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Summary

Rare (or orphan) diseases are serious health conditions that affect a small number of people. The European Medicines Agency (EMA) defines rare diseases as life-threatening or chronically debilitating conditions that have a prevalence of fewer than 5 cases per 10,000 population (Smith, 2015). Ultra-rare conditions affect an even smaller number of persons, often defined as less than 1 case per 50,000 population (Pant and Visintini, 2018). Despite the low numbers of persons with any specific disease, rare and ultra-rare diseases occur in up to 4% of births and affect 6-8% of the population in the EU, or around 27-36 million people (European Medicines Agency, 2018). In the UK, this is equivalent to around 4-5 million people.

Treatments for many rare and ultra-rare conditions are available and more are being developed, but there are a number of economic and ethical challenges in development and evaluation of medicines for these conditions that are distinct from those faced by medicines for more common conditions. A recent study examined access to orphan medicines across Europe and found that less than half of all EMA-authorised orphan drugs were routinely funded by the NHS and that the UK had the longest mean time between marketing authorisation and HTA recommendation (Zamora et al., 2019). We reviewed the literature to enumerate these issues, particularly in the context of the National Institute for Health and Care Excellence's (NICE's) appraisal of medicines for ultra-rare conditions.

The primary economic challenge is that, by definition, medicines for ultra-rare conditions are developed for very small patient populations and therefore commercialising the technology under standard value criteria is unlikely to generate sufficient revenues to cover the costs of research and development. In the absence of satisfactory economic incentives, the industry has little incentive to develop or market medicines for ultra-rare conditions. To compensate for this, a higher Cost-Effectiveness Threshold (CET) is warranted for ultra-rare medicines. This, however, implies that health outcomes in these conditions are deemed more valuable than health outcomes in more common conditions for which the CET is set lower. This prioritisation of outcomes in ultra-rare conditions over outcomes in more common conditions, requires specific ethical justifications, presenting additional challenges to medicines for ultra-rare conditions.

Publicly funded systems like the National Health Service (NHS) are typically organised around utilitarian principles or *the greatest good for the greatest number*. However, exceptions to this principle and greater priority for ultra-rare diseases can be justified by egalitarian principles given the inequality in access to medicines and health outcomes that these patients face. Egalitarian principles favour the allocation of resources in a way that improves the outcomes or the wellbeing of the least well-off (Gericke, Riesberg and Busse, 2005). Under these principles, guaranteeing a premium for ultra-orphan medicines is justified as long as it reduces inequalities between persons with ultra-rare conditions and those with more common conditions. Rights-based principles such as the *right of non-abandonment* and the *right to a minimum standard of care* would also support paying a premium for medicines for ultra-rare conditions.

These challenges appear to be implicitly acknowledged by NICE through the establishment of its Highly Specialised Technology (HST) appraisal route for medicines for ultra-rare conditions. This process is separate from its standard Single Technology Appraisal (STA) process and allows the evaluation of ultra-rare conditions' medicines against a substantially higher cost-effectiveness threshold – up to £300,000 per quality-adjusted life year (QALY) gained. Despite this tacit acknowledgement, however, there are concerns that the HST process does not fully address inequalities in access and health outcomes, primarily due to vague eligibility criteria for HST appraisal that have the potential be applied inconsistently. This vagueness means that some medicines for ultra-rare conditions are maybe appraised via the STA process against the conventional £20-30,000

per QALY threshold rather than the higher HST threshold. This duality has the potential to exacerbate inequalities and undermines the original rationale for a separate HST process. In addition, this process does not always acknowledge the difficulty of generating robust clinical and economic evidence in ultra-rare conditions, or the tension between generating the highest quality evidence and providing rapid patient access to new medicines. Finally, medicines that are licensed for more than one indication are excluded from the HST process if its use is not solely within the context of a specialised service. This, however, disregards the challenges of data generation and technology appraisal in the context of ultra-rare indications that still exist, regardless of the other indications for which a medicine may be licensed.

Key messages:

- Most medicines for ultra-rare conditions require exceptional economic incentives to encourage continuing research and development in them, as means to compensate for very small patient populations and therefore limited revenue potential under conventional value criteria. These incentives are typically in the form of a higher cost-effectiveness threshold (CET) for health outcomes in ultra-rare conditions.

- Paying a premium for health outcomes in ultra-rare conditions can be justified by egalitarian principles that would seek to reduce inequities and inequalities in access to new medicines and in health outcomes between persons with ultra-rare conditions and those with more common conditions.

- NICE's Highly Specialised Technologies (HST) appraisal process tacitly acknowledges these challenges and justifications but does not always succeed in addressing them due to vague eligibility criteria for HST review that may be inconsistently applied.

- The vague eligibility criteria mean that some medicines for ultra-rare conditions may be appraised against the conventional NICE threshold of £20-30,000 per QALY gained rather than the higher HST threshold. This duality has the potential to exacerbate inequalities and undermines the original rationale for a separate HST process.

- Medicines that are licensed for more than one indication are excluded from the HST process if its use is not solely within the context of a specialised service. This, however, disregards the challenges of data generation and technology appraisal in the context of ultra-rare indications that still exist, regardless of the other indications for which a medicine may be licensed.

- From the literature, it can be said that whilst in principle NICE's HST programme offers an important route to patient access for ultra-orphan medicines, there is significant potential for improved clarity and consistency regarding the criteria and methods applied.

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1 Introduction

Broadly defined, a rare (or orphan) disease is a health condition that affects a small number of people relative to more prevalent conditions that affect the general population (Richter et al., 2015). In the European Union, the European Medicines Agency (EMA) defines rare diseases as life-threatening or chronically debilitating conditions that have a prevalence of less than 5 in 10,000 individuals (Smith, 2015). Ultra-rare conditions affect an even smaller number of persons. Based on an environmental scan conducted by the Canadian Agency for Drugs and Technology in Health, the most common prevalence threshold for an ultra-rare condition is less than 1 in 50,000 persons (Pant and Visintini, 2018). In the UK, the National Institute for Health and Care Excellence (NICE) does not explicitly define a prevalence threshold for ultra-rare conditions but has used the term for diseases affecting less than 1,000 people in England and Wales, implying a prevalence threshold of 0.85 per 50,000, based on a combined population of 59 million (National Institute for Health and Care Excellence, 2004). In addition to prevalence, definitions of rare and ultra-rare conditions tend to include qualitative consideration of their impact, as in the EMA definition above.

According to Orphanet[1], there are approximately 6,000−8,000 rare diseases, and more than 250 new rare diseases are described in medical literature each year. These diseases are often serious, hereditary disorders, many of which appear in childhood and affect health over the patient's entire, and often shortened, lifetime (National Institute for Health and Care Excellence, 2004). Despite the low numbers of persons with any specific disease, rare and ultra-rare disease occurs in up to 4% of births and affect 6-8% of the population in the EU, or around 27-36 million people (European Medicines Agency, 2018). In the UK, this is equivalent to around 4-5 million people. In this sense, the aggregate impact of rare and ultra-rare diseases is substantial.

Treatments for many rare and ultra-rare conditions, often known as orphan medicines, are available and innovative new treatments are continually being developed. However, the unique circumstances of these medicines mean that they are likely to present economic and ethical challenges to health system decision-makers distinct from those encountered by treatments for more common conditions. This is especially true of treatments for ultra-rare conditions, where the challenges of rarity are magnified to a greater degree.

To elucidate the economic and ethical challenges associated with medicines for ultra-rare diseases, we conducted a literature review in the context of health technology assessment (HTA) using a 'pearl growing' search strategy based around key references in this area. We identified additional references by searching the bibliographies of the key references (backward searching) and for articles citing the key references (forward searching) using Web of Science.

In what follows, we provide a narrative summary of the results of this review. This summary is organised into three broad sections: 1) ethical arguments for and against special priority for ultra-orphan medicines; 2) the different appraisal processes for ultra-orphan medicines; and 3) why standard appraisal processes, designed for medicines for more common conditions, may not be appropriate for ultra-orphan medicines.

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[1] *List of Rare Diseases by Orphanet:*
http://www.orpha.net/orphacom/cahiers/docs/GB/List_of_rare_diseases_in_alphabetical_order.pdf

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2 Economic and ethical challenges

Medicines for ultra-rare conditions, by definition, treat a condition whose prevalence (and therefore potential market) is so low that, in absence of appropriate incentives, commercialising the technology under standard value criteria is unlikely to generate sufficient revenues to cover the costs of development and marketing (Côté and Keating, 2012; European Medicines Agency, 2018). This is reflected in EMA's definition of an orphan medication as one where it is unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development (European Medicines Agency, 2018). This need for additional economic incentives beyond the standard market mechanisms available to medicines for more common conditions represents the key economic challenge of ultra-rare medicines.

In economic terms, manufacturers typically need to charge a higher price for medicines for ultra-rare diseases to achieve a Rate of Return (RoR) comparable to medicines for more common conditions. As economic theory predicts that investment decisions will be driven by expected RoR, health systems must 'incentivize' R&D into medicines for ultra-rare diseases if they wish to ensure a 'socially optimal' level of investment across all conditions, including ultra-rare diseases. Such incentives, however, imply the payment of a premium for health benefits that accrue to patients with ultra-rare diseases compared to health benefits for patients with more common conditions. This premium requires specific ethical justification, further complicating the appraisal of medicines for ultra-rare conditions. These ethical considerations are discussed in the next section.

Is there an ethical case for prioritising ultra-orphan medicines?

Ethical support for prioritising health outcomes in ultra-rare diseases over outcomes in more common conditions is mixed, owing to different interpretations of distributive justice and different social welfare functions that are described in the economic literature. The key ethical arguments in this context are utilitarianism and egalitarianism, along with rights-based arguments such as non-abandonment and a minimum level of care.

Utilitarian theories of distributive justice are based on the notion that societal well-being is based on bringing "the greatest good to the greatest number" and usually forms the basis of economic evaluation (Hughes, Tunnage and Yeo, 2005). NICE's cost-effectiveness threshold approach to decision-making is based on utilitarian principles; under this framework, priority is a function of the efficiency with which health care spending can be converted into health outcomes. NICE typically measures these outcomes in terms of quality-adjusted life years (QALYs), which combine information on changes in the quality and the quantity (length) of life. In principle, the lower the cost per QALY gained associated with a particular treatment, the greater the priority, or perceived societal value, of that treatment. However, there is increasing evidence that the societal value of health gains to different patients depends on factors beyond the 'efficiency' with which healthcare resources can be translated into health outcomes. This is discussed in more detail below.

Health economic principles generally hold that the cost-effectiveness threshold should represent the cost to the healthcare system of producing one additional QALY. This is known as the marginal cost per QALY. Paying more than this cost-effectiveness threshold means that fewer QALYs are generated with the available funds than could have been generated if the resources were used in the most efficient manner. Any gap between the actual and potential QALY gains is known as opportunity cost. In the context of incentivising ultra-rare medicines, it means that paying a premium over and above the marginal cost of a QALY reduces potential QALY gains and introduces an opportunity cost associated with these financial incentives. Therefore, under strict utilitarian methods, it is unlikely that ultra-orphan medicines will be routinely funded if they are held to the same

cost-effectiveness threshold as medicines for more common conditions. As noted, these medicines are associated with small patient populations and relatively low demand compared to more common diseases and therefore tend to be more expensive to develop on a per-patient basis than medicines for more common (higher demand) conditions (Côté and Keating, 2012). Given this inherent disadvantage, some have proposed that using standard NICE processes to even evaluate such medicines is pointless and that these evaluation resources could be used more efficiently elsewhere (Drummond and Towse, 2014; Cowles et al., 2017).

In contrast, egalitarian principles advocate allocating resources so as to reduce inequalities and therefore favour the allocation of resources in a way that improves the outcomes or wellbeing of the least well-off (Gericke, Riesberg and Busse, 2005). As described by Daniels (1990), egalitarianism is willing "to forego delivering a greater benefit to someone who is already better off in order to deliver a lesser benefit to someone who is worse off." To the extent that higher costs and disadvantageous access to new medicines leads to inequalities in outcomes for persons with ultra-rare diseases, egalitarian principles would support special priority on the basis of rarity to address these inequalities. Under egalitarian principles, paying a premium for ultra-orphan medicines would be justified if it helped to reduced inequalities between persons with ultra-rare conditions and those with more common conditions. Outcome egalitarianism can also be seen in the 'fair innings' argument, which suggests that healthcare resources should be distributed so as to prioritise those individuals who have the greatest shortfall from a 'normal' life span in terms of quality and quantity (Williams, 1999). Consistent with the EMA's definition of ultra-rare diseases as life-threatening or chronically debilitating conditions, the fair-innings argument would seem to imply that ultra-orphan medicines deserve priority on the grounds that they often disproportionately affect children and have a substantive impact on normal, healthy lifespans.

Similar to egalitarian principles, the right of non-abandonment holds that society should not abandon individuals who are suffering from a serious condition and that social justice requires treating everybody with dignity and respect as a human being (Simoens, 2011). Denying treatment to persons with ultra-rare diseases solely on the basis of cost is clearly inconsistent with this principle. Likewise, the right to a minimum level of health care holds that "social solidarity requires that all members of the society have access to a decent minimum standard of healthcare because it is the right and fair thing to do." (Zelei et al., 2016). This argument is seen in the European Union (EU) Regulation (EC) No 141/2000 on orphan medicinal products (OMPs) which states that *"patients suffering from rare conditions should be entitled to the same quality of treatment as other patients",* and is similar to egalitarian arguments around equality of access.

Finally, there exists evidence that individuals feel significantly greater *altruism* toward persons suffering more severe, uncommon diseases than milder normal ones and that for the case of health they value making sure that treatments are distributed equitably across patients and diseases, rather than ensuring that total health within society is maximized (Jena and Lakdawalla, 2017; Nord et al., 1995).

In addition to ethical arguments, in a publicly funded healthcare system such as the National Health Service (NHS) there must also be a willingness on the part of society to forego some potential health gains in order to give greater priority to those who suffer from ultra-rare diseases (Drummond and Towse, 2014). Most societal preference elicitations in this area do not find strong public support for greater priority for rare conditions (Hughes, Tunnage and Yeo, 2005; Guttman et al., 2008; Desser et al., 2010; Mentzakis, Stefanowska and Hurley, 2011; Linley and Hughes, 2013; Wiss and Levin, 2014; Bourke, Plumpton and Hughes, 2018). However, they do find a preference for treating diseases where there is no alternative treatment available, and for treating more severe diseases (Bourke, Plumpton and Hughes, 2018; Linley and Hughes, 2013; National Institute for Health and Care Excellence, 2004). As ultra-rare conditions are often associated with these characteristics, these preferences can be

seen to support prioritising ultra-rare over less severe conditions or those with more treatment options.

In addition, a NICE Citizen's Council reported that 16 out of 27 members felt that the NHS should, under certain conditions, consider paying 'premium prices' for drugs to treat very rare diseases (National Institute for Health and Care Excellence, 2004). A further 4 members felt that the NHS should pay premium prices for drugs to treat rare diseases under *any* conditions. The remaining seven members felt that funding decisions for an orphan drug should be conducted within the same cost-effectiveness framework as for any other drug.

Finally, Dragojlovic et al. (2015) highlight that "the literature also suggests that most members of the public are (1) not familiar with and do not have pre-existing preferences for the prioritization of orphan-drug funding; and (2) reluctant to engage with scenarios in which the funding of treatments for rare diseases must result in the reduction of care for those suffering from common diseases." They conclude that "these two factors create a significant barrier to using existing evidence about the societal value of treating rare diseases to inform orphan-drug funding policies. Specifically, low familiarity with the issue and use of the 'zero-sum' frame commonly used to describe the policy challenge posed by expensive orphan drugs both lead to choice-avoidance and unstable citizen preferences." Together, this means that the 'top of the head' preferences elicited in most studies may not be reflective of what might be observed following a full public debate on the topic and they suggest that the current evidence regarding citizen preferences for orphan-drug funding policies may not provide solid evidence for policymakers seeking to understand public preferences over the allocation of scarce resources.

3 Appraisal routes for ultra-orphan medicines in England

In England, the National Institute for Health and Care Excellence (NICE) undertakes technology appraisals to review the clinical and cost-effectiveness of new treatments. The majority of technologies are reviewed via a standard route known as the 'single technology appraisal' (STA) process. Technologies appraised via this process are assessed against a cost-effectiveness threshold of £20,000 - £30,000 per QALY gained (National Institute for Health and Care Evidence, 2013). Cancer drugs for which there is limited evidence can benefit from the Cancer Drugs Fund, which allows for patient access whilst additional data is collected (NHS England, 2016). A higher cost-effectiveness threshold of £50,000 per QALY is used if a treatment meets NICE's end-of-life criteria (National Institute for Health and Clinical Excellence, 2009).

NICE also undertakes a separate stream of appraisals parallel to STA's, via the Highly Specialised Technologies (HST) evaluation route. The aim of this alternative route is to evaluate high-cost, low-volume drugs for ultra-rare conditions under a higher cost-effectiveness threshold, implicitly acknowledging economic and ethical justifications for greater priority for ultra-orphan medicines relative to more common conditions. It also acknowledges that establishing the value-for-money of ultra-orphan drugs is not straightforward, particularly with regards to the quality of clinical and economic evidence.

Eligibility for consideration under the HST review process is based on meeting all of the following criteria (National Institute for Health and Care Excellence, 2017):

- The target patient group for the technology in its licensed indication is so small that treatment will usually be concentrated in very few centres in the NHS.

- The target patient group is distinct for clinical reasons.

- The condition is chronic and severely disabling.

- The technology is expected to be used exclusively in the context of a highly specialised service.

- The technology is likely to have a very high acquisition cost.

- The technology has the potential for lifelong use.

- The need for national commissioning of the technology is significant.

A number of these elements are contentious as they do not provide an explicit or consistent standard. For example, the selection criterion relating to the patient numbers is vague and does not explicitly define a maximum prevalence or absolute target population (MAP BioPharma, 2019). The relevant criterion is worded as follows: "The target patient group for the technology in its licensed indication is *so small* that treatment will *usually* be concentrated in *very few* centres in the NHS." This requirement is open to multiple interpretations, as indicated by the italicised segments. Without an explicit threshold, in terms of patient numbers or prevalence rates, decisions around whether medicines should be evaluated via STA or HST could be inconsistent.

In addition, defining a '*clinically distinct patient group*' is not a straightforward task, and it is not clear from the HST criteria what NICE deems to represent 'clinically distinct'. Heterogeneity in disease presentation can make it difficult to categorise and subsequently identify patients with ultra-rare conditions (Nestler-Parr et al., 2018). This is exacerbated by the inexperience of most physicians with ultra-rare conditions. In addition, although patient subgroups may be identified through genotyping, biomarkers or age of disease onset, there is little evidence to suggest that NICE always takes patient subtypes into account when considering relative rarity or 'clinical distinction' as part of their eligibility considerations.

In a recent patient charter conducted by Genetic Alliance, patient representatives felt that explicitly incorporating the number of current treatment centres into the eligibility criteria for HST appraisal may perpetuate existing inequities in the health care system and allow "an artefact of a health system to affect decisions that should be made entirely on the merit of medical need" (Petchey, 2014). The group also felt that further clarification of other criteria was needed; they specifically advocated for the modification of the fourth criteria, arguing that technologies used to treat ultra-rare conditions in a greater number of centres should not be disadvantaged simply because of the distribution of centres. Lastly, the sixth criteria (technology has the potential for lifelong use), could discriminate against one-off curative treatments by inferring that these therapies can be dealt with adequately through other commissioning routes, which may not be the case given the economic challenges of quantifying the health benefits of a curative treatment spread over a lifetime.

There are some concerns in the literature regarding the exclusion of extensions of indications from the HST pathway if the orphan medicine has already been evaluated for its initial indication. From a patient perspective, it was agreed that "repurposing of existing drugs has the potential to address significant unmet need … and should be actively encouraged in health care policy", arguing that excluding new indications creates unnecessary further barriers to patient access (Petchey, 2014).

Under the HST process, medicines are assessed against a baseline cost-effectiveness threshold (CET) of £100,000 per QALY gained, but depending on the magnitude of QALY gains, the HST review can apply a multiplier that weights QALY gains up to three times, effectively extending the threshold to £300,000 per QALY gained. Furthermore, special considerations regarding the innovative nature of the technology, equality concerns and impacts beyond direct health benefits may also be included in the decision.

To date, only 11 medicines have been evaluated since the introduction of the HST programme in 2015; an average of less than 3 per year. In 2018 alone, 27 medicines with orphan designation received marketing authorisation in Europe, 10 of which met the EMA criteria for an ultra-orphan medicine. In addition, none of the HST-assessed medicines was for conditions with a prevalence of more than 1 case in 100,000 (Towse and Garau, 2019). Capacity constraints and ambiguous NICE HST eligibility criteria mean that some drugs that met EMA's ultra-orphan definition were evaluated under conventional STA process, where they will be considered under a less flexible decision-making framework and against much stricter cost-effectiveness thresholds, which would seem to disregard the economic and ethical motivations for the separate HST process. Ultra-orphan medicines are evaluated by NICE against the same thresholds as applied to occurs for more common conditions, with no explicit consideration of rarity or for the challenges associated with appraising medicines for rare diseases.

The process of evaluating ultra-orphan medicines varies between England, Scotland, Wales and Northern Ireland. In Scotland, the Scottish Medicines Consortium (SMC) is responsible for evaluating all new medicines for NHS Scotland. Like NICE, it has a specific appraisal pathway for ultra-orphan drugs, but unlike NICE it includes a specific prevalence threshold among its criteria for consideration (Scottish Medicines Consortium, 2018):

- The condition has a prevalence of < 1 in 50,000 or less in Scotland.,
- The medicine has an EMA orphan designation for the condition and this is maintained at time of marketing authorisation,
- The condition is chronic and severely disabling, and
- The condition is recognised to require highly specialised management.

Submissions by manufacturers for medicines that meet this definition are made available to patients through NHS Scotland for a period of up to three years whilst further data on clinical and cost-effectiveness is collected. After this period, SMC makes a final decision on routine use of the medicine in NHS Scotland based on the final evidence.

In Wales, the All Wales Medicines Strategy Group adopts NICE guidance where available but also appraises additional medicines which are not on the NICE work programme using their own methods. This process includes greater considerations for societal benefit and involvement of the patient and clinical voice (MAP BioPharma, 2019). In Northern Ireland, there is no separate health technology agency and NICE recommendations are adopted.

A comparison of access to orphan medicinal products in Europe found that less than 50% of EMA-authorised orphan medicines were routinely funded by the NHS (Zamora et al., 2019). France and Germany had the highest rates of authorised orphan medicines with national reimbursement status, with 81.1% and 93% respectively. This study also found that the devolved nations of the UK had the longest mean and median times between EMA authorisation and HTA recommendation, whereas in Germany medicines are effectively reimbursed as soon as marketing authorisation is granted. Delays between authorisation and HTA approval shorten the effective period of market exclusivity, whilst longer decision times for orphan and ultra-orphan medicines compared to non-orphan reduce expected returns for orphan medicines. Both have the effect of disincentivising investment and innovation in medicines for rare and ultra-rare diseases, again undermining the objectives of the HST process.

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4 Are standard appraisal processes appropriate for ultra-orphan medicines?

As noted earlier, development costs for medicines for ultra-rare conditions are typically higher than for medicines for more common conditions, at least on a per-patient basis, although there is debate over how often and to what degree this holds across all ultra-orphan medicines (Drummond et al., 2007). In general, higher development costs need to be recouped by the manufacturers from a much smaller patient group, typically through higher prices for orphan and ultra-orphan medicines. These higher prices, even when ultra-orphan medicines deliver benefits similar to those for more common conditions, mean that ultra-orphan medicines are unlikely to meet NICE's standard £20,000-£30,000 cost-effectiveness threshold. Indeed, Nicod et al. (2019) found that around 70% of orphan and ultra-orphan medicines evaluated by NICE or SMC had cost per QALY estimates greater than £30,000.

Berdud, Drummond and Towse (2018) investigated issues associated with orphan drug pricing and assessment and proposed a method to adjust the cost-effectiveness threshold for orphan drugs in a way that promotes efficient and socially-valuable use of limited resources and not deter pharmaceutical companies from investing in the development of drugs for rare diseases. Their method aimed to establish a reasonable price for an orphan drug by adjusting the cost-effectiveness threshold (CET) based on patient heterogeneity, the costs of research and development (R&D) and potential market revenue. One of the underlying sentiments of their method is that orphan drugs should be sufficiently incentivised but, at the same time, the rates of return for investments should not be greater than the industry average. The authors estimate that a reasonable CET for orphan drugs (as defined by EMA) would be £39.3k per QALY and that the adjusted CET for ultra-orphan drugs (defined as a prevalence of less than 1 in 50,000) would be over £900k per QALY. These authors also acknowledge that these thresholds do not necessarily indicate what society should be willing to pay for orphan drugs, but rather represent the maximum allowable price that society would be willing to pay based on a reasonable rate of return.

In addition to the higher costs of developing ultra-orphan medicines, there are related challenges in generating robust clinical evidence. The rarity of the diseases often means that recruiting sufficient patients into a standard randomised controlled trial is difficult and time-consuming (Hughes, Tunnage and Yeo, 2005; Drummond et al., 2007; Nestler-Parr et al., 2018). In part, this is attributed to a lack of clinical awareness of rare diseases and difficulties in recognising and diagnosing less severe presentations of conditions. In addition, a high degree of inter-individual variability is often seen in rare diseases, sometimes even within families with multiple affected children presumably all with the same mutation, when paired with limited sample size the statistical power of a study is likely to be vastly diminished (Augustine, Adams and Mink, 2013). This is especially true in the case of ultra-orphan diseases where there may be fewer than 3000 patients across all the EU. This means it is difficult or impossible to generate evidence to the same standard as medicines for more common conditions (Drummond et al., 2007; Gutierrez et al., 2015).

An area of contention is around orphan and ultra-orphan medicines with multiple indications. The pharmaceutical industry is often criticised for maintaining relatively high prices even when multiple indications are licensed for the same medicine. Some argue that the prevalence of each indication should be aggregated when considering rarity, but this aggregation may create a barrier to the development of new product-indication combinations as it fails to recognise the indication-specific

costs of development (Denis et al., 2010). Additional indications may avoid the costs of early-phase safety trials but many of the distinct challenges associated with collecting evidence in ultra-orphan drug trials and appraising these more limited evidence bases, as discussed above, remain, regardless of the number of previous indications.

There are also challenges in demonstrating the treatment effects of new ultra-orphan medicine, particularly because of a lack of validated, disease-specific, sensitive and robust outcome measures (Nestler-Parr et al., 2018). Reporting clinical evidence on ultra-orphan conditions is regularly based on short-term surrogate outcomes such as biomarkers or generic measures such as the six-minute walk test rather than longer-term, disease-specific outcomes. Combined with necessarily small trial populations, it is difficult to generate robust, statistically significant evidence of the efficacy of innovative ultra-orphan medicines (Nicod et al., 2019). Heterogeneity of patient populations, non-standardised treatment pathways, a lack of data about the natural history of the disease and limited comparator data – if there are any comparator therapies at all – add to the difficulty of demonstrating effectiveness appropriate for a rigorous health technology assessment. Given that cost-effectiveness must be determined relative to a relevant comparator, in the absence of a comparator therapy, cost-effectiveness must be evaluated against a placebo (Simoens, 2011). It is, therefore, not always possible to collect the required data due to ethical issues as evidenced by the example below.

As experimental medicines are often the only first-line treatment for an ultra-rare disease, it is not uncommon for placebo-controlled clinical trials to be terminated early on ethical grounds, resulting in further challenges in demonstrating robust clinical and economic evidence (Simoens, 2011). An illustration of this is provided by Drummond *et al.* (2009). In the clinical trial of sorafenib in advanced renal cell carcinoma compared to best supportive care, an interim analysis of progression-free survival showed that sorafenib reduced the risk of progression by 56%. Following this result, the US food and Drug Administration (FDA) requested that all trial participants be unblinded and offered treatment with sorafenib. The data collected to that point were used to estimate the difference in overall survival and a corresponding cost per QALY for submission to the Canadian Agency for Drugs and Technologies in Health (CADTH), but CADTH judged that due to the early termination of the trial, survival estimates and consequently the cost-effectiveness estimate was too uncertain. A re-estimation of the cost per QALY by CADTH doubled the original cost-effectiveness estimate and as a result, sorafenib was not listed. Drummond *et al.* argue that the manufacturer was caught in an "ethical no man's land": as the trial was cut short there was insufficient evidence to prove cost-effectiveness of the drug, but to continue the trial would have been unethical.

This example demonstrates conflicting priorities in the assessment of ultra-orphan medicines, between the FDA's priority to accelerate approval and CADTH's priority to make a recommendation based on the robust clinical and economic evidence. This tension would also apply in the UK, where NICE similarly prioritises the strength and generalisability of the clinical and economic evidence. In the UK, there is also the complication of the Cancer Drugs Fund (CDF). The CDF allows for certain oncology drugs to be approved on the condition that additional data is collected to address clinical uncertainty. Despite this apparent opportunity, in some cases, it may not feasible to collect sufficient data to address the uncertainty within a realistic timeframe, especially if evidence of long-term clinical effects are required or constraints around study design exist (Drummond et al., 2007).

The CDF process has the potential to benefit medicines used for rare and ultra-rare cancers, but medicines for other ultra-rare diseases have no such avenue to support addition evidence generation and therefore places them at a disadvantage relative to cancer medicines. Indeed, there is evidence that NICE has never approved a non-cancer orphan or ultra-orphan drug within its full marketing authorisation (MAP BioPharma, 2019).

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The SMC's revised ultra-orphan pathway allows manufacturers to make a submission that emphasises the benefits that may not be captured by the QALY benefits; this may include quality of life gains that are not easily captured by generic preference-based outcome measures, such as the EQ-5D instrument. This is the case regarding benefits beyond direct health gains to patients but also to the patients' families and carers and ethical considerations relating to health gains for children with life-threatening diseases. The SMC pathway integrates added value to patients and their families through Patient and Clinician Engagement (PACE) meetings. These meetings enable patient groups and clinicians to engage with the SMC committee and are particularly valuable when evidence bases are limited. NICE alludes to the limitations of QALYs within the context of orphan drugs by having significantly higher cost-effectiveness threshold in their HST pathway. However, some ultra-orphan drugs that are not selected to undergo the HST programme are held to the same thresholds as drugs for more common diseases.

5 Discussion

As described above, medicines for rare and ultra-rare conditions face ethical and economic challenges distinct from those faced by medicines for more common conditions. This includes the need for exceptional economic incentives to encourage investment in the development and commercialisation of innovative medicines for very small patient groups and inequalities in access to innovative medicines and in health outcomes faced by these groups relative to patient groups with more common conditions. The existence of an alternative evaluation route for highly specialised technologies suggests that NICE tacitly acknowledges many of these challenges. The HST review process is intended to improve patient access to technologies for chronic and severely disabling ultra-rare conditions that would otherwise be unlikely to be approved as good value-for-money under NICE's standard appraisal process.

However, it can be argued that the current HST process fails to address many of the challenges it was arguably established to address. Principal amongst these shortcomings is a lack of clarity, consistency and transparency that theoretically underpin all NICE processes. The vague wording of the criteria for eligibility for review under the HST process, including terms such as "very few centres", "distinct for clinical reasons", and a "significant" need for national commissioning, means it can be difficult to understand the specific justifications by which different medicines for ultra-rare conditions are eligible or not eligible for this special appraisal route and to ensure they are being applied in a consistent manner.

As a consequence of this ambiguity, some ultra-orphan medicines are likely to be appraised under NICE's standard STA process and face a much more stringent cost-effectiveness threshold than that applied under the HST process. This consequence could be as extreme as the difference between a threshold of £20,000 under STA and £300,000 under HST. Arguably, patients with an ultra-rare condition whose medicine was rejected under the stricter STA threshold have been treated unequally and inequitably relative to patients with similarly rare conditions whose medicine was evaluated under the HST process. This includes patients whose condition was a subsequent indication of an existing medicine. By definition, these ultra-rare indications that follow a more common indication are not eligible for appraisal under the HST process despite facing many of the same challenges as other ultra-rare indication technologies, including difficulties in identifying and recruiting patients, ethical challenges in trials with no standard treatment, and a lack of robust disease-specific outcome measures.

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The ambiguity also includes the lack of an explicit prevalence threshold for highly specialised technologies. Indeed, NICE is something of an outlier amongst countries that have an alternative route for assessing medicines for rare and ultra-rare conditions in not explicitly defining a prevalence threshold. In practice, NICE appears to apply a highly restrictive threshold in the range of 1 case per 100,000 population, less than half the prevalence SMC, as an example, accepts as ultra-rare. The lack of an explicit threshold and the vagueness of "very few centres" makes it difficult to understand NICE's decision-making around rarity in a consistent and transparent manner. This is exacerbated by a relative lack of evaluation capacity within the HST programme. It has appraised only 11 medicines since 2015 whilst 10 medicines that met EMA's criteria for ultra-orphan were introduced in 2018 alone. It is therefore not clear that NICE's decisions to decline to review ultra-orphan medicines under the HST process are driven by clear and consistent criteria or by a simple lack of capacity that disadvantages patients with ultra-rare diseases and extends inequalities and inequities between patient groups rather than reducing them. This is especially disconcerting given NICE's stated commitment to evaluate *all* available medicines and significant extensions of indication by April 2020. The dramatic increase in the number of appraisals of medicines for more common conditions that this commitment will entail risks crowding out capacity to appraise ultra-orphan medicines.

In conclusion, the existence of NICE's HST appraisal route tacitly acknowledges many of the distinct challenges associated with medicines for ultra-rare conditions and the need for a separate appraisal process to ensure equitable access to innovative medicines and equality of patient outcomes relative to more common conditions. However, the discussion above suggests that ambiguous eligibility criteria and a lack of evaluative capacity within the HST evaluation programme may be undermining these efforts and exacerbating rather than reducing inequalities and inequities faced by patients with ultra-rare conditions.

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