harm* making this patient significantly different to a group of patients with the condition in question" (emphasis added). That accords with the test for exceptionality, which focuses on whether the patient is likely to gain significantly more clinical benefit from taking the drug than the comparative cohort.

48. The Panel acknowledged that there may be some patients with PKU who for various reasons cannot adhere to the strict diet, but agreed that the severity of S's autism made him exceptional even to this cohort. They specifically pointed out that a nasogastric tube or gastrostomy could not be considered for S as it might be for others. They were plainly carrying out the requisite comparative exercise and deciding what the impact on S was likely to be, in terms of his capacity to benefit from taking Kuvan (or, perhaps more accurately, his capacity to suffer harm through not taking Kuvan) as compared with the impact on the comparator cohort. In answering the first question "yes," the Panel must have decided that the threshold was met because the severity of S's autism adversely affected his ability to control the phenylalanine levels in his blood by diet alone and no alternative treatment would work in his case.

49. Indeed, once it is accepted that the incidence and severity of S's autism is such that, compared with the other children of a similar age with PKU (even those who also have less severe autism) his behaviour precludes his phenylalanine blood levels from being satisfactorily managed within target levels on the standard treatment of diet and supplements alone, it is difficult to see how the Panel could reach any other rational conclusion than that he was likely to gain significantly more clinical benefit from taking Kuvan than other children with PKU whose condition could be managed by the conventional treatment alone, (or even those whose condition could not be so managed, but which could be managed by other means, such as intravenous feeds). In S's case, unlike other children, if he is receptive to it, taking Kuvan could make all the difference between being able to keep his phenylalanine blood levels consistently within a safe range, and keeping them outside that range for most of the time, as is currently the case. Once the first limb of the threshold test is established, the second follows almost as a matter of course.

50. Stage 3 of the framework document, on which Ms Richards relied, poses the question "*is there robust evidence that this drug/intervention has been or will be effective in this individual case and that they will gain significantly greater clinical benefit than other patients with the same clinical condition and stage of disease?"* However, that question is asked specifically in the context of the exercise of discretion, on the assumption that the threshold has been passed, at a juncture where the strength of the evidence regarding the patient's actual or likely response to the proposed treatment is subjected to more thorough scrutiny as one of many factors in the cost/benefit analysis. That accords with paragraph 1.20 of the IFR Policy which requires it to be demonstrated that "*exceptional circumstances apply and … for the individual patient, the proposed treatment is likely to be clinically … effective"* [emphasis added]. The requirements are conjunctive. At the threshold stage the focus is on comparing the applicant's likely benefit with that of the cohort; at the later stage the focus is on how much benefit he is in fact likely to gain.

51. Admittedly there are some passages in the framework document, including the consideration of the questions posed at stage 3, that suggest that the Panel, or at least some of its members, thought that S's phenylalanine levels were, or may have been capable of being satisfactorily managed with conventional dietary treatment alone, and that it did not particularly matter that the majority of the readings were above the upper limit of the target range, because they were not far above the limit; but it will be seen that this view arose out of a misunderstanding of what Dr Santra had said, and confusion as to when the risk of neurological impairment arises.

52. The Defendant has decided that S meets both limbs of the exceptionality test and his application for funding qualifies for consideration on its merits. Against that background, I turn to consider the three grounds of challenge to the decision to refuse the application.

## GROUND A: IRRATIONALITY/WEDNESBURY UNREASONABLENESS

53. The next step in the decision-making process was the step at which, according to the decision letter, the application failed. Stage 2 in the framework document poses the question "*does the Panel consider that there is robust evidence of the clinical effectiveness of this drug/intervention?"* The letter says "*the Panel agreed to decline this application on the basis that the clinical effectiveness of this drug/intervention had not been demonstrated.*"

54. Mr Wise QC, on behalf of S, submitted that either the Panel misapplied or misinterpreted the Policy or reached a decision that was irrational. The Panel apparently equated "clinical effectiveness" with "long-term clinical effectiveness" when there was no requirement in the IFR Policy that the latter be demonstrated. Ms Richards submitted that the Panel was entitled to reach that decision in the light of the CCP, to which it was obliged to have regard, and the fact that the application was for long-term funding. She submitted that it was possible for different people reasonably to hold different views on an issue such as clinical effectiveness, and that within the statutory scheme it is NHS England's understanding and assessment of clinical effectiveness that prevails.

55. I agree that it is possible for different people to hold different views about whether the administration of a drug would achieve a particular clinical outcome; but it is not possible to have different interpretations of what is meant by "clinical effectiveness" for the purposes of the IFR Policy. Since it is incumbent on the clinician making the request to demonstrate to the satisfaction of the IFR Panel that the various criteria are met, clinicians applying for funding must have a sufficient understanding of what the criteria mean, and the Policy must be interpreted uniformly.

56. Unlike the expression "exceptional clinical circumstances" the IFR Policy does not define the expression "clinical effectiveness". In the absence of a definition, one would expect that phrase to interpreted in the way in which an ordinary clinician would understand it. It cannot be ascribed a meaning by the Panel which differs from that understanding, or which is not known to the requesting clinician. The question whether a drug is clinically effective, i.e. whether it achieves the intended clinical outcome in respect of the relevant condition from which the patient is suffering (or, as a lay person would put it, it works) is self-evidently a different question from the question of how long it works for. The answer to the latter question may well be relevant, but it arises only after clinical effectiveness has been established.

57. I am fortified in my conclusion as to the meaning of "clinically effective" by the Ethical Framework which, in its glossary of terms, defines "effectiveness – clinical" in these terms: "*Clinical effectiveness is a measure of the extent to which a treatment achieves pre-defined outcomes in a target patient population"*. This means that clinical effectiveness must be measured against the target outcome(s). That target outcome may differ, depending on the specific context in which the question "is this drug clinically effective?" is asked: for the purposes of the CCP, it appears that the

target was not simply the reduction of phenylalanine in the blood, but an improvement in cognition and/or nutritional uptake, and it was the latter aspect, not the former, on which the longer-term evidence was found to be lacking. NHS England decided that without further evidence on those specific aspects there was insufficient justification for funding Kuvan treatment for *all* children with PKU.

58. However, this application for funding was not sought on the basis of a wish to improve those matters, it was based on a wish to avoid the deleterious effects on S's brain of being exposed consistently to phenylalanine blood levels above the range regarded as safe. Put another way, the treating clinicians were seeking to use Kuvan as a means to achieve precisely the same clinical objectives as the standard dietary treatment, to which S is unable to respond sufficiently, aims to achieve. The fact that the Defendant's CCP to refuse funding as a matter of course is justified by the absence of sufficient clinical evidence as to the long-term effect of taking the drug on cognition and nutritional uptake is of little relevance in this context.

59. In this case, the IFR Panel should have asked itself "is there robust evidence that this drug is clinically effective?" on the basis that the target outcome was the reduction of blood phenylalanine levels and improved phenylalanine dietary tolerance. It is small wonder that Dr Santra states in his witness statement that he was surprised that issue was taken by NHS England as to the clinical effectiveness of Kuvan (in that sense) as he considers it to be well-established. It is not just Dr Santra's (and Professor MacDonald's) view that there is substantial rigorous evidence of the efficacy of Kuvan in reducing phenylalanine levels in receptive children; it is NHS England's own view, reflected in its findings in the CCP, which I have already quoted. Indeed, as Mr Wise submitted, the clinical evidence in that regard is all one way. Both the short-term and the 10 long-term studies quoted in the CCP demonstrated that Kuvan reduced phenylalanine levels in the blood, and improved dietary phenylalanine tolerance in receptive patients, with no adverse effects on safety. There was no clinical evidence suggesting otherwise. If the Panel had approached the matter with that in mind, it could not have reached the conclusion that it did.

60. It appears from the framework document that it did not take that approach. First, the Panel stated that only 10-15% of patients with PKU will be responsive to Kuvan. The correct figure for children between 4 and 12 years old is 20%. That figure is not just supported by Dr Santra in his application, for reasons which he explains by reference to a substantial body of medical literature, but replicated in the CCP. Of course, the fact that a drug only works in certain patients with certain characteristics does not mean that it is not clinically effective. It is still capable of achieving the intended clinical objectives in those patients who are receptive. The Panel made no reference in this specific context to the evidence from Dr Santra as to why it was that he believed that S fell within the 20% who would be responsive to the treatment, although they accepted that evidence later in their discussions: at section 3 of the framework document they stated that S was in the "mild to moderate group".

61. Next, the Panel said there was "*limited evidence of clinical effectiveness of this drug in the short term in treatment sensitive patients*." On the face of it the labelling of this evidence as "limited" (with the underlying implication that it is of little value) was irrational. The CCP describes the evidence of short-term clinical effectiveness as "*good*"; and the clinical reference group is quoted in that policy as finding that "*the strength of the evidence demonstrates that [Kuvan] is effective for reducing blood*

*phenylalanine levels and improving dietary phenylalanine tolerance (increased by at least 2 to 4 fold) in the short term.*" There is no explanation of why the Panel decided to take a different view of the evidence on clinical effectiveness from the view of the clinical reference group adopted by NHS England with apparent approbation in the CCP. There was no further evidence before it which would have justified such a departure.

62. It is true, as the Panel next stated in the framework document, that there is less evidence of long term *benefit* – but such evidence as there was, in the form of the 10 clinical studies quoted in the CCP, points towards long-term clinical *effectiveness*, which is not necessarily the same thing. The target outcome may be formulated as the conferring of a specific (positive) clinical benefit, but that will not always be the case. A drug can be established to achieve certain clinical outcomes (e.g. reducing blood phenylalanine levels) without it also being established that those outcomes, which address a known risk, also create a measurable benefit (or a benefit over and above standard treatment), such as a positive improvement in behaviour or growth. The reason why the CCP decided against routine funding was the absence of sufficient evidence of long term *benefit* (for responsive patients) not the absence of sufficient evidence of long term *effectiveness*. An alternative analysis of the rationale behind the CCP is that the target outcomes in terms of clinical effectiveness set for the purposes of the CCP were wider than the specific outcome being sought in this application. However, the IFR Policy is only concerned with the question whether the proposed treatment is likely to work in this patient, who is exceptional to the cohort.

63. In any event, the mere fact that there is less evidence relating to the long-term effectiveness of Kuvan on blood phenylalanine levels than there is about its effectiveness in the short term, does not mean that such evidence as there is about it, is insufficient to support the conclusions drawn, or is not "robust". The Panel did not address the quality of the evidence in the longer-term studies, let alone explain why they felt that 10 long-term studies of patients suffering from a very rare condition, all pointing towards the same conclusions, were insufficient evidence that Kuvan works in the manner it was intended to work with this patient, or that their methodology was insufficiently robust.

64. The Panel either misinterpreted the phrase "clinical effectiveness" or they misunderstood or materially mischaracterised the evidence on that topic, including what had been accepted already by NHS England in the CCP as being established by the clinical studies. They appear to have fallen into the error of assuming that, because the CCP was based on an evaluation by NHS England that there was as yet insufficient evidence of long-term clinical benefit, in the absence of any further long-term clinical studies the applicant could not demonstrate that the drug was clinically effective. There may be cases in which an IFR Panel could legitimately take the view that the relevant CCP precludes any successful IFR application being made in the absence of fresh clinical evidence of the effectiveness of the drug in question, but this is not one of them.

65. If "clinical effectiveness" is properly interpreted, the evidence that Kuvan is clinically effective is overwhelming. In my judgment, there is no room for a rational conclusion that Kuvan is not clinically effective or that the evidence of its clinical effectiveness (for the precise purposes for which it is sought to be used here) is insufficient. Given that the supposed absence of evidence of clinical effectiveness was the specific reason

given to Dr Santra for turning down the application, that is such a material error that it suffices in and of itself to warrant quashing the decision and sending it back for reconsideration.

66. However, if there had been any doubt as to whether this decision falls within that rare category with which it is legitimate for this Court to interfere, it is put to rest by the way in which the Panel went on to consider the rest of the questions in the framework document and sought to justify the decision in its letter to Dr Santra.

67. Ms Richards submitted that the Panel reached a view that they simply did not have enough evidence as to the likely benefit to S of taking Kuvan to be able to embark on a cost-benefit analysis, and that this view was reasonably open to them. On the face of it, given the nature of the discretion, that was a submission that might have carried considerable force, and it might well have done in other circumstances. However, this decision was informed by error upon error, the most fundamental of which was that the Panel misunderstood (and/or mischaracterised) what Dr Santra was saying about the clinical implications of S's inability to control his blood phenylalanine levels to levels falling consistently within the target range. Whilst it is open to an IFR Panel to disagree with the requesting clinicians if they have valid reasons for doing so, a decision based on a misinterpretation of what the clinicians are saying will be fundamentally flawed, and so it is with this one.

68. In the decision letter, the Panel said the following:

"*[Dr Santra] explained that given current levels would be unlikely to result in significant neurological impairment but the efforts required to sustain this are not sustainable…*"

"*One of the key issues around the information presented was that the Panel were not absolutely clear about the impact of the current variation in phenylalanine levels on the patient's potential for sustaining neurological impairment. Given that the evidence provided on phenylalanine levels which [sic] that the patient is not currently at risk of imminent neurological impairment, the Panel were not clear about the benefit/advantage which would result from funding the intervention at this time…*

*The Panel were not clear at what point would the levels described become harmful/dangerous…"* [emphasis added].

69. The Panel's framework document, consistently with the decision letter, states that the Panel "*were not clear at what point the levels described would become harmful/dangerous therefore the Panel could not tell whether even if those levels were reduced, there would be a positive effect on actual outcomes, to justify expenditure and demonstrate cost effectiveness. If the treatment did work, Panel were not clear did this success rate mean below/normal thresholds*."

70. The background section in the framework document includes this passage:

"*The application also describes how if phenylalanine levels are high over time the patient is at risk of becoming brain damaged. It was discussed that it was not clear from the application what the risk of brain damage was given the recent phenylalanine levels which were shared by the consultant. It was clear that a number*

*of the levels were raised. The Panel discussed how they do not know how high or for how long levels need to be before brain damage is caused. The average of all the readings given was just below the normal level."* [emphasis added].

There was a suggestion later in the framework document that because there was "*no narrative around the levels described within the chart*" of S's phenylalanine levels the Panel could not tell whether a reduction in those levels would give rise to a positive effect on actual outcomes. The Panel were plainly having difficulties in understanding whether, in the light of the figures in the chart, the risk yet existed or would only potentially arise in the future if, as Dr Santra feared, current levels could not be maintained.

71. It appears that the Panel believed or assumed that the current situation was acceptable, and that S would not be exposed to any appreciable risk if matters remained as they are, when that was plainly not what they were being told. I have already referred to what Dr Santra said in the original application form, which made a clear link between S continuing to run blood phenylalanine levels outside the target range, and the risk of ongoing brain damage from phenylalanine toxicity, which could be prevented. The treating clinicians were seeking funding for Kuvan with the aim of bringing the levels consistently within safe parameters. Elsewhere in the framework document the Panel accurately described the goal of the requested treatment as "*to keep the patient's levels within range*", but they did not appear to understand why that was imperative.

72. The Panel obviously failed to understand why the target range was set in the first place and what the treating clinicians were saying about the risk posed by failing to keep phenylalanine levels within it. 360 μmol/L is generally accepted to be the upper end of the safe limit of phenylalanine concentration in the blood; it is not a threshold between "normal" and "abnormal" levels. That is the very reason why dietary treatment is initiated once a child's blood phenylalanine levels are consistently at or above 360 μmol/L. It is the point at which there is both some neurological impairment (correlating to the levels of phenylalanine), and the point at which there is a risk of that impairment becoming irreversible, as demonstrated in the papers quoted in the CCP. Readings consistently above that level expose any child to a real risk of long term brain damage, irrespective of whether that child is autistic. What the charts showed was that over a period of 12 months it had been possible for S's parents to bring them within those parameters for less than half the time, whereas the blood phenylalanine levels for S's sibling were consistently within those parameters (with only the occasional reading outside the range).

73. The question of the period of time over which the unacceptably high phenylalanine levels have to be maintained before the risk matures is one that self-evidently could not be answered without unethical experimentation, and in any event may depend on the physiology of the individual patient. This no doubt explains why the clinical consensus is no more precise than that consistent exposure to phenylalanine blood levels above the upper end of the target range, exposes a child to a sufficient risk of irreversible neurological damage to justify seeking to do something to bring those levels inside the range. Logically, the longer the exposure, the higher the chance that the risk will mature, but that does not mean that it could not mature at any time.

74. At no stage did Dr Santra suggest that current levels were unlikely to result in significant neurological impairment, unless one were to equate "significant" with

"severe and irreversible", but that is what the Panel have done, and in so doing, they materially mischaracterised the doctor's evidence. The obverse of equating "significant" with "severe and irreversible" is that any brain damage less than severe and irreversible is to be treated as insignificant, which I am sure was not the Panel's intention. What Dr Santra said, which appears to have given rise to the confusion, was that higher levels than those that were currently being achieved with great difficulty would undoubtedly lead to severe neurological damage which had nothing to do with S's autism.

75. Before the matter was referred to the Panel, Dr Santra was asked the following question by the Screening Group: "*Please could you provide a clear statement of the impact of the phenylalanine levels over and above the impact of the child's autism?*" The relevance of that question is not immediately apparent, and could be open to the interpretation that if a child is already severely autistic, it would be necessary to demonstrate the measurable extent of the further brain damage likely to be caused by phenylalanine toxicity alone, before funding could be considered. One would hope that the question was asked for some different reason. As Dr Santra had made clear, the purpose of this application was to help S achieve his maximum functioning potential by treating his PKU effectively, even if doing so could not improve the learning disability attributable to his autism.

76. Perhaps unsurprisingly, the doctor found the question difficult to answer. His response was "*At the current level of control, I would not expect S to experience severe neurological impairment due solely to PKU. I suspect S's overall developmental outcome will mostly be affected by the severity of his autism"*. He added that without the extreme effort being put in by his parents, S's control would worsen *"and his levels would be predicted to climb to 600 µmol/l or even higher. Even with this effort, behavioural problems leading to sudden outright refusal of protein substitute in any form might lead to very high levels. If such very high levels were sustained, then there is no doubt that S's poor PKU control would lead to progressive and non-reversible neurological impairment over and above what is already evident from his autism. This is well documented in the evidence already submitted.*"

77. The higher the levels, the greater the damage caused by phenylalanine toxicity is likely to be, hence Dr Santra's view about the type of damage likely to be sustained if the exposure is to "very high" levels over 600µmol/L. An average of the readings is meaningless in this context. What Dr Santra was saying was that if S's blood phenylalanine levels were consistently above 600 µmol/L, he would sustain severe (and irreversible) neurological impairment which Dr Santra could confidently state would have nothing to do with his autism. He was <u>not</u> saying that consistent blood phenylalanine levels above the accepted target range but under 600 µmol/L would <u>not</u> expose S to the risk of some long-term neurological impairment, or that such a risk was not imminent, or that the current situation was tolerable or gave rise to no risk. Dr Santra's position is most clearly articulated in his letter of 26 September 2016, where he said "*if [S's] control remains at this level I would not expect the [same] degree of neurological impairment due to PKU that he could sustain should the levels have remained at 600 or higher*." In other words, at current levels the likely neurological impairment attributable to phenylalanine toxicity would not be "severe". He did not

otherwise attempt to quantify it. Dr Santra went on to explain why he considered that current levels were unlikely to be maintainable.

78. One of the panel members has given evidence in these proceedings that she thought that "*S's PKU levels [sic] were relatively well controlled at that point in time*" and "*it wasn't that despite all efforts the patient had uncontrolled PKU"*. There is no mention of that view being articulated either in the decision letter or the framework document, but once again it betrays a fundamental misunderstanding of the case that was being put to the Panel. The problem was not a lack of control as such, but an inability to control to levels that were consistently within acceptable limits. If S's parents had managed to control his phenylalanine levels to between 450 and 500 μmol/L, the levels could be fairly described as "relatively well controlled" but they would still be unacceptably high. S's levels of PKU were being controlled to within certain parameters, with huge effort, but they were still not being kept consistently within what, as a matter of clinical consensus, is the acceptable range. The treatment was intended to create the consistency that could not be achieved by diet alone.

79. If there were any doubt that the Panel were labouring under a misapprehension, it is resolved by a statement made in the decision framework document (though not repeated in the letter to Dr Santra) at section 7: "*The Panel noted that it is very important to point out at this stage that the patient is currently within the desired range for phenylalanine levels."* That statement is demonstrably incorrect. Even the most recent two readings were above the range. At best, it is a half-truth, because the evidence was that S's levels were within the range for less than 50% of the time, and then, just about within the upper limit, a situation which, according to the treating clinicians, was likely to be well-nigh impossible to sustain going forward, given his behavioural difficulties. The focus on the "current" levels (whatever was meant by this) ignored the overall pattern, but perhaps more disturbingly appeared to assume that the higher readings were within the acceptable range.

80. The Panel went on in the same section of the framework document to say that "*given that levels are not currently at a critical level, funding the treatment may not deliver a significant improvement to patient outcomes given that the risk is currently not high".* Thus, far from saying there was insufficient evidence to form a view about the level of risk, the Panel expressed the view that the risk was "currently not high", in the teeth of evidence that S's blood levels had been above the target range more often than not during the previous year. It appears that the Panel were treating the "critical level" as the level at which S would sustain permanent severe neurological impairment (i.e. over 600 μmol/L.) They were therefore either misinterpreting Dr Santra's evidence as meaning that the risk of *any* neurological impairment was low (or even non-existent), or had not yet arisen, because the blood phenylalanine levels were below 600 μmol/L, or mixing up the existence of risk with the incidence of severity of the brain damage if the risk matured (or both).

81. There are many problems with this approach, not least that it produces a Catch-22 scenario. On Dr Santra's evidence, consistent blood phenylalanine levels above 600 μmol/L would be likely to cause severe irreversible neurological impairment - and thus put S beyond the stage at which Kuvan could have any impact on avoiding the risk of that, or of any less serious neurological impairment, maturing. By the time any application based on a series of sustained longer-term readings above 600μmol/L could be put to an IFR Panel, it could well be too late. Given that the purpose of the

application is to *avoid* a child sustaining avoidable neurological damage by lowering the phenylalanine levels in the blood to consistently within acceptable limits, it can hardly be appropriate to expect the child to be exposed to sufficiently high levels for long enough to potentially sustain severe irreversible brain damage before deciding that a case of clinical benefit is made out.

82. Moreover, one of the reasons that Dr Santra felt able to classify S as falling within the class of mild/moderate PKU patients who are likely to be receptive to Kuvan as a means of bringing his phenylalanine levels consistently within the target range was that his blood phenylalanine levels had not strayed farther than they did from the upper limits of that range, despite all the problems in controlling his diet caused by the severity of his autism. If his levels went beyond 600 μmol/L for any significant length of time then, quite apart from the problems adverted to above, it could be said by a Panel that there was insufficient evidence that he would be receptive to Kuvan because his PKU could not be demonstrated to be mild/moderate. The irony is that because he falls within the mild/moderate class, as the Panel appear to have accepted, it was felt that he was not demonstrably at risk (or sufficiently at risk) to justify the treatment.

83. Ms Richards submitted that it was legitimate for the Panel to ask over what period S would have to maintain blood phenylalanine levels in excess of 360 μmol/L, and how high the levels would have to be, before sustaining [some] neurological impairment. She contended that the target levels did not define or quantify the risk, and that if a Panel does not know where on the scale between remote and imminent, or low and high a risk lies, it could lawfully reject an application, because without that information it could not reach a conclusion on the likely benefit and cost-effectiveness of the treatment.

84. But the upper target level *does* define the point at which the risk arises: that is its very purpose. Treatment is initiated at the level of 360μmol/L precisely because that is the level above which the risk of long-term neurological impairment is regarded as sufficient to warrant medical intervention to bring the phenylalanine levels down. This is confirmed by Professor MacDonald's second Witness Statement in which she states that there is [already] a risk that S is suffering cognitive impairment. I am conscious that this statement was not before the Panel when they made their decision, and therefore I have simply used it as a reference to check that my understanding of the clinical case that was put before the Panel is correct. Dr Santra and his colleagues believed there to be a strong chance that S would respond in a meaningful way to Kuvan therapy and that this would improve his phenylalanine control *into the target range* and thus, by avoiding the risk of long-term brain damage, achieve his maximum functioning potential.

85. Of course, the question whether the evidence produced by Dr Santra demonstrated that there has been consistent exposure to phenylalanine levels above the target range or that there was likely to be such consistent exposure in the future despite the best endeavours of S's parents, is a matter of judgment on which there may be room for more than one view. "Consistent" is not the same thing as continuous, but requires there to be sufficient frequency: plainly the occasional reading above the range would not demonstrate consistency. It is a value judgment; the treating clinicians plainly consider that there has been such consistent exposure and the risk already exists, and suffices to warrant treatment by more than dietary control alone, but their view is not

binding on the Panel. If the Panel had asked themselves that question by reference to the evidence supplied, and formed a view on it that differed from the treating clinicians, their decision may well have been unimpeachable. However, the Panel did not ask themselves that question.

86. So far as quantification of the risk is concerned, I do not accept the premise that a decision maker could rationally conclude that he needs to be able to further quantify the risk of a child sustaining brain damage from toxic levels of a chemical building up in his or her bloodstream, above and beyond the risk regarded as high enough to warrant some form of medical intervention, before being able to take a view as to whether it is justifiable to fund medical treatment that would address that risk. In any event, even if it were legitimate to seek to quantify the risk above and beyond the risk regarded as high enough to warrant medical intervention, one wonders how the Panel could have thought anyone would be able to provide such information. Plainly, scientists could not experiment on children to find out the answers to those questions. Just as with the period of exposure, one could only ascertain at what level of toxicity the risk of brain damage would materialise in a particular child, by waiting to see.

87. Had the Panel wanted a measure of the progressive detrimental impact of higher levels of phenylalanine in the blood on neurological function, they could have referred to the findings of the Waisbren study quoted in the CCP, demonstrating that for each 100 point elevation in blood phenylalanine levels, there is a defined detrimental impact on IQ levels. The higher the levels, the worse the impairment. Many of the levels on S's chart at the time were above 400, three of these were above 500, and one above 600. Five more readings were in the range of 370-390. This was not a case in which the graph demonstrated only the occasional reading above the range.

88. Given that this decision is going to be sent back for reconsideration, and it will no doubt be necessary for updated information on S's blood phenylalanine levels to be provided, it would be advisable for Dr Santra to spell out the position in a way that leaves no room for misunderstanding. He should state, in the clearest possible language, what conclusions he (and the team) consider can be drawn from the data about S's blood phenylalanine levels and the historic pattern in terms of the existence and nature of the risk of neurological impairment, the reasons for drawing those conclusions, and what bringing the levels consistently within target range would achieve in terms of addressing that risk. If it is their view that on the basis of the current data S risks some long-term cognitive impairment, which, if it materialises, may not be as severe as the likely damage caused at phenylalanine levels consistently in excess of 600μmol/L but which would still have an impact on his neurological functioning independently of his autism, they should express that view, and explain why they hold it. If the potential severity of the damage to which S is currently exposed can be measured, they should say so and explain how; if it cannot, they should say why not.

89. The Claimant's treating clinicians will have had the considerable benefit of seeing the framework document which articulates the Panel's areas of concern in far more detail than the decision letter, and anything more that can be said or provided by way of further evidence to meet those concerns would no doubt improve the chances of success next time.

90. Professor MacDonald expresses the view that any risk of cognitive impairment is unacceptable and requires action to address it. That is a sentiment with which it is very difficult to disagree, when the child is already exposed to that risk. In fairness to this Panel, they did not appear to dissent from that view, but reached the decision they did because they were labouring under the misapprehension that the risk in this case had not yet arisen because S's blood phenylalanine levels were under 600μmol/L. However, even when the risk is real rather than theoretical, the form of the action that can be taken to address that risk (i.e. the type of treatment available) may be circumscribed by budgetary constraints and the demands made on the health service by other patients. The difficult decision that a Panel of this nature are given the responsibility of taking is a more nuanced one than the decision of a clinician that *some* form of treatment must be administered, and involves balancing numerous competing and complex factors. Thus, the risk of neurological impairment faced by S, and the ability of Kuvan to ameliorate or eliminate that risk, must be balanced with the likelihood of the treatment working on him and its projected cost, bearing in mind that if the treatment does not work, or is no longer needed, it will cease (and there will be no further cost), but if it does work, funding would continue for the long term.

91. Any concerns about long-term clinical effectiveness or benefit must be balanced against the carefully individualised management protocol proposed by S's treating clinicians, which involves six-monthly appraisals after the initial trial. Whilst it is legitimate to consider the likely exposure to cost of providing the drug into adulthood, there are numerous imponderables that have a bearing on the future cost, including the fact that once he reaches the age of 12, S is expected to have an increased tolerance to phenylalanine, and the prospect that the cost of Kuvan may be greatly reduced when the existing patent expires. The likely cost over the next few years, during the critical period to age 12, may be more reliably calculated. The Panel will no doubt also bear in mind the cost that is already being expended on treatment for S's PKU and the prospective financial burden that the NHS might incur if, due to the ineffectiveness of dietary control, S's blood phenylalanine levels do reach a level of toxicity where he suffers severe irreversible brain damage unrelated to his autism.

## GROUND B – FAILURE TO HAVE REGARD TO THE DUTY TO SAFEGUARD AND PROMOTE THE WELFARE OF CHILDREN.

92. I propose to say very little about the two remaining grounds of challenge to the substantive decision, both of which I found to be fundamentally misconceived for the reasons adumbrated by Ms Richards. The first complaint is that there is nothing in the decision that suggests that the Panel had regard to NHS England's statutory duty under s.11(2) of the Children Act 2004 to safeguard and promote the welfare of children. Mr Wise's submission was postulated on the premise that this duty manifests itself not just in terms of general policies and procedures, but also in respect of each individual application for funding.

93. The Children Act 2004 arose out of the Government's response to the Victoria Climbié inquiry (the Green Paper entitled "*Every Child Matters*"). Section 11(2) of the Act requires each person or body subject to the section (including NHS England) to make arrangements for ensuring that their functions are discharged having regard to the need to safeguard and promote the welfare of children. The explanatory notes and the statutory guidance both indicate that the focus is on safeguarding.

94. In *Kensington and Chelsea Royal London Borough Council v Mohamoud* [2015] EWCA Civ 780, the Court of Appeal held that the duty under s.11(2) was not free-standing and could not be detached from the statutory functions it was designed to secure. It ought not to be construed so that it changed the nature or scope of those functions. Sharp LJ quoted with approval the analysis of Pitchford LJ in the earlier case of *Castle v Commissioner of Police of the Metropolis* [2012] 1 All ER 953 at [51] in which he said that "*The impact which the duty will have on the performance of a function will depend to a significant degree on the function being performed and the circumstances in which it is being performed."* Therefore, in any case it is necessary to identify the particular statutory function to which the duty is said to apply, and the appropriate context in which it arises.

95. Mr Wise relied heavily on the decision of the Supreme Court in *Nzolomeso v Westminster City Council* [2015] UKSC 22. However, that case concerned a very different context, in which the relevant statutory duty to find "suitable" accommodation for a homeless family necessarily required consideration of the needs of each member of the family. The welfare of the children was plainly a relevant and significant consideration in that context, although even then, as Lady Hale stressed, it was not a paramount one.

96. In the present case, the statutory duty on NHS England is not focused on individuals. It is a general or target duty to arrange for the provision of services, including highly specialist metabolic disorder services, *"to such extent as it considers necessary to meet all reasonable requirements"*. NHS England has paid due regard to the need to safeguard and promote the welfare of children in the CCP, by specifically considering the extent to which children with PKU might benefit from taking Kuvan. It has ultimately concluded, having regard to whether its use represented the best use of NHS resources, that there was insufficient evidence to support routine commissioning of the drug.

97. The IFR Policy has been formulated in a manner that seeks to provide a fair and structured means of assessment of those cases where an exception to the relevant standard policy, in this case, the CCP, can be justified. The IFR Panel take their decisions in relation to individuals as part of an overall system that seeks to balance the best interests of all patients within a system with finite resources. Funding a treatment for an individual child in the absence of sufficient evidence of clinical or cost effectiveness depletes the resources available to meet the needs of other children, whose welfare must also be considered.

98. I accept Ms Richards' submission that section 11(2) of the Children Act did not require the IFR Panel to take a different approach to that mapped out in the IFR Policy. There was no additional obligation for the Panel to have had regard to the welfare of S (or to state that they had done so in their decision) since the welfare of the child on whose behalf an application for exceptional funding is made, in terms of clinical benefit, is something that is necessarily an integral part of the decision-making process whenever an individual decision is taken in accordance with the IFR Policy. There is nothing in s.11(2) that compels NHS England to take S's welfare, in any wider sense, into consideration when deciding on an application of this nature. This ground of challenge therefore fails.

## GROUND C – FAILURE TO HAVE REGARD TO THE BEST INTERESTS OF THE CHILD.

99. Mr Wise did not seek to argue that there had been any infringement of S's right to private and family life, but rather that the Defendant has breached the so-called "procedural" requirement inherent in Article 8 ECHR, read together with Article 3 of the United Nations Convention on the Rights of the Child ("UNCRC") to evaluate the impact of its decision on S and assess whether it was consistent with his best interests. He relied on the decision of the Court of Appeal in *R(Gudanaviciene) v Director of Legal Aid Casework* [2015] 1 WLR 2247. That was a very different case, relating to the provision of legal aid for the purposes of claims in immigration proceedings, a field in which Article 8 ECHR is frequently engaged. Mr Wise realistically accepted that the procedural obligation under Article 8 does not arise in a case in which the substantive decision does not engage Article 8.

100. As Ms Richards pointed out, the best interests of the child under Article 3 of the UNCRC, an international treaty which is not part of domestic law, may be relevant to questions concerning the rights of children under the ECHR. Therefore, it may become part of the proportionality assessment under Art 8 in a case in which that article is engaged. However, it is well established that a decision to decline to fund a particular course of medical treatment does not constitute an interference with the Claimant's article 8 rights: see e.g. *RR v Poland (2011) 53 EHRR 31*; *R(Condliff) v North Staffordshire PCT* (above), especially per Toulson LJ (delivering the judgment of the Court of Appeal) at [40] and [41].

101. That case concerned an adult patient who was complaining about the decision of an NHS Primary Care Trust refusing to fund bariatric surgery. In conclusion, at [52], Toulson LJ said this:

> *"Nothing in the authorities … leads me to conclude that the policy of the PCT, properly understood, is to be regarded as showing a lack of respect of Mr Condliff's private and family life, so as to bring article 8 into play. If, however, article 8 is applicable, there were legitimate equality reasons for the PCT to adopt the policy that it did and its decision was well within the area of discretion or margin of appreciation properly open to it,"*

102. This case involves two policies adopted by NHS England, as opposed to a PCT, but the same principles apply to those policies with equal force. The fact that S is a child makes no difference to the underlying principles. There was no specific obligation on the IFR Panel to have regard to the best interests of S over and above the extent to which those interests were already catered for in the IFR Policy. Therefore, this ground of additional challenge also fails.

## THE DECISION OF THE SCREENING GROUP NOT TO REMIT

103. In the light of my findings on the substantive 14 December 2016 decision it is unnecessary to dwell on the challenge to the subsequent decision by the Screening Group not to refer the matter back to the IFR Panel. Suffice it to say that it is rather difficult to understand how the Screening Group could legitimately reach a view that there was no reasonable prospect of the IFR Panel, properly directing themselves to the definition of exceptionality, finding the patient exceptional, given that an IFR

Panel had already done so (and indeed, could have reached no other rational conclusion on the material before them). However, as the substantive application is going to be reconsidered by the IFR Panel, and it is accepted by all parties that it will be open to Dr Santra to place such further information as he considers relevant before the Panel before they take their decision, the challenge to the decision not to remit the matter has become academic, and I propose to say no more about it.

## CONCLUSION

104. For the above reasons, the claim for judicial review succeeds on the first ground only. The decision of 14 December 2016 is quashed and must be remitted to the IFR Panel for reconsideration in the light of this judgment. In practical terms, the starting point for reconsideration, in the light of my findings, will be stage 3 of the framework document.

105. Whilst this judgment is bound to give rise to a degree of optimism, I must caution against raising hopes too high. The fact that this claim for judicial review has succeeded does not mean that there will necessarily be a favourable outcome to this IFR application. However much one might hope that on the next occasion the Panel will decide that the net additional expenditure of treating S with Kuvan would be justified having regard to the likely clinical benefit of keeping his blood phenylalanine levels consistently within the range that would avoid his suffering any additional neurological impairment, thereby potentially enabling him to realise his maximum functioning potential, they could still lawfully decide to refuse funding. It is their decision, and their decision alone; and provided it is taken on the basis of the correct interpretation of the IFR Policy, and a proper understanding of the case put before the Panel and the supporting evidence, it will not be open to challenge.