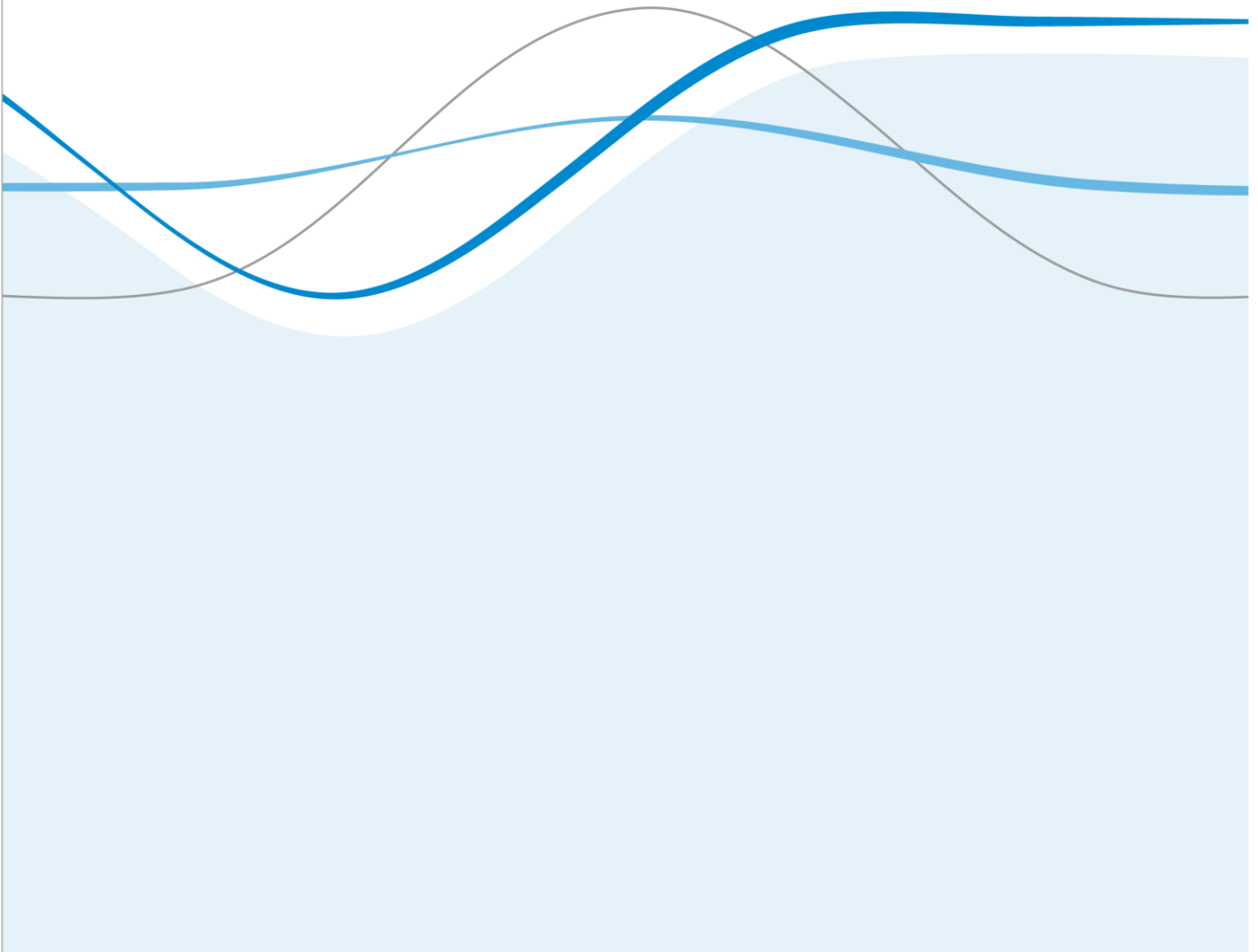# Appraising Ultra-Orphan Drugs: Is Cost-Per-QALY Appropriate?
A Review of The Evidence

March 2018

Adrian Towse and Martina Garau

Appraising Ultra-Orphan Drugs: Is Cost-Per-QALY Appropriate? A Review of The Evidence

Adrian Towse[a], Martina Garau[a]

[a]Office of Health Economics

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Table of Contents

1. EXECUTIVE SUMMARY

In April 2017, following a public consultation, NICE changed the method for appraising drugs and other health technologies reviewed through its Highly Specialised Technology (HST) programme. Highly Specialised Technologies constitute treatments for very rare diseases. This report addresses the implications of NICE assessing HSTs using a cost-per-QALY gained decision rule of the type used by NICE in its Technology Appraisal Programme to appraise therapies for more common conditions.

We identify a number of challenges to the use of the QALY in the appraisal of health technologies:

- the QALY may not accurately reflect the health gain experienced by patients in a particular disease area;

- the QALY does not capture all the relevant benefits of the treatment for patients including impact on the process of care;

- there is evidence challenging the principle that 'a QALY is a QALY is a QALY', including studies suggesting that people are willing to sacrifice aggregate health in order to give priority to the severely ill;

All three of these challenges apply to Highly Specialised Technologies.

Given the importance of non-QALY elements in the assessment of HSTs, such as treatment impact on the process of care and on the patients' or their carers' ability to go to school or to work respectively, and issues in measuring quality of life when the population affected are infants or young children, it is inappropriate to focus the HST appraisal solely on a cost-per-QALY measure.

Given the lack of an empirical basis, the new £100,000 cost per QALY threshold, and its possible uplift by a factor of up to three, seems arbitrary.

An empirical basis for an HST threshold could be generated by looking, for example, at social preferences for treating patients with very rare conditions, or at the typical scale of any impact beyond direct health benefits, or at the adjustments for low patient numbers that might have to be made to enable pharmaceutical companies to get a return on investment from HSTs. However such evidence in support of NICE's change is currently lacking.

2. INTRODUCTION

The National Institute for Health and Care Excellence (NICE) uses a form of Health Technology Assessment (HTA) in order to decide if new treatments should be made available to NHS patients. HTA is defined by HTAi (one of the leading international groups of professionals and organisations undertaking HTA) as:

"a field of scientific research to inform policy and clinical decision making on the introduction and use of health technologies. Health technologies include pharmaceuticals, devices, diagnostics, procedures and other clinical, public health and organizational interventions."

"HTA is a multidisciplinary field that addresses the clinical, economic, organizational, social, legal, and ethical impacts of a health technology, considering its specific healthcare context as well as available alternatives. The scope and methods of HTA may be adapted to the needs of a particular health system, but HTA processes and methods should be transparent, systematic, and rigorous."

"In health systems throughout the world, HTA plays an essential role in supporting decision making.[1]"

The pan-European Union network of HTA bodies (EUnetHTA), which includes NICE, has developed a Core Model for undertaking HTA. This identifies nine dimensions of an HTA of which the first four are prioritised in EUnetHTA's Rapid Relative Effectiveness Assessment. These are as follows:

1. Health problem and current use of technology

2. Description and technical characteristics of technology

3. Safety

4. Clinical effectiveness

5. Costs and economic evaluation

6. Ethical analysis

7. Organisational aspects

8. Social aspects

9. Legal aspects

NICE uses different approaches in the programmes it runs. These are summarised in the Table at Appendix 3. It focuses on health outcomes for patients using the Quality Adjusted Life Year (QALY), and on costs incurred by the NHS and by Personal Social Services (PSS). In contrast to methodologies applied by some other HTA bodies, NICE

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[1] http://www.htai.org/htai/what-is-hta.html

does not consider other costs, for example, those incurred by patients, family and carers, or by employers from having ill and absent workers.

There are two exceptions to this approach. In the case of Medical Technologies Guidance, which covers new, innovative medical devices and diagnostics, because of limited evidence, NICE undertakes a cost-consequences analysis. It sets out the costs of the intervention to the NHS and the possible health benefits for patients, but does not undertake a cost-effectiveness analysis and recommend whether or not a technology should be used by the NHS.

The other exception, before the 1st April 2017 changes, has been the Highly Specialised Technologies (HST) programme where there was no formal assessment of cost-effectiveness, and broader criteria were considered.

Following a public consultation, NICE introduced a number of changes to the method for evaluating drugs and other health technologies appraised through NICE's HST programme in April 2017 (NICE and NHS England (2016); NICE (2017a)).

The report addresses the implications of assessing Highly Specialised Technologies (HSTs), which constitute treatments for very rare diseases, using a cost-per-QALY gained decision rule of the type used by NICE in its Technology Appraisal Programme to appraise therapies for more common conditions.

3. THE USE OF THE QALY AND ITS CHALLENGES

NICE uses the QALY as a measure of health gain. The QALY combines an estimate of the additional life years (or part thereof) gained from the treatment with an estimate of the value of the improvements (if any) in the health related quality of life of the patient. The QALY represents a year of life adjusted for its quality; one QALY equates to one year in perfect health. It is illustrated in Figure 1 below.

In Figure 1 the *y* axis shows quality of life which is measured between 0 (death) and 1 (full health). Years of additional life are shown on the *x* axis. Here we see the expected number of QALYs a patient will get from Treatment A. The patient's quality of life begins at around 0.8 and declines to death after around 1.6 years. With Treatment B, life expectancy is extended to nearer to 2 years (a gain of 0.4 years or around 5 months) and the patient's quality of life is higher than with Treatment A. The shaded area gives the QALYs gained by using Treatment B as compared to Treatment A.

There are a number of theoretical assumptions that underpin the use of the QALY, not all of which are likely to hold in the real world or in all circumstances. The consensus amongst health economists is, however, that the QALY is a valid concept. It is measurable and it represents good starting point in understanding the impact of an intervention on the health of a patient. Notwithstanding that, there are four types of challenge to the use of the QALY in the appraisal of health technologies.

Figure 1: Calculating QALYs

Calculating QALYs
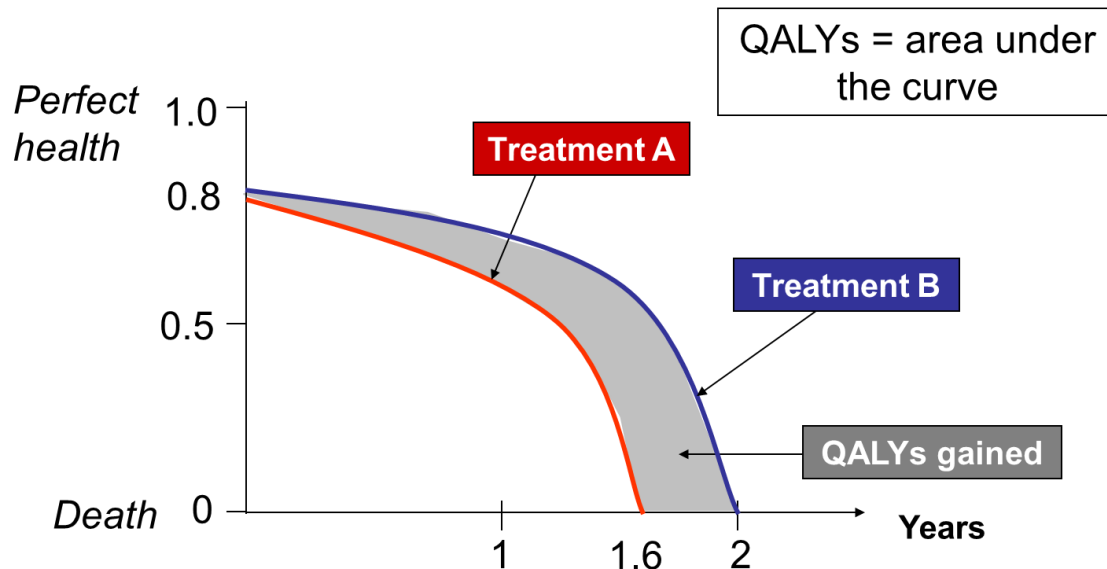
Challenge 1: The QALY may not accurately reflect the health gain experienced by patients in a particular disease area

There are usually two stages to estimating Health-related Quality of Life. Stage 1 involves measuring the health status of the patient. NICE prefers the use of the EuroQol instrument EQ-5D (Devlin and Brooks, 2017; NICE, 2013). Patient state of health is measured on five dimensions with the patient responding by ticking one of three levels[2]. Appendix 1 includes a copy of the questionnaire. This is a generic questionnaire, i.e. can be applied to all disease areas. Stage 2 involves valuing that health state, i.e. translating the patients' description of their health on the questionnaire to the quality of life weighting used in calculating QALYs. These quality of life weightings (or 'values') range from 1 (full health) to 0 (a quality of life close to dead) and can take negative values for health states considered worse than being dead. These values are obtained by asking members of the UK population to engage in a series of tasks designed to find out how good or bad they think various health states are.

Typically three challenges arise (Nord et al., 2009). Firstly, the EQ-5D works better in some disease areas than others. Secondly, in many cases patients are not given the EQ-5D to complete, but a different, disease specific, questionnaire to complete. This will be better at picking up the things that matter to patients focused on the particular disease under consideration, but the questionnaire then often has to be translated into, or mapped across to, an EQ-5D health state. Thirdly, the use of population (rather than

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[2] There are two versions of EQ-5D: the 3L with three levels, which is currently recommended by NICE and an improved, more sensitive version of it; the 5L, with 5 levels. NICE has recently issued a statement indicating that the EQ-5D-5L version is not recommended for use and that the position will be reviewed in August 2018 in light of new evidence. See https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisal-guidance/eq5d5l_nice_position_statement.pdf

patient) valuations of health states may be problematic if it is difficult for members of the population completing the valuation exercise to really understand what living in a particular health state involves. This might lead to underestimation or overestimation of the effect that a treatment might have on the quality of life of people with the condition. All three of these issues can arise in health technology appraisals. However, they occur more frequently in the area of Highly Specialised Technologies. For example, only one of the four HSTs we discuss in Section 3 has evidence on EQ-5D collected from patients, and all four affect children, where collecting information on health state is more difficult.

HSTs are likely to often involve assessing the impact on quality of life when the population affected are infants or young children. A recent systematic review found relatively few studies had attempted to elicit utilities for paediatric populations being vaccinated, and, where they had, the methods and sources used to obtain those utilities were often inappropriate, unclear, poorly reported, or based on weak underlying evidence (Herdman et al, 2016). Another recent systematic review in acute lymphoblastic leukaemia came to a similar conclusion (van Litsenburg et al., 2014). A brief published this year by the US Institute for Clinical and Economic Review (ICER), confirmed the persistence of this issue in orphan drugs and pointed out that: "the parents of affected infants (or other caregivers) may be proposed as proxies for the measurement of these patients' quality of life, although it is unknown how accurately such responses reflect patients' actual quality of life" (ICER, 2017).

Challenge 2: The QALY does not capture all the relevant benefits of the treatment for patients including impact on the process of care

We have commented above on the challenge of fully capturing the health effects of a treatment in particular disease areas in the EQ-5D questionnaire. There may be other aspects of benefit from a treatment, for example, taking a pill once a day is less onerous than having a daily infusion lasting several hours. This would not necessarily be captured in the EQ-5D instrument. There are other non-health related effects, such as the impact on patients' and carers' ability to go to school or to work, respectively, which are included in NICE's HST evaluation programme under the heading "Impact of the technology beyond direct health benefits" (NICE, 2013b), but not in the main Technology Appraisal programme. The latter can include costs (or savings) occurring outside the health sector on an exceptional basis. The carers' cost of providing care would need to be in a separate analysis from the reference case, but the health impacts on carers (as measured by the QALY) can be part of the reference case (NICE, 2013a).

Challenge 3: There is evidence challenging the principle that 'a QALY is a QALY is a QALY'

It is widely assumed by health economists conducting HTA that the principal objective of health care is to maximize population health using available resources (Culyer, 1997). Given that the QALY has been developed to provide a generic measure of health effect, it follows that health care resource allocation should seek to maximize the number of QALYs generated (Dolan, 2001). This is commonly referred to as the QALY-maximization rule. It can be seen as a form of ethical utilitarianism and Culyer (1992) refers to this position as 'QALY egalitarianism' – all QALYs are of equal social value, regardless of whom they accrue to and the context in which they are enjoyed. In other words, 'a

QALY is a QALY is a QALY' under all circumstances. Three circumstances in which this is clearly not the case are discussed in Nord et al. (2009).

First, the standard QALY approach gives no regard for the pre-treatment utility level of the individuals concerned. Both ethical theory and public opinion in a number of industrialised countries suggest that in setting priorities, society emphasises how badly off the individuals would be if intervention did not take place. That is to say, the worse off an individual would be without an intervention, the more highly society tends to value that intervention. This aspect of societal valuation is often referred to as an independent concern for severity. Empirical studies of severity-related preferences suggest that people are, on the whole, willing to sacrifice aggregate health in order to give priority to the severely ill. In quantitative population preference studies (see Ubel et al., 1999; Richardson, 2007; Dolan et al., 2005; Nord, 1999; Shah, 2009), QALY gains to severely ill groups have been weighted two to 10 times more highly than gains to less severely ill groups.

Second, the conventional QALY model implies that the value of an intervention is proportional to the beneficiary's capacity to benefit. The model therefore favours those with more treatable conditions and those with greater potential for health, in terms of functioning and/or longevity. This is somewhat at odds with both ethical theory and public opinion, which suggest that it should not be held against people that they happen to have conditions for which there are no complete cures or that their remaining lifetime is somewhat limited. In a UK study, Dolan and Cookson (1998) found a reluctance to discriminate in situations where groups differed in terms of potential for gaining life years (e.g., 10 vs. 20 years). Evidence that this aspect of benefit is of concern to the public has also been found in other countries (Nord et al., 1995; Nord, 1999; Abellan-Perpinan and Pinto-Prades, 1999; Ubel et al., 1999). People seem to believe that there should be some priority accorded to those in urgent need of medical attention. Capacity to benefit does matter, but there is some sort of trade-off.

The third problem is a special case of the second issue. Valuing health gains in terms of QALYs means that life-years gained in full health—through, for instance, prevention of fatal accidents in people in normal health—are counted as more valuable than life-years gained by those who are chronically ill or disabled (e.g., averting fatal episodes in people with asthma, heart disease, or mental illness). This also runs counter to results obtained in studies of public preferences for priority-setting.

Social Values have been discussed by the NICE Citizens Council, and NICE's "end of life" criteria which give an uplift to QALY values in some disease settings, also attempts to reflect circumstances in which some QALYs are worth more to society. All three of the circumstances we set out above apply to Highly Specialised Technologies.

Challenge 4: The difficulty of establishing a cost-per-QALY threshold representing the opportunity cost of funding a treatment, or the maximum willingness to pay of the NHS for a treatment

In its Technology Appraisal programme, NICE uses a "base" cost-per-QALY threshold of £20,000, which can increase to £30,000 if the Committee finds particular issues that merit use of a higher threshold. In the case of treatments that meet "end of life" criteria a threshold of £50,000 is used. Whether £20,000 is the correct value of the base threshold is much debated, but there is agreement that the threshold should reflect (i)

the health gain that might be lost elsewhere if more is spent on NICE recommendations (i.e. the opportunity cost), and (ii) that it should be adjusted in particular circumstances, for example if the QALY is not picking up all health gain, or if the QALYs gained are likely to be more highly valued by society, perhaps for the reasons set out above.

4. NICE'S METHODOLOGY FOR EVALUATION OF HIGHLY SPECIALISED TECHNOLOGIES AND APPROACH USED TO EVALUATE ULTRA-ORPHAN DRUGS BEFORE 2013

As noted above, between May 2013 when NICE commenced evaluating HSTs, until the 1st April 2017 changes, NICE departed from its usual cost effectiveness approach when evaluating medicines for very rare conditions, often termed ultra-orphan drugs. It is important to note that from a regulatory perspective, there is not a distinction between orphan and ultra-orphan drugs. The eligible criteria to obtain orphan designation from the European Medicines Agency (EMA) indicates that "the prevalence of the condition in the EU must not be more than 5 in 10,000 patients". Most countries have adopted this definition in their HTA processes. In the UK (and to our knowledge nowhere else), a specific separation between orphan and ultra-orphan medicinal products has been used for commissioning purposes (mainly because only a few centres within the NHS would deal with these conditions) and maintained over time. When NICE first used the term "ultra-orphan drugs" it defined it as treatments for "conditions occurring in less than 1000 people in the UK" or with a "prevalence of less than 1 in 50,000" (NICE, 2004). The NICE HST programme does not have a formal prevalence cut off point, but in practice has appraised treatments targeting diseases with only a few cases in the UK, i.e. below 1000 people in the UK.

Ultra-orphan conditions represent a subset of orphan conditions and have similar characteristics including debilitating impact on patients (Regulation (EC) No 141/2000 requires that a medicinal product designated as an orphan medicinal product is intended for the diagnosis prevention or treatment of a life-threatening or seriously debilitating condition). However, ultra-orphan conditions often present specific issues, such as a genetic component, onset at birth or at a very young age, and substantial challenges in conducting clinical research, given very small patient populations and presentations of disease that are often heterogeneous. Allowing pharmaceutical companies to recoup their research and development investment for ultra-orphan drugs is more challenging as compared to orphan drugs, given the very small numbers of patients.

We need to look back on recent policy developments in the English NHS to understand why the HST programme was established and why the HST programme, unlike the Technology Appraisal programme (TA), considered:

- cost and savings outside NHS and PSS on a regular basis; and
- a wide range of decision criteria including "impact of the technology beyond direct health benefits" (Brockis et al.; 2016; See also Appendix 3 of this report)

In 2004, NICE was asked by the Department of Health to consider the feasibility of applying the cost effectiveness methodology to appraise ultra-orphan drugs through a pilot study using the case of enzyme replacement therapy (ERT) for Type I Gaucher's disease, a rare metabolic disorder. Although there was a recognition of the high level of uncertainty surrounding evidence for these types of medicines, making it difficult to produce a robust estimate of cost per QALY, NICE indicated that that clinical and cost

effectiveness could in principle be assessed using a standard approach. It was emphasised, however, that, given the price of ERT, even if full health was restored, the treatment could not be cost effective if the conventional threshold of £20,000 to £30,000 per QALY was applied. The conclusion was that if NICE were to appraise ultra-orphans, there would be a need for:

- clear directions from DH on criteria to make decisions;
- the setting up of a separate NICE Committee to appraise these treatments (NICE, 2004).

The NICE Citizens Council reinforced these findings by indicating that although cost effectiveness should be evaluated, premium prices for these treatments could be justified. The majority of participants thought that:

"the NHS should consider paying premium prices for drugs to treat patients with very rare diseases. The main criteria that the Citizens Council thinks the NHS should take into account when deciding to pay premium prices for ultra-orphan drugs are, in descending order of importance":

- *The degree of severity of the disease*
- *If the treatment will provide health gain, rather than just stabilisation of the condition*
- *If the disease or condition is life-threatening"* (NICE Citizens Council, 2004).

Following the pilot study, the Department of Health took the decision that NICE should *not* appraise ultra-orphan drugs. The Department of Health did not explain its decision. However this might have been because there was a recognition that ultra-orphans would not fit into the traditional cost-per-QALY route and NICE did not want to compromise its remit by developing an alternative route.

Funding decisions on treatments for very rare conditions therefore stayed within the remit of the National Commissioning Group until 2009 when the Advisory Group on National Specialised Services (AGNSS) was set up. The role of AGNSS, among other things, was "considering a small number of highly specialised new drugs and technologies that are not suitable for consideration by NICE" (Godfrey, 2012). The methodology used by AGNSS did not involve a standard assessment of cost-effectiveness or application of a cost per QALY limit, beyond which products would not be recommended. The key features underpinning the AGNSS approach were: a holistic decision making framework including 10 criteria (Appendix 2 shows a pictorial representation of the framework), and a participatory process closely involving stakeholders (industry, patient groups, NICE, Department of Health, and clinical experts). A pilot study appraising an existing treatment, idursulfase for Hunter syndrome, was conducted between 2010 and 2011. Key learnings emerging from the pilot pointed out the importance of considering all criteria, including wider benefits to patients, families and carers, and how the different criteria interact in order to reach funding or commissioning decisions (Godfrey, 2012).

With the reorganisation of the NHS under Andrew Lansley, AGNSS was abolished. NICE took over AGNSS's responsibilities from 2013. The AGNSS principles were maintained and reflected in NICE's interim method and process guide for HSTs (NICE, 2013b). Behind the establishment of a separate programme, there was a recognition of three types of problem.

Firstly, the challenges faced by the developers to generate evidence in the context of very rare diseases, due to:

- small and heterogeneous populations, which make it difficult to recruit and identify trial participants;
- lack of epidemiological data and natural history data;
- lack of validated endpoints to predict long term effects;
- lack of consensus on comparators (Annemans et al. 2017).

The absence of data leads to the:

- need to extrapolate from other similar diseases areas; and
- difficulty in validating many of the assumptions that have to be made.

All these aspects are inherent to rare conditions in general, but are particularly acute in the context of very rare conditions, leading to a high level of uncertainty in the evidence available at the time of the appraisal. This makes a case for not using the standard approach to uncertainty (in effect to use the higher end of the cost effectiveness threshold range or to otherwise reduce the willingness of the Committee to approve the technology in some way).

Secondly, there was a recognition that conventional cost effectiveness methods could not be applied because small population sizes meant that companies, particularly small and medium size enterprises, could not recover their research and development costs and earn a return on investment at the base cost-per-QALY threshold.

Thirdly, very rare conditions have some recurrent characteristics (beyond the number of patients affected) which need to be considered as decision criteria. These are reasons why the use of the QALY has to be modified by other decision criteria reflecting social values. These characteristics are partially embedded in the regulatory definition of orphan drugs provided by Regulation (EC) No 141/2000, which provides that they have to be:

- "for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating"[3]; put another way, these conditions are "severely disabling and can reduce life expectancy and impair physical and mental ability" (Annemans et al. 2017).
- "no satisfactory method of diagnosis, prevention or treatment of the condition concerned can be authorised, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition"[3]. This means that in many cases patients do not have effective or disease-modifying treatments and their conditions are managed with interventions relieving their symptoms.

What the Regulation does not state is that many rare conditions affect infant and young patient populations, that they often affect multiple organs and are difficult to manage, which gives rise to other negative consequences. There are substantial burdens on caregivers who are usually family members forced to reduce or give up their roles at work to provide care. In addition, given the complexity of some of these conditions, carers have to devote substantial time, and sometimes money, to deal with different parts of the social and health system providing support to the patient. An international study found that the annual cost of supporting a patient with Duchenne muscular

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[3] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000029.jsp

dystrophy exceeded $120,000. Less than half were direct medical costs (Landfeldt et al., 2014).

The 2013 HST Interim Methods Guide (NICE, 2013b) had various limitations including the lack of detailed explanation on how uncertainty should be dealt with by the Appraisal Committee. Nevertheless, it maintained, in principle, the spirit underpinning the AGNSS holistic framework. The decision-making criteria stated in the guide were:

- Nature of the condition
- Impact of the new technology
- Cost to the NHS and Personal Social Services
- Value for money
- Impact of the technology beyond direct health benefits
- Impact of the technology on the delivery of the specialised service

NICE decisions on ultra-orphan drugs to February 2017

Using the Interim Methods Guide (NICE, 2013b), NICE HST programme issued recommendations on four treatments up to June 2017[4] (NICE (2015a), NICE (2015b), NICE (2016), NICE (2017c)), respectively. A summary of the aspects considered by the Committee and reported in the guidance for the four treatments are presented in the Table at Appendix 4. Key issues to note are:

- all the four conditions considered affect children; two of them have onset from or before the age of three;
- there was substantial uncertainty on the actual number of affected patients in England and the rate of uptake of the treatment following the guidance implementation;
- in all four cases, NICE's Evaluation Committee recognised that there were substantial benefits not captured by the conventional HRQoL measure of the QALY. In HST 4, migalastat could help to address some of the standard of care (ERT) limitations because it is an infusion. These are not fully captured in the QALY. In HST 2 it was noted that "evidence on QoL was limited, and was synthesised using methods that had not been fully developed or validated." This reflects the fundamental challenges in measuring QoL of some very rare conditions where no previous research is available;
- while the decisions by the Evaluation Committee took into account a range of factors, QALYs were calculated; however the Committee or its advisory Evidence Review Group (ERG) concluded that only one of the four treatments was

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[4] This report was wrote and submitted in June 2017. Since then, guidance on three treatments have been issued: Eliglustat for treating type 1 Gaucher disease, Asfotase alfa for treating paediatric-onset hypophosphatasia, and Strimvelis for treating adenosine deaminase deficiency– severe combined immunodeficiency. The first two guidances do not seem to apply the changes to the interim method guide (i.e. the use of the £100K per QALY threshold and potential weights). They were both recommended, as were the previous four interventions considered in this report. Strimvelis was the first intervention to be appraised using the new methods and it was recommended on the ground of cost effectiveness (applying the threshold uplift given the large QALY gains) and the consideration of "wider benefits" not included in the economic model. We note that the manufacturer of this intervention has publicly stated that this highly innovative technology (one of the first examples of gene therapy) has not been priced at a normal commercial rate (https://www.fiercepharma.com/pharma/gsk-promises-bubble-boy-gene-therapy-will-not-break-bank-as-new-pricing-model-revealed). We don't think that the consideration of these three additional interventions impacts the relevance of our argument, which is focused on the use of QALY to capture all the benefits generated and the evidence (or the lack of) to set a cost effectiveness threshold for HSTs.

associated with large health gains using NICE's new measure of at least 10 incremental QALYs. Eculizumab for treating atypical haemolytic uraemic syndrome had an incremental QALY gain of 10.14, as calculated by the ERG[5]. The Committee did not express a view as to where they believed the correct QALY gain lay, but stated that the overall health gains were "of a magnitude that is rarely seen for any new drug treatment". For all other treatments the ERG calculated incremental QALYs gained below 10. The lowest gain was in the case of migalastat for Fabry disease, generating 0.34 to 0.98 incremental QALYs;

- wider societal benefits were deemed as substantial in all cases, although they were not quantified. These benefits included allowing young patients to take part in education; "parents and carers staying in work for longer"; and "cost savings from personal expenses for patients and carers for transportation and housing".

5. ISSUES RAISED BY THE 2017 CHANGES FROM A HEALTH ECONOMICS PERSPECTIVE

The changes to the HST methodology introduced from April 2017 (NICE, 2017a) may be summarised as:

- The use of a standard cost-effectiveness methodology involving calculation of incremental QALYs and the associated cost per QALY gained;
- The application of a £100,000 cost per QALY threshold over which HSTs will not generally be recommended by NICE;
- A weighting system for QALYs produced by HSTs which generate more than 10 incremental QALYs over the time horizon of the disease, so that HSTs producing total incremental QALYs of 11-29 will be weighted between 1 and 3 (applying equal increments) and HSTs producing 30 QALYs or more will be weighted 3 times.

To assess the appropriateness of these changes, we refer back to the key issues of the conventional QALY-based cost effectiveness approach outlined in Section 3 of this paper. It could be argued that the introduction of a cost-per-QALY threshold of £100,000 recognises that in the context of very rare diseases, a premium price should be paid to reflect (i) elements of health gain not well captured in the QALY (ii) additional benefits of care not reflected in the QALY (iii) the social value of a QALY in this disease setting (a QALY is not a QALY). However, it is unclear what the rationale (both theoretical and empirical) is for adjusting the base threshold from £20,000 to £100,000, rather than some other figure.

In addition, the updated HST Interim Process and Methods guide, which incorporates at paragraph 46 the changes referred to above, does not recognise the need to adjust the standard methodology for handling uncertainty. It seems to be similar to that for conventional NICE appraisals, as explained in this paragraph:

"When the estimated ICERs presented are less than £100,000 per QALY gained but the Committee judges that particular interventions should not be recommended the guidance will make specific reference to the Committee's view on the plausibility of the

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[5] In this report we focus on the estimates provided by the ERG as representing an independent assessment of cost effectiveness.

inputs to the economic modelling and/or the certainty around the estimated ICER. This might be affected, for example, by sensitivity analysis or limitations to the generalisability of findings regarding effectiveness" (NICE 2017a, paragraph 51).

There will inevitably be greater uncertainty in the area of Highly Specialised Technologies, which might make it more difficult to the Appraisal Committee to exercise their judgments consistently across decisions. In addition, uncertainty should only be relevant to decision making if it can be reduced by, for example, collecting more evidence, or by using a different payment mechanism (for example paying only for successful treatment outcomes.) This issue is discussed in Barnsley et al. (2016) and Marsden and Towse (2017).

The question as to the social values that should be considered in decision making, is only partially addressed. The additional weights which might be applied to the threshold (to be further raised from £100,000 to a maximum of £300,000) are exclusively based on the size of the therapeutic improvement as measured in QALYs. As empirical evidence and, previously, the NICE Citizen Council has pointed out, this should only be one of the decision criteria in the context of rare conditions. The importance of criteria such as the seriousness of illness is supported by several studies, as shown in a review by Shah (2009). Recommendations of a European working group on rare disease involving multiple experts, including the NICE HST Director, emphasise the substantial burden of these conditions not only on the patients but also on their families and carers (with a reduced ability to work). They conclude that a societal perspective should be taken when assessing the value of orphan drugs (Annemans et al. 2017).

In summary, while in the past NICE and other bodies (such as AGNSS) have recognised that use of a standard QALY based methodology alone is unsatisfactory when applied to HSTs, the new methodology introduces such a threshold as the value for money criterion without addressing its deficiencies and without explanation for its change of view.

Alternative methods, which have been suggested in the literature and in the policy debate, should have been considered (Garau and Devlin, 2017; Devlin and Sussex, 2011; Paulden et al. 2015). A recent consultation of health economics experts indicated that there was support for the view that HTA should go beyond cost effectiveness and other decision making should be incorporated, such as severity (Karlsberg Schaffer et al, 2016). Therefore, there is a need to determine:

- a broad decision criteria framework based on the one used by AGNSS and potentially others in the literature;
- societal and patient preferences across the selected criteria to understand how trade-offs are made and explicitly to take them into account in decision making;
- a decision making rule or hurdle for adoption which incorporates these factors to provide the basis to judge value for money and inform funding decisions.

Clearly the NHS needs to make choices about the Highly Specialised (and other) Technologies it should make available from limited resources, and value-for-money is, and should be, one of the criteria NICE considers in the HST process. However, an appropriate process would need to take account of:

- a composite measure of benefit embracing multiple criteria;
- determination of a cut-off point based on previous decisions (revealed preferences) or an exploration of societal preferences or willingness to pay for elements of value.

An alternative approach would be to inform the threshold by reference to population size. The prime reason why ultra-orphan drugs have a high price is because of small patient numbers over which companies need to recover research and development costs and earn a return. The threshold could be adjusted to reflect the (typical) difference between the population size of a conventional therapy and an HST. This would have the objective to recognise that companies need to earn similar returns on HST drugs as on conventional therapies if there is evidence showing that the society is willing to encourage companies to develop such treatments.

6. SUMMARY AND CONCLUSIONS

In 2004 NICE was asked to look at taking on the appraisal and assessment of ultra-orphan drugs but was reluctant to do so as it could not see how it could run a programme in parallel to its mainstream Technology Appraisal programme operating to very different decision criteria. From 2013 it was given no choice by Ministers. Accordingly it set up a process that mirrored that developed by AGNSS, i.e. it adopted a framework, rather than developing its own. As external observers, it seems to us to have managed that process successfully through four HST appraisals. Given the importance of non-QALY elements in the assessment of HSTs, it does not seem appropriate for it now to move to a simple cost-per-QALY measure.

Further, any threshold needs to have some sort of empirical basis. A multiple of five times the basic threshold is arbitrary, as is a further possible uplift up to a factor of three. As indicated above, the patient populations eligible for treatment with products undergoing standard technology appraisal are typically far greater than five times the size of those who may receive treatment with HSTs and there is no explanation how the current £100,000 per QALY threshold captures this. An empirical basis for an HST threshold could be generated by looking, for example, at social preferences over treating patients with very rare conditions, or at the typical scale of the impacts beyond direct health benefits, or at the adjustments for low patient numbers that might have to be made to enable pharmaceutical companies to get a return on investment from HSTs.

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https://www.ohe.org/publications/comparing-access-orphan-medicinal-products-omps-united-kingdom-and-other-european

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	❏
I have some problems in walking about	❏
I am confined to bed	❏

Self-Care

I have no problems with self-care	❏
I have some problems washing or dressing myself	❏
I am unable to wash or dress myself	❏

Usual Activities *(e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities	❏
I have some problems with performing my usual activities	❏
I am unable to perform my usual activities	❏

Pain / Discomfort

I have no pain or discomfort	❏
I have moderate pain or discomfort	❏
I have extreme pain or discomfort	❏

Anxiety / Depression

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[6] UK (English) © 1990 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

I am not anxious or depressed ❑

I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Best imaginable
health state

100

9 0

8 0
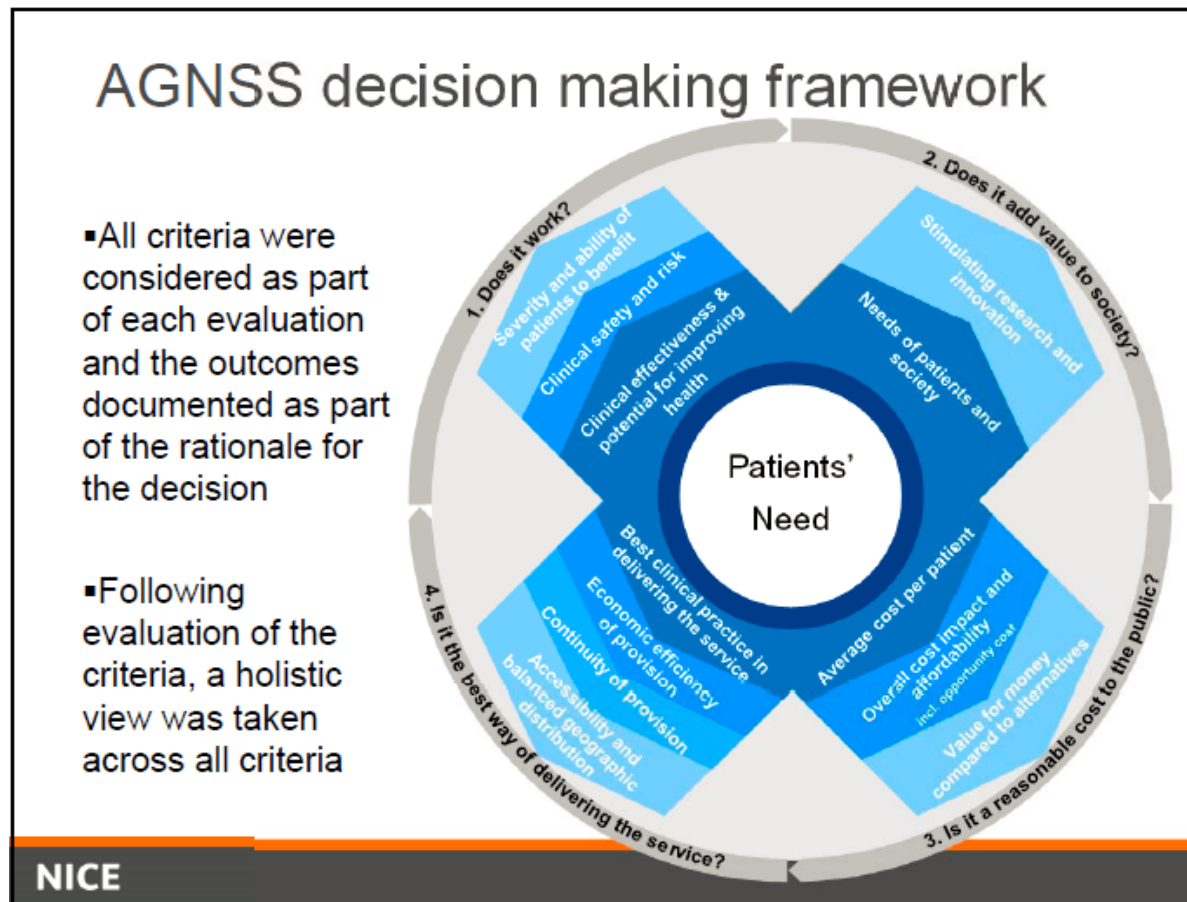
7 0

6 0

5 0

4 0

3 0

2 0

1 0

Worst imaginable
health state

2 1

0

APPENDIX 2: AGNSS DECISION MAKING FRAMEWORK

Source: Godfrey J (2014). What is the best way to use MCDA in HTA? Presentation at ISPOR 2014. Available at
https://www.ispor.org/meetings/montreal0614/presentations/IP3-Godfrey.pdf

APPENDIX 3: TABLE OF METHODS OF EVALUATION AND DECISION MAKING USED IN EACH OF NICE'S HTA PROGRAMMES

	Technology Appraisal Programme	Medical Technologies Guidance	Diagnostics Assessment Programme	Highly Specialised Technology Programme	Clinical Guidelines
Reference case	✓	✗	✓	✗	✓
Perspective					
Outcomes	Health effects for patients and, when relevant, carers	Clinical and system outcomes	Health effects for patients or, when relevant, other people (principally carers)	Health effects to patients and, when relevant, carers.	Health effects for those using services, and, where relevant, family and carers Non-health benefits may also be included
Costs	NHS and PSS	NHS and PSS	NHS and PSS	NHS and PSS Impact outside NHS and PSS	NHS and PSS (health outcomes) Public sector and societal perspective (for non-health outcomes/ social care focus)
Clinical effectiveness	✓	✓	✓	✓	✓
Cost effectiveness	✓	✓	✓	✗	✓
Type	CUA	CCA	CUA	n/a	CUA (CEA, CCA, CBA, CMA if non-health outcomes)
Decision making criteria	Clinical effectiveness Cost effectiveness	Benefits to patients over current technologies. Benefit to NHS in terms of reduced burden on NHS staff and resources compared with current management	Quality of evidence Diagnostic test accuracy Clinical effectiveness Cost-effectiveness	Nature of condition Impact of the new technology Cost to the NHS and PSS (including budget impact in NHS and PSS) Value for money Impact of the technology beyond direct health benefits The impact of the technology on the delivery of the specialised service (staffing and infrastructure)	Quality of evidence Trade-off between benefits and harms of intervention Trade-off between economic considerations and resource use Availability of evidence to support implementation Size of effect and potential impact on population health Wider basis (e.g. ethical issues, social value judgements, equity and inequalities, policy imperatives, equality legislation) Equality considerations

					"NICE social value judgements usually take precedence over economics"
Budget impact determined	✓	✓	✓	✓	✓
Sensitivity analysis	✓	✓	✓	Not stated	✓

Source: Brockis et al. (https://www.ohe.org/publications/review-nice-methods-across-health-technology-assessment-programmes-differences)

NICE (2011a), NICE(2011b), NICE(2011c), NICE(2011d*), NICE(2011e*), NICE (2013a), NICE (2013b), NICE (2013c), NICE (2015a), NICE (2015b), NICE (2015c).

APPENDIX 4: TABLE OF NICE HST APPRAISALS PUBLISHED BEFORE JUNE 2017 AND THE CRITERIA CONSIDERED

Reference	Title	Decision	Number of patients	Nature of the condition	Does the disease occur in children?	Availability of other treatment options	Cost to the NHS and Personal Social Services	HRQoL evidence	Incremental QALYs compared to SoC (ERG, or Committee estimate)	Value for money	Impact beyond direct health benefits and on the delivery of the specialised service
HST 1	Eculizumab for treating atypical haemolytic uraemic syndrome	Recommended subject to a number of conditions for use	20–30 per year in England (newly diagnosed)	Patients have a greatly impaired quality of life, from both the severe symptoms they experience and the burden of treatment with dialysis and plasma therapy, and that the families and carers of patients with aHUS also experience substantial burden. Onset occurs in childhood more frequently than in adulthood	Yes. 60% of all cases (in 70% of these patients the disease presents at under age 2 years)	Plasma therapy and dialysis were the main treatment options, both of which have limited impact on disease morbidity and mortality but a substantial negative effect on a patient's quality of life.	The budget impact of eculizumab was substantial and likely to increase with the onset of new cases (potentially ranging from £36 million in the first year to £68 million in year 5)	The Committee concluded that other benefits of a substantial nature were not adequately captured in the model	10.14 QALYs	While there is no specific budget for the provision of highly specialised services in the NHS in England, it remained uncertain on whether the results of the cost–consequence analysis demonstrated good value for money	Non-health effects were likely to be substantial but proportionate to the health effects. They include ability to contribute to society or continue education, and cost savings from personal expenses for patients and carers for transportation and housing
HST 2	Elosulfase alfa for treating mucopolysaccharidosis type Iva	Recommended with MAA and PAS	88 people in England, and about 3 new diagnoses made per year	MPS IVa is a serious condition that severely affects life expectancy and quality of life and leads to dramatic effects on the lives of	Yes. More than 70% of people presenting before age 3 years	There were no treatments that address the underlying disease.	Budget impact of £17.3 million in year 1 to £28.8 million in year 5 (before commerical agreement)	There are additional challenges in caring for people who are dependent on a wheelchair	5.04 QALYs	Concerns about the true value for money provided by elosulfase alfa (mitigated by conditions in MAA and PAS)	The Committee understood that elosulfase alfa may provide important benefits to patients and their families in addition to the direct health

Reference	Title	Decision	Number of patients	Nature of the condition	Does the disease occur in children?	Availability of other treatment options	Cost to the NHS and Personal Social Services	HRQoL evidence	Incremental QALYs compared to SoC (ERG, or Committee estimate)	Value for money	Impact beyond direct health benefits and on the delivery of the specialised service
				people with the condition and their families and carers.				(in addition to those captured in the model). Evidence on QoL was limited, and was synthesised using methods that had not been fully developed or validated.			benefits of treatment. These include mental health and education benefits
HST 3	Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene	Recommended with MAA and PAS	NA	DMD is a serious, progressive condition that reduces life expectancy and causes debilitating symptoms associated with loss of muscle strength that severely affect the quality of life of people with the condition, and their parents and siblings.	Yes. Dystrophin production affected from birth and symptoms appear by age 3 years	Corticosteroids, which are associated with delay in loss of walking but significant adverse effects	Budget impact of £8.6 million in year 1, rising to £16 million in year 5 (before PAS)	By increasing the disutility faced by caregivers, the company's model partially reflect the impact of the condition and ataluren on the patient and caregivers' quality of life.	2.03 QALYs	The potential benefits associated with ataluren treatment were great enough to justify its high cost when the PAS and MAA were applied.	Wider societal benefits included ability to contribute to society, continue education and spend more time with friends and family. The potential cost savings include parents and carers staying in work for longer, a reduction in out-of-pocket expenses for travel to appointments and delaying moving house or making home

Referenc e	Title	Decision	Number of patients	Nature of the condition	Does the disease occur in children?	Availability of other treatment options	Cost to the NHS and Personal Social Services	HRQoL evidence	Increment al QALYs compared to SoC (ERG, or Committe e estimate)	Value for money	Impact beyond direct health benefits and on the delivery of the specialised service
											modifications.
HST 4	Migalastat for treating Fabry disease	Recommend ed with PAS and only if enzyme replacement therapy (ERT) would otherwise be offered	855 people with Fabry disease in England, 142 of which would be eligible for migalastat	Progressive condition that causes a variety of symptoms, and can greatly affect quality of life and can reduce life expectancy	Age of onset is variable but it includes young populations	Enzyme replacement therapy (ERT; agalsidase alfa or agalsidase beta) every 2 weeks, or supportive care to manage the symptoms and complications . n inconvenient dosing schedule every 2 weeks causing variation in enzyme levels, risk of infusion-related reactions and infections and the possibility of developing antibodies against treatment.	Budget impact analysis showed that migalastat would be associated with savings for the NHS, compared with ERT. Estimates not available	There were a number of limitations of ERT because it is an infusion, and migalastat may help to address some of these limitations and so have additional benefits beyond direct health benefits.	0.34 to 0.98 QALYs	Migalastat provides additional health benefits at a lower cost compared with ERT, but the size of any additional benefits was highly uncertain. NICE has not evaluated ERT so the value for money of migalastat is uncertain	As an oral therapy, migalastat may help to address some of these limitations and so have additional benefits beyond direct health benefits. The company presented infusion disutilities to capture this. Additional savings from the reduced need for homecare were also captured in the model.

Abbreviations:

ERG: Economic Review Group

MAA: Managed Access Agreement

PAS: Patient Access Scheme

HRQoL: health-related quality of life

SoC: Standard of care

Sources: NICE (2015a), NICE (2015b), NICE (2016), NICE (2017c)