Consultation Report

Topic details

Title of policy or policy statement:	Interim clinical commissioning policy: Sapropterin for Phenylketonuria (All Ages)
Programme of Care:	Women and children
Clinical Reference Group:	Metabolic medicine
URN:	1840

1. Summary

This report summarises the feedback we received from consultation during the development of this policy, and how this feedback has been considered. This policy proposition and associated evidence review, impact assessment and equality and health inequalities impact assessment were available for review on the NHS England consultation hub for a period of 1 month.

2. Background

Phenylketonuria (PKU) is a rare genetic disorder. In this disorder, the amino acid phenylalanine (Phe) (found in food proteins) cannot be broken down and accumulates in the body. High levels of Phe are extremely toxic to the brain and untreated PKU causes profound brain damage resulting in very low intelligence quotient (IQ), seizures, muscle stiffness, autism and persistent behavioural problems. In pregnancies of women with PKU the foetus can be affected by high levels of Phe.

There is currently no cure for PKU. Since brain damage in PKU is caused by high levels of Phe, treatment consists of lifelong clinically prescribed dietary management aimed at reducing Phe levels towards a safe range, using a diet which removes almost all-natural sources of protein (i.e. meat, fish, eggs, soya, nuts cheese, bread, pasta and milk). Except for fruit and some vegetables there are few foods that can be eaten freely. The prescribed diet involves calculation of daily Phe intake based on food portions and nutritional information of food labelling.

Early detection and treatment prevents severe brain damage and seizures, but even with prescribed diet treatment IQ is reduced and in adults with treated PKU there may still be poor planning and decisioning-making skills, abnormal changes on brain scans and tremors. Specialist metabolic teams conduct regular dietary reviews to avoid nutritional deficiencies and encourage dietary adherence.

Sapropterin is a treatment taken orally once daily dissolved in water. It improves a cohort of patient's ability to process Phe, reducing or stabilising the level of Phe in the body to below or closer to the recommended levels set out in the European Guidelines, thus protecting brain function and development. The reason for using sapropterin in PKU is to sustain Phe control over time which is generally difficult to achieve with prescribed diet alone. As natural protein intake increases and reliance on synthetic protein and special low protein foods is reduced the diet becomes more manageable, thus improving dietary adherence and improving cognitive outcomes.

This policy proposition has been developed by a Policy Working Group made up of metabolic medicine consultants, specialist dieticians and a patient and public voice representative who is a member of the National Society for Phenylketonuria.

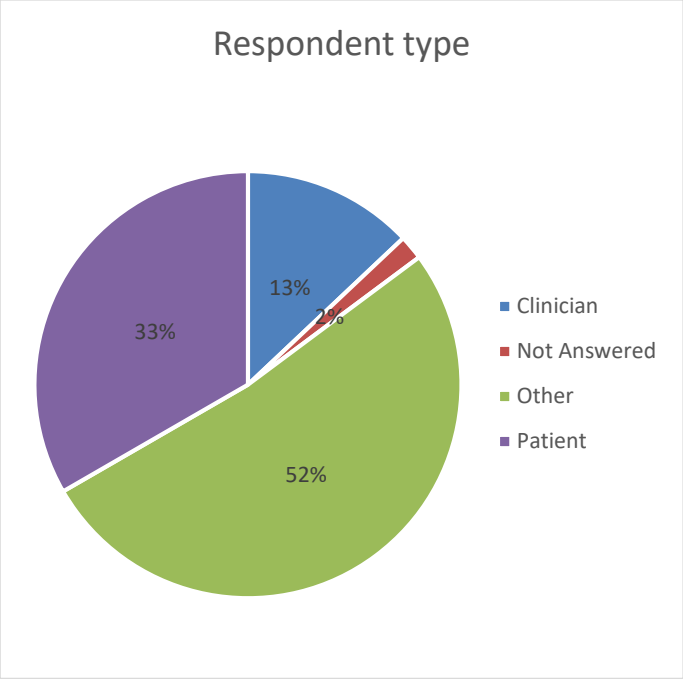
3. Publication of consultation

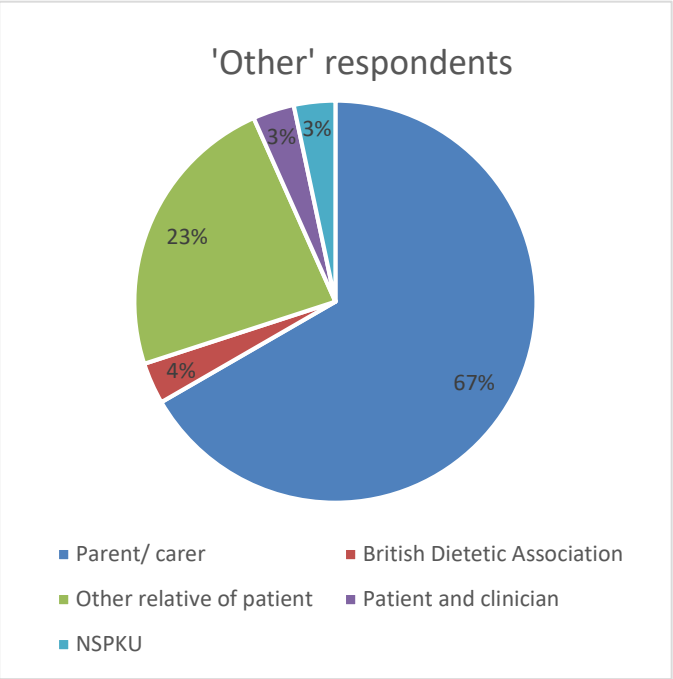
The policy proposition was published and sign-posted on NHS England's website and was open to consultation feedback for a period of 30 days from 24th March 2020 to 23rd April 2020. Consultation comments have then been shared with the Policy Working Group to enable full consideration of feedback and to support a decision on whether any changes to the policy might be recommended.

Respondents were asked the following consultation questions:

- Has all the relevant evidence been taken into account?
- Does the impact assessment fairly reflect the likely activity, budget and service impact? If not, what is inaccurate?
- Does the policy proposition accurately describe the current patient pathway that patients experience? If not, what is different?
- Please provide any comments that you may have about the potential impact on equality and health inequalities which might arise as a result of the proposed changes that have been described?
- Are there any changes or additions you think need to be made to this document, and why?

4. Results of consultation





There were 56 responses to public consultation from patients, carers, relatives, clinicians and professional organisations. The manufacturer of the treatment also responded to the consultation.

How has feedback been considered?

Responses to engagement have been reviewed by the Policy Working Group and the Women and Children Programme of Care (PoC). The following themes were raised during public consultation:

Keys themes in feedback	NHS England Response
Relevant Evidence	
35% of respondents queried why the benefit of sapropterin in preventing maternal PKU and allowing patients more choice in planning pregnancies had not been included in the evidence review.	The PICO document developed by the PWG guides the evidence review which the policy proposal is based on. The PWG did not specifically include pregnancy / pre pregnancy in the PICO as there was an intention to review this group separately in future. The policy proposes the use of sapropterin in all patients who respond, which would cover women planning pregnancy and pregnant women not accounted for in the current sapropterin in pregnancy policy https://www.england.nhs.uk/wp-content/uploads/2013/04/e12-p-a.pdf
27% responses highlighted that there was a lack of focus on the relationship between Phe levels and mental health outcomes and cognitive outcomes in the evidence review.	The PWG recognise there is a well-established link between lower Phe levels and cognitive outcomes. This link between Phe levels and cognitive outcomes is emphasised in the background. The evidence review is designed to review the comparison between these outcomes in patients on sapropterin and those on dietary management alone.
24% of responses stated that the evidence review should have considered the impact on the patient, wider family and carers.	The PICO document developed by the PWG guides the evidence review which the policy proposal is based on. The purpose is to establish the clinical effectiveness, safety and cost-effectiveness of sapropterin. The impact on patients, wider family and carers is outside the scope of the evidence review. The policy working group have reviewed the background to ensure adequate description of the challenges faced by patients, families and carers.
18% of respondents felt there was a failure to contextualise the limited evidence base related to the rarity of the condition.	The policy will be presented to the Rare Diseases Advisory Group (RDAG).

17% of responses stated that the evidence review statement 'disease-orientated outcomes, such as blood test results, which are not proven to result in benefits in patient-orientated outcomes, for example, cognitive functioning or physical growth' was incorrect, stating there was a recognised association between these.	The PWG recognise there is a well-established link between lower Phe levels and cognitive outcomes and have detailed this in the background. The evidence review is designed to review the comparison between these outcomes in patients on sapropterin and those on dietary management alone.
10% of respondents queried why no evidence of cost-effectiveness was included in the evidence review.	The PICO document developed by the PWG guides the evidence review which the policy proposal is based on. Evidence on the cost effectiveness was defined as an outcome of interest in in the PICO by the policy working group and so was explored in the evidence review. No peer review published evidence was however retrieved and this is stated in the evidence review.
8% of responses (duplicates) stated that the improvement in stability of Phe levels was not emphasised enough in the evidence review.	The evidence review factually reports the finding for each outcome specified in the PICO.
1 response highlighted that the evidence review did not mention the significant improvement in inattention symptoms in children found by the Burton study.	The PICO document developed by the PWG guides the evidence review which the policy proposal is based on. Inattention was not identified by the policy working group as an outcome of interest, and therefore has not been included in the evidence review.
Impact Assessment	
36% of response stated that the wider savings in terms of social care, benefits, education resulting from improved cognitive functioning and behaviour in patients treated with sapropterin should have been accounted for in the impact assessment.	Wider societal cost savings such as improved employment or reduced reliance on social care cannot be accurately accounted for in detail in the impact assessment. This is the case of all policies and therefore is not included in any policy proposition impact assessments.
27% of responses highlight that they believed saproterin would come off patent at the end of the year, and therefore the impact assessment should take account of the potential availability of generic versions.	The impact assessment uses the currently available list price, as for all clinical commissioning policies.
19% of respondents highlighted that in addition to artificial amino acids, patients with PKU are also prescribed special low protein food, a cost which	The financial model already takes into account the savings resulting from the reduction in prescribed foods.

has not been included in the impact assessment.	
14% of responses stated that the savings on dietary products prescribed in CCGs should be counted as a saving for NHS England, and therefore the cost impact was incorrect.	The financial model already takes into account the savings resulting from the reduction in prescribed foods.
12% responses queried why a dose of 12.5mg/kg/day was used for adults in the impact assessment.	The dose included in the impact assessment is based on that used in the papers included in the evidence review, though we recognise there is variation in the dose used. For the purposes of the financial model the most optimistic scenario has been used, therefore the impact assessment has been amended with a dose of 10mg/kg assumed for adults and children. The policy itself allows use of the clinically appropriate dose to achieve response.
11% responses queried why free product provided by Biomarin for response test was not accounted for in the impact assessment.	NHS England works directly with manufacturers of treatments which are the subject of clinical commissioning policy development and this is also the case for this policy proposition. The aim is to agree commercially confidential offers which improve the affordability of proposed treatments. Affordability is a consideration for CPAG prioritisation.
8% responses highlighted that there may be additional savings associated with improvement management of PKU due to lower reliance on health services for co-morbid conditions such as eczema, epilepsy and mental health conditions.	The methodology used is the same for all policy propositions that are developed and funded by NHS England and NHS Improvement Specialised Commissioning. Where it is possible to quantify costs or savings to the budgets of other commissioners this is acknowledged in the Impact Assessment but cannot be taken into account in the budget impact to NHS England and Improvement.
The patient numbers in the impact assessment were questioned - 1 response queried whether the rate of uptake, compliance and adherence was correct. 2 responses queried how the eligible patient population had been calculated.	The assumptions included are based on clinical advice from the PWG, as well as incidence figures for PKU gleaned from PHE blood spot tests.
1 (1.5%) respondent queried whether home delivery costs had been included in the impact assessment.	This has already been included in the financial assumptions.
Current Patient Pathway	

Several respondents highlighted issues faced in accessing care for PKU at present. 6% of respondents highlighted that they felt there is a lack of support for patients transitioning between paediatric and adult services. 2 responses highlight that adult metabolic clinics not being funded by NHS England. 3 responses highlighted there is a cohort of adult patients who were discharged historically/ lost to follow up. 3 responses highlighted there is difficulty accessing specialist prescription foods in the community. 2 respondents felt there is current inequality of access to specialist metabolic centres by region.	Out of scope of this clinical commissioning policy proposition, However, this information has been shared with the POC to enable it to review the issues as part of service specification.
3% respondents highlighted that genotyping not part of routine care at the moment and the requirement for this may disadvantage patients in timely access to sapropterin.	This query has been reviewed by the clinicians on the PWG, who have advised that the requirement for genotyping is both feasible and useful, as it will avoid response testing in patients with specific genetic mutations who will not respond. Genetic testing has been included in the financial assumptions.
The requirement of a review of treatment at 6 months was queried by a number of respondents. 3% of responses queried whether a single 6-month review of response was too early for some patients, and whether a longer period for confirming responsiveness should be considered. 2 responses queried whether a patient who previously did not respond/ did not properly comply with treatment could have another trial of treatment.1 response stated that metabolic clinics would see an increase in workload with six monthly follow up – additionally highlighting that Neurocognitive assessment not currently routinely done. One respondent queried as to whether the six-monthly review could be done via telephone or video link.	The PWG have reviewed the timing and format of the review of response to treatment and have confirmed that the stopping criteria already allows for treatment for up to 12 months prior to withdrawal. When there is a reasonable justification for a patient not attaining treatment targets at 6 months, treatment can continue for a further 6 months, as set out in the stopping criteria. Clinicians can apply clinical judgement on a case-by-case basis within this criteria. Clinicians confirmed that the 6 month review could be completed as a virtual appointment, provided a patient had submitted their blood spot tests. The monitoring and stopping criteria have remained unamended, though a footnote has been added to clarify that review at 6 months can be virtual.
1 response stated that age-specific thresholds for treatment of PKU from the European guidelines had been mis-interpreted.	Change in eligibility criteria to state Target Phe levels are defined as:120-360 µmol/l up to 11 years, 12 years onwards 120-600 µmol/l, women who

	are planning a pregnancy 120-360 µmol/l. This brings the criteria in line with the European guidance which was always the intention of the policy criteria. This change does not impact eligibility or the financial model.
Potential impact on equality and health inequalities	
21% of responses highlighted that there is a high risk of health inequalities in patients with PKU. Respondents highlighted a broad range of people facing health inequalities could benefit from sapropterin, including people on low incomes, those with mental health problems, those with intellectual disabilities. 2 respondents highlighted the inequality faced by women with PKU, stating that poorly controlled PKU had a large impact on family planning decisions.	Each of these groups has been identified in the equalities and health inequalities assessment, which has been made available for public consultation. The Equality and Health Inequalities Assessment (EHIA) has been reviewed and slightly revised by the PWG following public consultation to ensure each group is adequately described.
Changes/addition to policy	
20% of responses stated that the policy should have highlighted that difficulties coping with prescribed diet in patients with cognitive impairment meant this cohort were left without an effective treatment.	The policy working group have reviewed the background to ensure adequate description of the challenges faced by patients in adhering to diet. It has been noted that patients on sapropterin continue to require a restricted diet.
14% of responses requested that more information on the social exclusion faced by PKU patients due to the diet be included.	The policy working group have reviewed the background to ensure adequate description of social exclusion faced by patients on a phenylalanine-restricted diet. It has been noted that patients on sapropterin continue to require a restricted diet.
11% of respondents stated that more information requested on the reasons people struggle to adhere to the diet.	The policy working group have reviewed the background to ensure there is an adequate description of the significant challenges faced by patients in adhering to diet. It has been noted that patients on sapropterin continue to require a restricted diet.
Additional comments	
8% of responses (duplicates) highlighted concerns about the transparency of the CPAG process and requested that the upcoming prioritisation round remain in public as previously.	The comments about CPAG process and NICE TA are noted but are outside the remit of the PWG in respect of changes to the policy proposition.

1 response disagreed that NICE should assess the treatment as part of the technology appraisal (TA) process and stated that the rarity of PKU had not been properly accounted for.	The approach taken by NICE to assess the treatment is outside the scope of this policy proposition.

5. Has anything been changed in the policy as a result of the consultation?

The following change(s) based on the engagement responses have(s) been made to the policy:

An additional sentence has been added to the policy background to explain the impact of the proposed treatment as follows: 'Successful treatment is particularly reduced in families and patients with pre-existing social vulnerabilities such as poor literacy, health literacy and poverty.'

Change in eligibility criteria to state:
Target Phe levels are defined as:120-360 µmol/l up to 11 years, 12 years onwards 120-600 µmol/l, women who are planning a pregnancy 120-360 µmol/l.

A footnote has been added to clarify that review at 6 months can take place virtually.

The dose for adults in the impact assessment has been amended from 12.5mg/kg to 10mg/kg.

The EHIA has been updated to include further information for 2 protected groups: pregnant women and those planning pregnancy and race and ethnicity.

6. Are there any remaining concerns outstanding following the consultation that have not been resolved in the final policy proposition?

No outstanding concerns within the remit of the PWG to amend the policy.