MAP BioPharma
ACCELERATING PATIENT ACCESS

Access to Orphan Medicines: A Case for Change

February 2019

About this Report

MAP BioPharma (MAP) works with over 70 global biopharmaceutical and medical technology companies and a growing number of health charities. We provide a unique, validated, 'virtual' expert, which is designed to help companies achieve pricing and reimbursement and to support health charities to understand how they can support patient access to new innovative treatments and medical technologies. We also support many companies to develop and submit health technology appraisal applications, as well as supporting wider stakeholder and policy engagement.

Many of MAP's clients are small companies with a particular focus on orphan medicines. Based on short-term research projects, and anecdotal evidence and feedback from patient groups, clinicians and companies, MAP has convened a Steering Group of MAP Online members to review the data and policy environment for orphan medicines, and to make recommendations for improvement. This report sets out the Group's findings and recommendations. We look forward to discussing this report with stakeholders in the coming months.

The Steering Group members are:

- Amicus Therapeutics
- AveXis
- bluebird bio UK
- Chiesi Limited
- Gilead Sciences, Inc
- Kyowa Kirin International
- Santhera Pharmaceuticals

Each company has made an equal financial contribution to support this work. MAP retains full editorial control.

Table of Contents

Executive Summary

There are an estimated 7,000 rare diseases that affect about 3.5 million people in the UK and around 80% of these diseases are genetic.[1] Rare diseases are often chronic and life-threatening, and can have a significant impact on those affected and their families. It is reported that 95% of rare diseases have no approved treatments available.[2] Regulatory initiatives for orphan medicines from both the European Medicines Agency (EMA) and US Food and Drug Administration (FDA) have encouraged greater investment in research and development for orphan medicines and there has been an increase in the number of treatments that receive marketing authorisation in recent years.

The UK Rare Disease Strategy, published in 2013 recognised that "it is important that we have appropriate procedures for evaluating the benefits and costs of treatments as they become available. These procedures should be transparent and robust enough to be able to take account of the particular challenges that occur when evaluating treatments for rare diseases".[3] England's implementation plan was subsequently published in early 2018, and although it stated that the Government would continue to "incentivise the development and marketing of medicines for rare diseases", there was limited reference to any steps that have been taken to adapt national health technology appraisal processes for orphan medicines.[4]

Although orphan designation helps to remove the bias against rare diseases in the marketing authorisation process, this bias remains in the reimbursement process.

Experience has shown that there can be a very fine line between National Institute for Health and Care Excellence (NICE)'s two appraisal programmes. The default referral route for the majority of orphan medicines is for a Single Technology Appraisal (STA) but many will be close to meeting the selection criteria for NICE's Highly Specialised Technology (HST) programme. Stakeholders have frequently sought to make the case for a HST referral which is a more appropriate route for orphan medicines. The nature of the incremental cost-effectiveness ratio (ICER) means that those in the HST can demonstrate an ICER of between £100,000 to £300,000, but those in the STA must meet an ICER of between £20,000 to £30,000 (or up to £50,000 for end-of-life treatments). This means that very small differences between treatments in terms of patient numbers or clinical management can have a significant impact on the criteria against which they are assessed, which severely disadvantages those that are routed for STA.

The Government has maintained a public position that it is appropriate for orphan medicines to be considered under NICE's standard STA and that orphan medicines have been successfully reviewed under the STA programme. However, charities representing people with rare diseases and other stakeholders continue to raise concerns that the STA process is not appropriate for orphan-designated treatments, particularly for non-cancer orphan treatments that do not benefit from the Cancer Drugs Fund (CDF). Both the Scottish Medicines Consortium (SMC) and All Wales Medicines Strategy Group (AWMSG) have adapted their processes to increase the input of clinicians and patient group experts in HTA decisions for certain orphan medicines.

This report assessed qualitative and quantitative data on HTAs for orphan designated medicines that received marketing authorisation between 2013 and 2017 to determine the extent of the issues. It identifies

a range of findings, including that the number of non-cancer orphans reviewed by STA is very small (6) and that none of these have been recommended within their full marketing authorisation, whereas over two thirds of non-orphan medicines have.

Based on the information in this report, MAP believes it is time for NICE to revisit its arrangements for the very small number of non-cancer orphan medicines assessed via the STA programme. NICE has a history of adapting its processes to ensure they are fit for purpose: end of life-criteria, CDF arrangements and the fast-track appraisal all fit under the STA umbrella. The forthcoming review of NICE's STA methods provides an opportunity to do this.

Industry also has a role to play and will continue to champion initiatives that can bring treatments to patients at the earliest opportunity.

We recommend that NICE, NHS England and the Department of Health and Social Care (DHSC) consider, without delay, the following flexibilities. We believe strongly that these will help to deliver a more equitable system:

- Introduce formal changes to the evidence requirements for STAs for orphan medicines. The nature of this flexibility should be informed by a range of stakeholders with experience of developing and assessing orphan medicines
- Drawing from the HST methodology, consider introducing a sliding ICER scale for orphan medicines
- Consider adapting the Evidence Review Group brief for orphan treatments within the STA programme, and explore a role for the Rare Disease Advisory Group (RDAG) when orphan medicines are appraised by the STA process
- Embed formal opportunities for negotiation between companies and NHS England for orphan medicines assessed within the STA work programme
- Consider an interim recommendation for orphan medicines, in line with the CDF and new processes from the SMC to support real-world evaluation of treatment impact

These adaptations will help to level the playing field so that patients, clinicians and companies can be sure that all treatments for rare diseases will be considered under a fair appraisal, and that access to new innovation will not be held back as a result of treatments being referred for an inappropriate appraisal.

Background

There are an estimated 7,000 rare diseases that affect about 3.5 million people in the UK and around 80% of these diseases are genetic.[5] In the UK, a single rare disease could affect up to 30,000 people with the EMA definition of a rare disease being one that affects less than 5 in 10,000 people. Rare diseases are often chronic and life-threatening and can have a significant impact on the people affected and their families. It is reported that 95% of rare diseases have no approved treatments available.[6] The challenges in diagnosing rare diseases and ensuring that patients have access to appropriate specialist care, an approved treatment and ongoing support, are significant. Against this backdrop, it is extremely important that efforts are made to meet the gap in available treatments and ensure that new medicines are made available routinely, and without delay, once regulatory approval is granted and aligned with access in comparable advanced countries.

The regulatory environment has played a significant role in incentivising research and investment in medicines for rare diseases, including the introduction of the EMA's Orphan Medicinal Product (OMP) designation, and the US Food and Drug Administration (FDA)'s Orphan Drug designation. Over the past two decades, with greater understanding of the human genome, there has been a shift within the pharmaceutical industry towards developing targeted medicines for rare diseases, with a rapid increase in the number of medicines granted orphan drug designation by the European Commission. Just four medicines were granted orphan designation in 2000 compared with over 200 in 2016.[7]

The UK's Rare Disease Strategy, published in 2013, recognised that "it is important that we have appropriate procedures for evaluating the benefits and costs of treatments as they become available. These procedures should be transparent and robust enough to be able to take account of the particular challenges that occur when evaluating treatments for rare diseases".[8] Despite this statement, there was very limited reference to any steps that have been taken to adapt national appraisal processes for orphan medicines in the implementation plan for England that was published in February 2018, aside from reference to the HST programme, which has in fact become more restrictive since the Rare Disease Strategy was first published.[9]

The challenges in evaluating orphan medicines via HTAs are multifaceted:

- Application requirements differ between marketing authorisation and HTAs
- Small clinical trial populations limit statistical power beyond primary endpoints
- Clinical pathways and endpoints can be uncertain
- A lack of natural history and other comparative data (even outside treatments/comparators)
- Limited clinical and quality of life data (particularly challenging for young children)
- Difficulties developing robust health economic analyses with limited data sets. Short duration of follow up in clinical trials when having to model long-term claims in terms of clinical efficacy is often a driver of uncertainty
- Challenges to demonstrate value for money to the standard usually expected in HTA

Against this backdrop, it is unsurprising that research from MAP and others has identified that it can be challenging for orphan medicines to demonstrate cost-effectiveness as part of health technology assessments (HTAs).[10] There is little flexibility to consider the nature of orphan medicines that are assessed as a STA, and

only a very small number of orphan treatments are deemed eligible for review under the HST programme. Nevertheless, the Government has maintained the position publicly that the NICE STA programme is an appropriate route for assessment of orphan medicines.[11, 12]

This report sets out findings from a review of EMA orphan-designated treatments that received marketing authorisation between 2013 and 2017. It makes the case for NICE, DHSC and NHS England to work together to review and update NICE's methodology for orphan medicines that are not considered as part of the HST programme.

Methodology

MAP has taken a number of steps to inform this report:

- We reviewed health technology assessments and other routes to market in England for EMA orphan designated products that received marketing authorisation between 2013 and 2017. We focused on 2013 onwards because this is the point at which NHS England formally took on commissioning responsibility for specialised treatments.
- Although we reflect on different assessment routes for orphan treatments in the report, including NHS England and NICE evaluations, our primary focus was the nature of the NICE STA and its applicability to orphan medicines.
- It is too soon to evaluate the success or otherwise of new HST arrangements because the methodology was only recently updated and is still described as interim. However, after over five years of an interim process, a formal review is due and should perhaps be considered alongside NICE's forthcoming review of the NICE STA methods.
- We considered what assessment route had been undertaken, whether assessments have been concluded, and whether treatments are routinely available.
- We compared the status and outcome of reviews for orphan drugs compared with non-orphan drugs that received marketing authorisation between 2013 and 2017 and were assessed via the STA route.
- We reviewed data excluding cancer indications given that these treatments have additional flexibilities through the CDF, and frequently via the application of end-of-life criteria.
- We considered 'live' case studies such as the ongoing appraisal of nusinersen for spinal muscular atrophy (at the point of publication, only the appraisal consultation document had been published).
- We undertook a detailed review of other research and commentary on this issue, including that relating to international and devolved nations comparisons.
- We had discussions with leading coalitions, charities and industry groups in relation to this project.
- We worked with Steering Group members to develop recommendations that could help to address these areas of unmet need.

We would welcome the opportunity to discuss our findings further and to work collectively to expand our understanding of the challenges and work constructively with NHS England, NICE and DHSC to implement changes that will improve the access environment for orphan medicines.

The market access landscape for orphan medicines in England

This section of the report provides MAP's review of the market access landscape for orphan medicines. There are five possible routes in which an orphan treatment may be reimbursed (Table 1).

NHS England has commissioning responsibility for the majority of orphan medicines in England. It plays a key role in determining whether treatments will be available, either via its own clinical commissioning policy process, through discussions relating to patient access schemes (PASs), or after the budget impact test is triggered and commercial discussions with a company are initiated. Given this significant role, this report has focused on the 63 treatments that received marketing authorisation between 2013 and 2017, to align with the introduction of national commissioning for specialised services.

Table 1 - The main routes for orphan treatments in England

Assessment type	Summary
Single technology appraisal (NICE)	▸ The maximum allowable ICER is usually £30,000, up to £50,000 for end-of-life treatments ▸ There are no further adjustments for orphan treatments reviewed by the STA ▸ There is a Fast Track Appraisal Scheme for the most cost-effective products, which only takes 100 days ▸ Cancer drugs with limited data can benefit from an interim recommendation with data collection requirements via the CDF
Highly specialised technology evaluation (NICE)	▸ Seven qualification criteria for this process (very small number of patients concentrated in small number of centres in England; clinically distinct patient group; serious chronic, disabling condition; high cost treatment; highly specialised service; potential for life-long use; significant need for national commissioning) ▸ The standard incremental cost-effectiveness ratio (ICER) threshold is £100,000, or for products offering a greater magnitude of benefit, the threshold is up to £300,000 per quality adjusted life year (QALY) ▸ The process applies a broader range of decision-making criteria, placing more emphasis on the family burden and impacts outside of healthcare ▸ Managed Access Agreements have been agreed with NHS England for most HSTs

Assessment type	Summary
Clinical commissioning policy (NHS England)	▸ Clinical Reference Groups play a role in setting priorities in clinical areas, but NHS England determines what receives funding via a twice-yearly prioritisation process. Some products may go through the prioritisation process multiple times ▸ The prioritisation benefit ranks all the proposed treatments by magnitude of benefit and cost per patient per year, in order to decide which products will be funded ▸ There are no timelines specified ▸ Sometimes used for products outside their marketing authorisation (e.g. cancer medicines)
Commercial Medicines Unit (NHS England)	▸ Haemophilia treatments are not subject to NICE appraisals so are generally reviewed as part of national procurement processes led by the CMU
Individual funding requests (NHS England)	▸ Clinicians can request funding for each individual patient ▸ If an application for an individual could constitute a cohort of patients, it will be rejected and trigger the development of a commissioning policy. This means very few IFRs are accepted by NHS England [13]

How is the type of NICE evaluation determined?

New medicines are considered under NICE's topic selection and scoping process. Most orphan treatments are automatically selected for consideration as an STA. All of the following selection criteria must be met if technologies are to be reviewed by the HST programme:

1. The target patient group for the technology in its licensed indication is so small that treatment will usually be concentrated in very few centres in the NHS
2. The target patient group is distinct for clinical reasons
3. The condition is chronic and severely disabling
4. The technology is expected to be used exclusively in the context of a highly specialised service
5. The technology is likely to have a very high acquisition cost
6. The technology has the potential for life long use
7. The need for national commissioning of the technology is significant

Several of these criteria will be met by orphan and non-orphan treatments alike, but it is the terminology relating to patient numbers and a highly specialised service that are particular areas of contention.

Most orphan medicines will benefit a relatively small patient population and will require specialist support via nationally commissioned services. There are some instances where a treatment may not immediately meet the criteria because the services were not previously in place to support the use of a high-cost treatment. For example, in conditions that have had no prior treatments and have therefore relied on supportive care, there may not be the networked

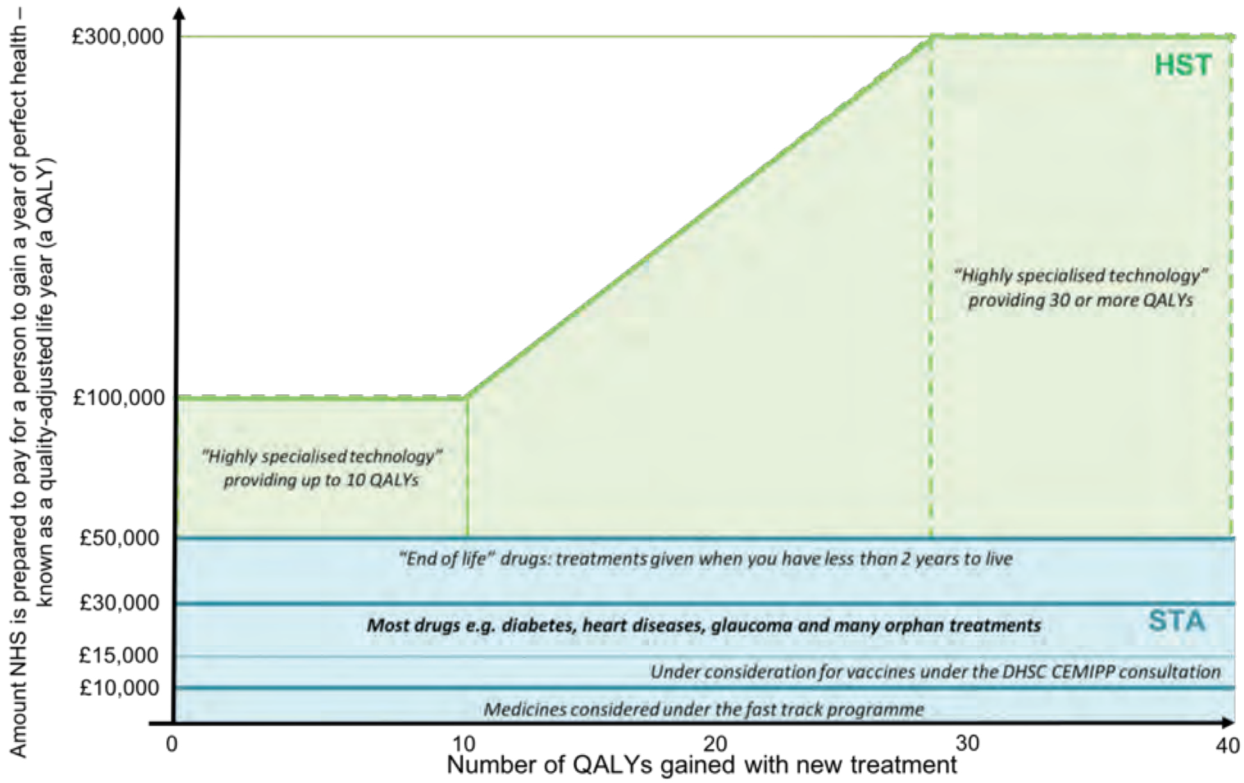
arrangements or specialist centres in place that would become necessary with the introduction of a new treatment. In such cases criterion four will never be met. Several of the criteria are liable to be interpreted differently, for example whether a patient group is distinct for clinical reasons and the size of the patient group where actual numbers are not specified. There can be a very fine line between the final referral decision to one of NICE's work programmes.

These present challenging judgements for the decision-problem meeting of NICE's Topic Selection team. The number of treatments will be small but may represent a marked administrative burden in terms of both the scoping process and implementation of the standard STA process for treatments that require additional consideration.

The differences between the STA and HST process are notable but the differences between conditions and treatments that are eligible for either the STA or HST can be minimal. This means that NICE's Committees may be reviewing similar types of evidence for comparable patient populations under very different criteria.

Figure 1 sets out the different incremental cost-effectiveness ratios (ICERs) that are considered by HTA bodies (and one that is currently being considered by the DHSC for vaccinations). It demonstrates the significant impact that a referral for STA compared to HST can have for a company in terms of demonstrating cost-effectiveness. This is particularly pertinent in certain disease areas, for example, three treatments for Duchenne muscular dystrophy (ataluren, eteplirsen, drisapersen) were referred for review via a HST but another (idebenone) was referred for review via STA. The chart also demonstrates that the Government has introduced flexibilities within the system to enable an effective review of a range of treatment types.

Figure 1 – how do the cost-effectiveness thresholds vary between NICE's programmes?



Is STA an appropriate route for orphan medicines?

In a debate relating to the Cystic Fibrosis combination drug, Orkambi, in July 2018, the Minister Steve Brine emphasised that although some Members of Parliament (MPs) had raised concerns about the suitability of NICE's STA methodology for orphan medicines, a number of orphan treatments had been recommended by NICE which demonstrated the suitability of that NICE process for orphan medicines. He cited two examples in his speech: pirfenidone for idiopathic pulmonary fibrosis and mifamurtide for osteosarcoma.[14]

Upon closer analysis, we would suggest that these examples demonstrate that there are challenges with the current NICE STA process and that by looking only at the final outcome, the Government is ignoring significant challenges within the STA process.

Pirfenidone for idiopathic pulmonary fibrosis: [15]

- NICE issued a restricted recommendation in April 2013 (TA282). A review of this recommendation was initiated in 2016
- A second NICE restricted recommendation was subsequently published in February 2018 (TA504), the re-review lasted almost two years:
  - Initial committee papers were published in April 2016
  - An appraisal consultation document was published in June 2016 recommending that restrictions be maintained
  - A final appraisal determination followed in September 2016. This decision was subject to appeal by the manufacturer (Roche)
  - A second final appraisal determination followed in June 2017. This decision was subject to appeal by both the manufacturer (Roche) and the British Thoracic Society
- Of particular note are the comments from the British Thoracic Society that NICE's review failed to take into account updated evidence on the efficacy of pirfenidone since the initial TA was undertaken. The professional group raised questions about inequality for patients for whom data demonstrated efficacy and cost-effectiveness but where an apparently arbitrary cut-off point would restrict access [16]
- Despite these concerns, NICE's restricted decision was upheld by the Appeal Committee

Mifamurtide for the treatment of osteosarcoma*: [17]

- NICE issued a recommendation in October 2011 (TA235)
- An initial review of mifamurtide was paused in early 2009 when no price had been agreed. Following the acquisition of the manufacturer, IDM Pharma, by Takeda UK in June 2009, an updated economic evaluation was submitted in December 2009. The Committee considered the evidence in March 2010
- A negative appraisal consultation document was subsequently published in April 2010, followed by a negative final appraisal determination in October 2010

- Almost a year later, a positive final appraisal determination was published in September 2011 following the submission of a revised patient access scheme (PAS), several Committee Meetings (five in total), significant contributions from patient advocates and clinicians on the need to make the treatment available

* A cancer treatment so not a representative example of non-cancer orphan treatments

These examples show that whilst NICE has been able to recommend some orphan medicines via its STA programme, the process is not necessarily straightforward, and significant time and stakeholder input has been required to deliver a successful outcome. In the case of pirfenidone, concerns remain about the patient population restrictions.

It is disappointing that decision-makers appear to be ignoring these significant delays and concerns, and worse still highlighting these recommendations as an exemplar for a system that works for orphan medicines. We would therefore urge the Government to take a more nuanced approach to this complex topic. The subsequent analysis in this report seeks to shed further light on the reality of STAs for orphan medicines.

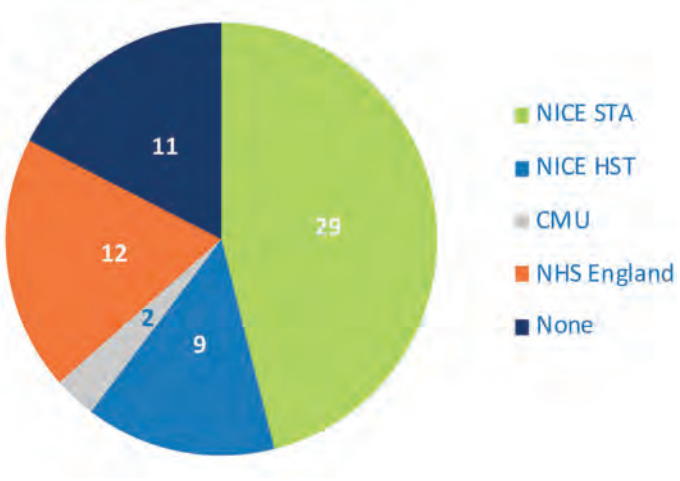
Past assessments of orphan medicines in England

This section of the report provides MAP's quantitative analysis of the access to orphan medicines.

Assessment route

Of the 63 products that received marketing authorisation between 2013 and 2017 that had orphan drug designation, the majority (46%) have been routed through NICE's STA programme, followed by NHS England's clinical commissioning policy programme (19%) (Figure 2). A significant proportion of orphan treatments have not been selected for review by either NICE or NHS England (17%). In these instances, clinicians will need to apply to individual hospital formularies for access or submit individual funding requests (IFRs) to NHS England. Given that orphan treatments often fall under the commissioning responsibility of NHS England, an IFR is the most likely route and is extremely restrictive.[18]

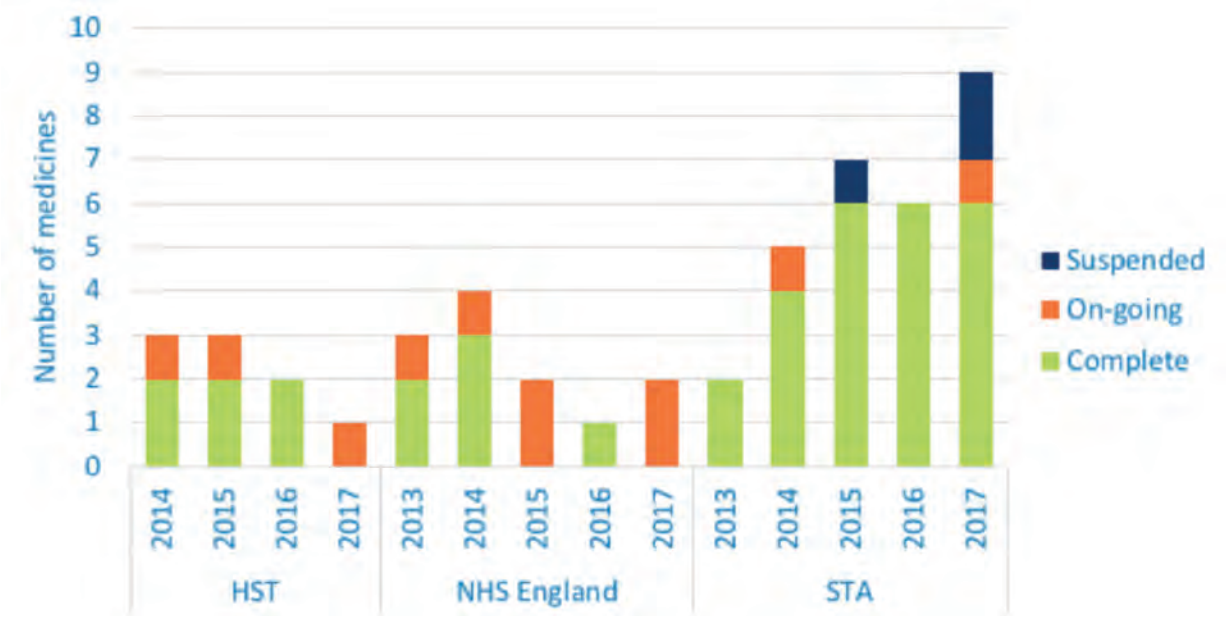
Figure 2 – Assessment route of all products with orphan drug designation, 2013-2017 (n=63)



STA: NICE STA, HST: NICE HST Appraisal; NHS England: NHS England Commissioning Policy; CMU: NHS England Commercial Medicines Unit

Of the 50 products that are under assessment by NICE and NHS England, the appraisal process has been completed for most STA products (68%) but only half of the assessments under NHS England have yet had a recommendation published (Figure 3). The products still under review by NHS England include one product that received marketing authorisation in 2013, one in 2014, two in 2015 and two in 2017. Similarly, in the NICE HST programme, decisions have yet to be reached for products that received marketing authorisation in 2014, 2015 and 2017. This analysis indicates that the NICE STA programme remains the most frequent route for orphan medicines and is associated with quicker decisions than the HST or NHS England process.

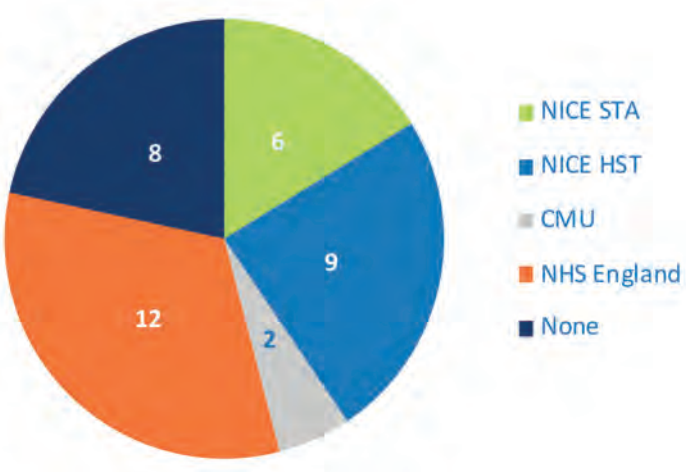
Figure 3 – Assessment status of products with orphan drug designation undergoing HTA review, 2013-2017 (n=50)



When removing cancer treatments from this analysis, the picture is very different, as shown in Figure 4. The largest assessment group is NHS England (32%). More non-cancer orphan medicines are assessed via the NICE HST route (24%) than the STA route (16%). As indicated by Figure 5, the HST and NHS England routes are associated with a longer time before a decision is published, so patient access is delayed.

Critically, this analysis shows that a substantial proportion (22%) of non-cancer orphan medicines have no national review (Figure 4). It is concerning that such a large proportion of non-cancer orphan treatments have not been considered by any national review body. This immediately makes it much more difficult for patients to get access to these treatments.

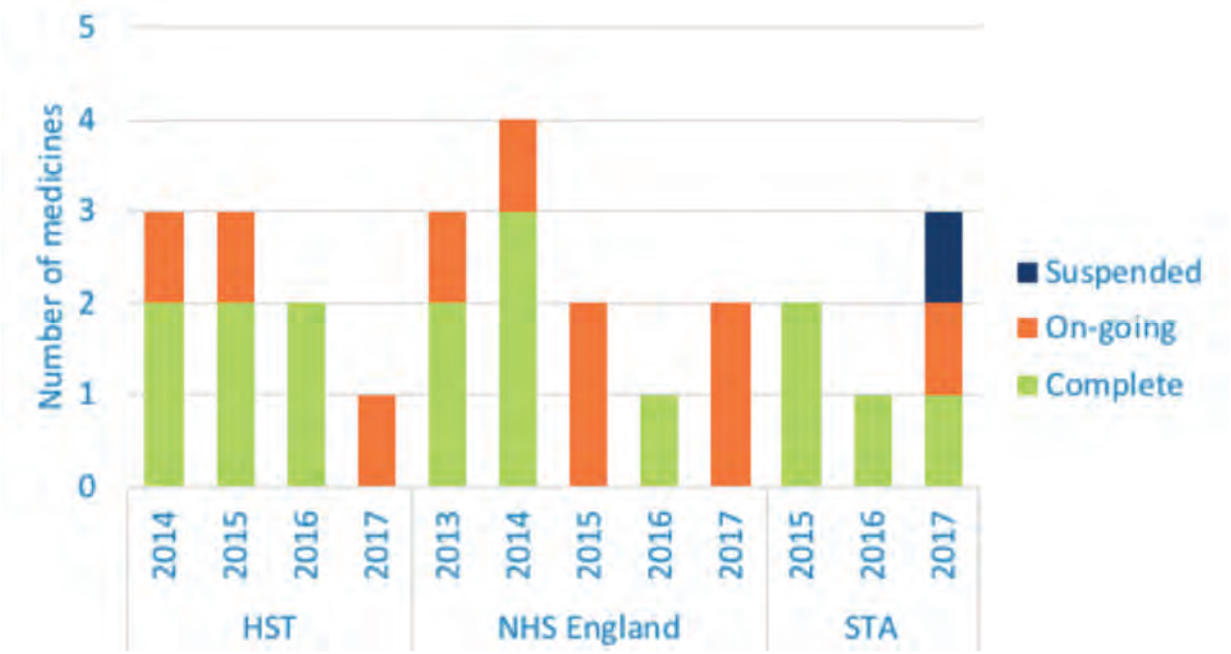
Figure 4 – Assessment route of non-cancer products with orphan drug designation, 2013-2017 (n=37)



STA: NICE STA, HST: NICE HST Appraisal; NHS England: NHS England Commissioning Policy; CMU: NHS England Commercial Medicines Unit

As outlined above, NICE and the Government have previously concluded that the STA is an appropriate route for orphan medicines that do not meet the criteria for NICE's HST evaluation. However, with only six non-cancer orphans having been reviewed as an STA, it raises questions about whether the STA methodology has truly been tested for orphan treatments.

Figure 5 – Assessment status of non-cancer products with orphan drug designation undergoing HTA review, 2013-2017 (n=27)



Assessment decisions

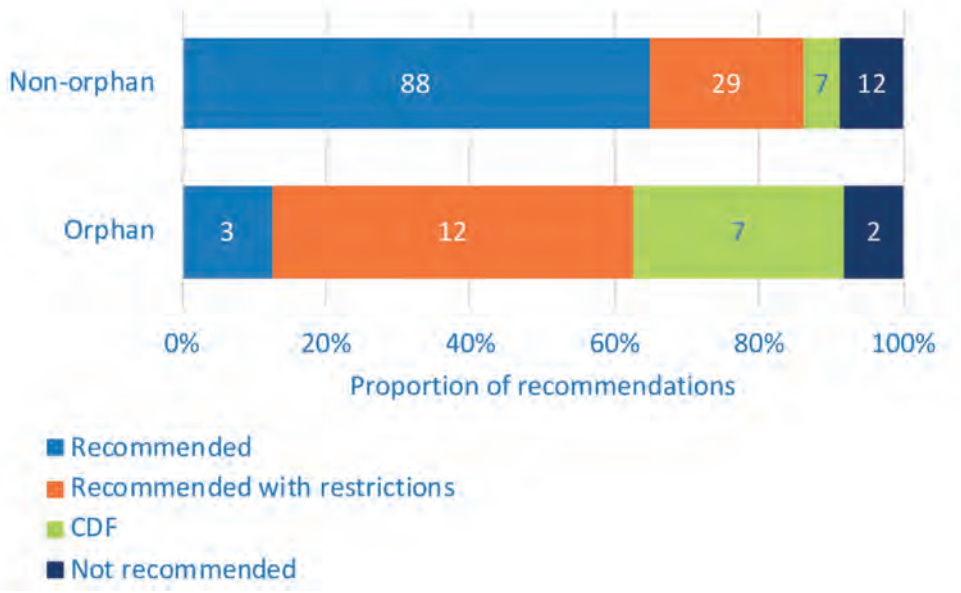
NICE can provide five possible conclusions following an assessment:

- Recommended (in line with the marketing authorisation)
- Recommended with restrictions (a subgroup of the marketing authorisation)
- Recommended for use in the CDF (cancer treatments only)
- Recommended only in research (with no reimbursement)
- Not recommended

To provide a comparison of orphan and non-orphan recommendation rates, outcomes from all NICE STAs between 2013 and 2017 were studied.

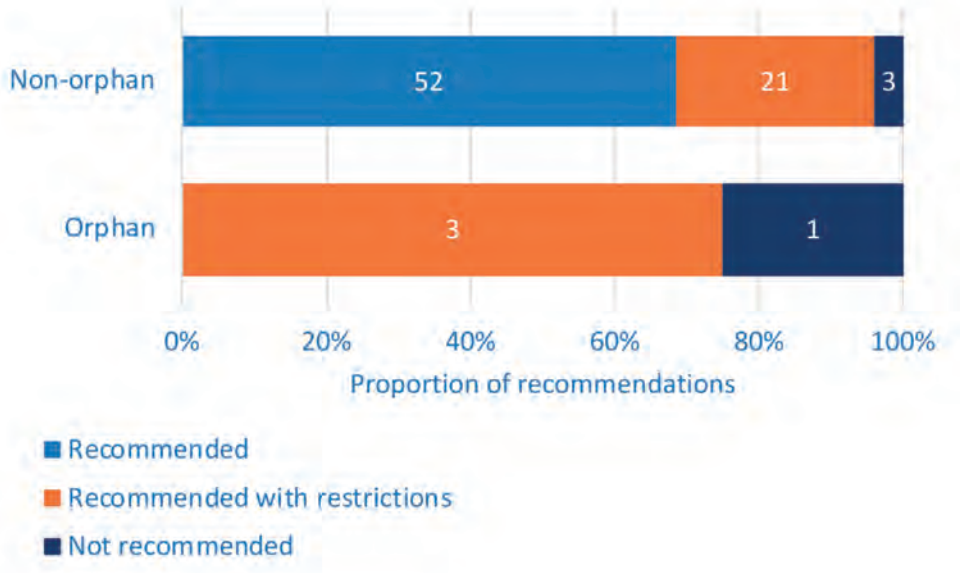
Figure 6 shows that orphan treatments were recommended with restrictions more than non-orphan treatments in the STA process. Of the 24 completed STA reviews of orphan treatments, 50% have been recommended with restrictions compared to 21% of non-orphan treatments. Very few (13%) orphan medicines have been recommended within their full marketing authorisation. The proportion of STA reviews resulting in non-recommendation is similar between orphan (8%) and non-orphan (9%) medicines. Within cancer treatments, a higher percentage of orphan treatments benefited from the CDF than non-orphan medicines. This demonstrates that in order to secure routine use, orphan medicines are more likely to require special consideration than non-orphan treatments.

Figure 6 – Comparison of orphan assessments in the NICE STA process compared with non-orphan assessments



Focusing only on non-cancer treatments reveals that orphan treatments are, at best, only recommended with restrictions; no orphan medicines have been recommended within their full marketing authorisation whereas 68% of non-orphan medicines have (Figure 7). This supports the suggestion that in order to secure routine use, orphan medicines are more likely to require special consideration than non-orphan treatments. The proportion of STA reviews resulting in non-recommendation is greater for orphan (25%, n=1) than non-orphan cancer medicines (4%, n=3). However, with so few STA appraisals of non-cancer orphan medicines, it is challenging to evaluate the suitability of the process.

Figure 7 – Comparison of non-cancer orphan assessments in the NICE STA process compared with non-orphan assessments



The reasons for a restricted recommendation are varied. It may be that a manufacturer puts forward a case based on a restricted population because the data is stronger for a smaller population. In other instances, NICE may decide that a treatment is only cost-effective for a sub-population. We looked at two of the non-cancer orphan medicines assessed between 2013 and 2017 that received a restricted recommendation to understand the nature of these decisions. The most common concerns raised by committee members were limitations and uncertainty in the data available, and in some cases, data not being available at all. Examples of the reasoning for restricted recommendation by NICE included:

- Uncertainty about the clinical relevance of findings from trials of a short-term nature
- Uncertainty when extrapolating short-term trial data over longer periods of time
- Using small sample sizes, especially when used as evidence of benefit in subgroups
- Limited data on quality of life
- Uncertainties in economic modelling that could substantially increase the ICER

The difficulty in doing high-quality research for disease areas with often highly heterogenous patient populations is recognised by NICE. Restrictions placed on orphan medicines appraised as an STA that resulted in a positive recommendation between 2013 and 2017 suggests the intrinsic uncertainties and limitations in evidence for these types of treatments are not sufficiently accommodated to avoid negative bias by a NICE STA.

Case studies highlighting the challenges in the system

SPINRAZA (nusinersen) for Spinal Muscular Atrophy (SMA)

Nusinersen is the first disease-modifying treatment for Spinal Muscular Atrophy (SMA). Following its assessment by NICE as an STA, in August 2018 it was not recommend for routine use in the NHS.[19] This has raised questions about the appropriateness of assessing this orphan medicine using the STA process, especially from patient groups.

HST v STA [20]

- Number of children who would be eligible for treatment may be approximately 900 (Genetic Alliance), which exceeds the limit for HST.
- No NHS England Highly Specialised Service specification exists and patients are managed across a number of neuromuscular centres.

The challenge for STA [21]

- Long-term benefits were highly uncertain in the absence of long-term evidence.
- Limitations and uncertainties exist in the economic evidence. For example, the Committee was concerned that modelled transition probabilities and survival were based on 'highly optimistic assumptions' (NICE ACD).
- Cost of nusinersen was considered too high for it to be cost-effective for the NHS, even when NICE considered rarity and severity of SMA, the nature of the population, uncertainties, and whether it could be considered as an end-of-life treatment.
- Significant variability in the diagnosis and awareness of SMA, including a lack of clarity on types of SMA (especially type 1 and type 2).
- Difference between the real-life perception of the benefits of nusinersen compared to trial data. Parents emphasised they see real differences that are not captured with the instruments used in the studies.

ORKAMBI (ivacaftor/lumacaftor) for cystic fibrosis

Ivacaftor/lumacaftor was licensed for the treatment of cystic fibrosis in patients with a F508del mutation in 2016. NICE's decision to not recommend lumacaftor-ivacaftor therapy (Orkambi) for routine use in the NHS in England has been highly contested by patients and their representatives, concluding in a high-profile public debate about access to orphan medicines for rare diseases.[22, 23, 24]

The Cystic Fibrosis Trust is campaigning against NICE's decision, which they summarise as centring on uncertainty regarding longitudinal effects, clinical significance of acute effects, elements of economic modelling and transferability of clinical trial results to routine use.[25]

During the appraisal of Orkambi, the British Thoracic Society and the Cystic Fibrosis Trust suggested that to reduce uncertainty, lumacaftor–ivacaftor should be made available with a commercial access agreement while data were collected for up to 2 years in the Cystic Fibrosis Registry. However, the committee had not received a proposal to identify how the longer-term uncertainties could be addressed through the data collection.

These concerns are consistent with our analysis of other orphan medicines that have been authorised with restrictions following a NICE STA and add further evidence to the argument that a NICE STA does not allow sufficient consideration of uncertain long-term evidence on the impact of orphan medicines.[26]

CHARITY PERSPECTIVES

Charities are actively campaigning on these issues, underlining current concerns that NICE's processes are falling short for people with conditions that would benefit from orphan medicines that do not qualify for NICE's HST criteria.

A survey of **Specialised Health Care Alliance (SHCA)** members in May 2018, undertaken by Incisive Health, identified the key themes charities highlighted with regard to improving the assessment of orphan medicines in England. There is support for a formal mechanism to give greater priority to rare disease treatments. There was frustration among charities with regard to the division between the HST and STA processes, as well as concern regarding how the budget impact test and lower cost-effectiveness threshold might affect access to treatments.[27]

Muscular Dystrophy UK is campaigning for faster access to new treatments. They have commented on the initial decision not to fund nusinersen saying that it "makes it clear that the appraisal process for rare disease drugs is not fit for purpose". The charity has underlined it will continue to fight for improvements alongside other charities.[28]

As outlined above, the **Cystic Fibrosis Trust** has been campaigning to support access to medicines for people with cystic fibrosis for several years, in particular the treatment Orkambi. The drug gained marketing authorisation two years ago, but it was unsuccessful in NICE's STA review in 2016. A Westminster Hall debate in March 2018 and a follow up debate in July 2018, emphasised the strength of support on this issue. 60 MPs participated in March and 22 MPs contributed to the latest debate, sharing stories of people living with cystic fibrosis and the need for new treatments like Orkambi to be made available.[29]

Is this an England-only problem?

The European experience

Patient access to orphan medicines varies significantly across Europe,[30, 31] with widespread agreement that this variation is affected by both their higher costs and their uncertain data.[32, 33] More than half of centrally authorised orphan medicines are available across Europe but different national reimbursement policies further restrict patient access to them, especially in the UK, Italy and Spain,[34] and most European countries have not implemented pricing and reimbursement policies specific to orphan medicines.[35]

According to the OHE, between 2001 and 2016 the German and French healthcare systems reimbursed the highest number of OMPs (133 and 116 respectively).[36] Overall, people in Germany, Scandinavian countries, Switzerland, France, and United Kingdom access larger numbers of medicines in a shorter timeframe than in other European countries.[37] This is perhaps unsurprising as these are some of the countries with the largest economies in Europe. England should be aspiring to align with Germany and France rather than poorer economies in the EU.

A common question raised across European countries is whether funding expensive treatments for a small number of people is sustainable.[38] A number of surveys across Europe have also looked at whether society is willing to pay more for rare diseases and found that there is 'little support' if those resources are being taken from more prevalent diseases, however there is more support for more serious conditions without treatment alternatives.[39] Recent data from an IPSOS MORI/Health Foundation survey suggests that 61% of those surveyed feel that the NHS should be making treatments available regardless of cost, a further 36% felt that the NHS should make treatments available providing they are value for money. There is strong support for ensuring people get access to new treatments.[40]

The wider European experience and variation in access further supports the question of whether orphan medicines should be considered as a separate group in reimbursement policies in order to increase patient access to them.[41]

The devolved nations

Inequalities in accessing orphan medicines for rare diseases are seen across the devolved nations. For example, overall the SMC in Scotland reviews more orphan medicines than NICE and has a higher approval rate, the treatment approval rate in England is 55 per cent versus 69 per cent in Scotland.[42] Wales has the highest approval rate at 70 per cent with Northern Ireland very similar to England at 56 per cent.[43]

Scotland's New Medicines Fund specifically for orphan drugs is instrumental in helping secure access to medicines for rare diseases. It does not exist in the other devolved nations. There are also multiple access routes for orphan medicines in England through NICE and NHS England, making policy more complex and less coordinated as companies try to navigate which route may be more appropriate for their products.

In Wales, a new process was introduced for orphan designated medicines in September 2015 and those with a similar patient population size. Changes included greater consideration of societal benefit and additional involvement of patient and clinical voice. An analysis by the AWMSG found that decisions for orphans compared with non-orphans were comparable with 90% either recommended in full or with a restriction.[44]

It appears that both Scotland and Wales have taken a more proactive approach to address concerns relating to the applicability of standard processes for orphan treatments. The different processes are summarised in Table 2.

Table 2 – Orphan medicines policies across the devolved nations

Country	Orphan medicine policies
England [45]	▸ NICE STA programme – no specific adaptations for orphan medicines ▸ NICE HST programme – varying from £100,000 per QALY per year for treatments that deliver less than 10 QALYs to a patient, up to a maximum of £300,000 for those that deliver more than 30 additional QALYs ▸ Budget Impact Test – an affordability test for drugs assessed by NICE that cost more than £20m in any of the first three years (not specific to orphan medicines but may have a disproportionate impact given the high cost of orphan drugs) ▸ Specialised products – Clinical Commissioning Policies, Commissioning through Evaluation or Individual Funding Request (IFR) process
Scotland [46, 47]	▸ Scottish Government has introduced a new definition of 'ultra-orphan medicines' that treat fewer than 1 in 50,000 people. 'Ultra-orphan medicines' that the SMC considers clinically effective will be made available on the NHS for at least three years while further information on effectiveness is gathered ▸ Peer Approved Clinical System (PACS) Tier 1 for ultra-orphan medicines, PACS Tier 2 for all others including a National Appeal Panel ▸ Patient and Clinician Engagement (PACE) ▸ Higher levels of uncertainty accepted in economic case, including conditional approval and more complex managed access arrangements for ultra-orphan drugs ▸ New Medicines Fund (NMF) available for orphan drugs
Wales [48]	▸ Additional consideration of societal benefit and opportunities for patient and clinical engagement ▸ Individual Patient Funding Request (IPFR), if the patient has a rare or specialist condition that falls within the service remit of the Welsh Health Specialised Services Committee (WHSSC) ▸ One Wales Interim Commissioning Process (will not apply to medicines that have been appraised by NICE/AWMSG and received a negative recommendation) ▸ Clinical and Patient Involvement Group (CAPIG)
Northern Ireland [49]	▸ Adopts NICE recommendations

Making a case for change

In reviewing commentary relating to orphan medicines, including the official responses to calls for changes to the current review processes in England, it is clear that, to date, there has been no public recognition from the Government of the need to alter the status quo. Nevertheless, as outlined in this report, as the number of orphan medicines reaching marketing authorisation continues to rise, it is likely to place increasing pressure on the system. This is an issue that health economies are grappling with around the world and as a global leader in health technology assessment, NICE should be facing this challenge head-on. Both the Scottish Medicines Consortium and All Wales Medicines Strategy Group have introduced adjustments for orphan treatments.

At present, the small number of non-cancer orphans that have been assessed as an STA means that the system cannot be claimed to be appropriate or successful. In examples where treatments have been made available, the journey to a positive recommendation has been long and complex leading to delay and uncertainty for affected people.

Ensuring that patients and clinicians are certain that new treatments have been considered by a fair, appropriate appraisal is also essential to retain confidence in the system and ensure a level playing field within the NHS. These are areas of high unmet need and although regulatory adaptations have been made, the long implementation timelines and variable success rates do suggest that appropriate reimbursement review systems are not in place. With the uncertainties and risks of Brexit in relation to the life sciences industry and beyond, this topic provides an opportunity for the UK Government to set itself apart from other countries by taking a proactive approach to meet the needs of people with rare diseases.

Industry is keen to support ways to enable England to be a leader in supporting access to orphan medicines. The Voluntary Scheme for Branded Medicines Pricing agreed between the DHSC and the Association of the British Pharmaceutical Industry in December 2018 aims to support innovation and a successful life sciences industry in the UK, as well as improving patient access to medicines by getting the best value and most effective medicines into use more quickly. Through this scheme, which replaces the 2014-2018 Pharmaceutical Price Regulation Scheme (PPRS), companies are expected to make payments of £744 million back into the DHSC Budget in 2019 alone.[50] Companies continue to offset uncertainty through STAs via discounting arrangements and also help to ensure patients can access new treatments by funding home care and testing to inform treatment decisions.

Industry would welcome the opportunity to work in partnership with NICE, NHS England and DHSC to realise the vision in relation to the collection of data as set out in the UK Life Sciences Strategy that was coordinated by Professor Sir John Bell. Managed access agreements could provide a vehicle to support ongoing monitoring of new treatments and set the UK apart as a leader in real-world evidence collection. With uncertainty facing the life sciences industry in light of Brexit, this could provide an opportunity for the UK to be a leader in innovative solutions to support access to new treatments and, in turn, encourage inward investment and companies to launch in the UK in a timely manner.

The recent consultation from the DHSC in relation to charging for NICE's appraisals suggested that it would enable NICE to adapt its processes to meet demand and "adapt its methods and processes to different types of technology".[51] NICE has also demonstrated

its ability to be flexible through the application of a sliding ICER for HST medicines, a fast-track process for highly cost-effective medicines, the introduction of end-of-life criteria and the operation of the Cancer Drugs Fund (CDF) since 2016.

In this vein, MAP has consulted with members of the Steering Group to consider possible flexibilities that could be introduced to the current STA so that it is better suited to the specific nature of rare diseases. We have developed a range of options for consideration and discussion with stakeholder groups, including NICE, DHSC and NHS England. It is essential that NICE and NHS England secures value for money for the NHS and the taxpayer, but we believe that the elements outlined below would achieve that, as well as meeting the significant unmet need for this group of patients.

A transparent, fair process is most likely to deliver equality for patients. The following flexibilities may help to deliver a more equitable system and we urge NICE and stakeholders to consider these as part of the NICE methods review and other efforts to support accelerated access to medicines in England:

- Introduce formal changes to the evidence requirements for STAs for orphan medicines. The nature of this flexibility should be informed by a range of stakeholders with experience of developing and assessing orphan medicines
- Drawing from the HST methodology, consider introducing a sliding ICER scale for orphan medicines up to £100,000
- Consider adapting the evidence review group brief for orphan treatments within the STA programme
- Embed formal opportunities for negotiation between companies and NHS England for orphan medicines assessed within the STA work programme
- Consider an interim recommendation for orphan medicines, in line with the Cancer Drugs Fund and new processes from the Scottish Medicines Consortium to support real-world evaluation of treatment impact

We welcome the opportunity to discuss the findings of this report with all those who have an interest in and/or responsibility for ensuring that patients in England can access the latest cutting-edge medicines for rare diseases.

Please contact MAP on enquiries@mapbiopharma.com to discuss the findings in this report and its recommendations.

References

[1] Rare Disease UK, *What is a rare disease*, https://www.raredisease.org.uk/what-is-a-rare-disease/ Accessed 15th February 2019

[2] PhRMA,*A decade of innovation in rare diseases*, 2015, available: http://phrma-docs.phrma.org/files/dmfile/PhRMA-Decade-of-Innovation-Rare-Diseases4.pdf Accessed 1st October 2018

[3] Department of Health, *UK Strategy for Rare Diseases*, 2013, available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/260562/UK_Strategy_for_Rare_Diseases.pdf accessed 14th September 2018

[4] Department of Health and Social Care, *UK Strategy for Rare Diseases: Rare Diseases Implementation Plan for England*, February 2018, available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/679123/UK_strategy_for_rare_diseases_-_implementation_plan_for_England.pdf accessed 10th October 2018

[5] Findacure, *Rare diseases*, https://www.findacure.org.uk/rare-diseases/ Accessed 30th August 2018

[6] PhRMA,*A decade of innovation in rare diseases*, 2015, available: http://phrma-docs.phrma.org/files/dmfile/PhRMA-Decade-of-Innovation-Rare-Diseases4.pdf Accessed 1st October 2018

[7] European Medicines Agency,*Orphan medicines in the EU – leaving no patient behind*, http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2017/12/WC500240710.pdf Accessed 30th August 2018

[8] Department of Health, *UK Strategy for Rare Diseases*, 2013, available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/260562/UK_Strategy_for_Rare_Diseases.pdf accessed 14th September 2018

[9] Department of Health and Social Care, *UK Strategy for Rare Diseases: Rare Diseases Implementation Plan for England*, February 2018, available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/679123/UK_strategy_for_rare_diseases_-_implementation_plan_for_England.pdf accessed 10th October 2018

[10] Garcia Sanchez JJ, Marshall J, Hill C – MAP BioPharma Limited, Cambridge, UK, "Review of the recommendations made by NICE and SMC relating to treatments for rare diseases", Presented at ISPOR 19th Annual European Congress; Vienna, Austria; October 31st November 2nd, 2016. Presentation Code: PHP280, https://mapbiopharma.com/wp-content/uploads/2016/07/ISPOR-Poster-NICESMC-submissions-in-rare-disease.pdf accessed 30th August 2018

[11] Hansard, *Rare diseases: drugs* (Question 169119), available at: https://www.parliament.uk/business/publications/written-questions-answers-statements/written-question/Commons/2018-09-03/169119 accessed 13th September 2018

[12] Hansard, *Access to Orkambi*, available at: https://hansard.parliament.uk/Commons/2018-07-17/debates/69A75F9C-184C-448A-A02D-1B747B91731C/AccessToOrkambi accessed 13th September 2018

[13] Roche,*Leaving no-one behind: improving access to medicines for rare disease patients*, April 2018

[14] Hansard, *Access to Orkambi*, available at: https://hansard.parliament.uk/Commons/2018-07-17/debates/69A75F9C-184C-448A-A02D-1B747B91731C/AccessToOrkambi accessed 13th September 2018

[15] National Institute for Health and Care Excellence,*Pirfenidone for treating idiopathic pulmonary fibrosis Technology appraisal guidance [TA504]*, February 2018, available at: https://www.nice.org.uk/guidance/ta504/history accessed 14th September 2018

[16] National Institute for Health and Care Excellence, *British Thoracic Society Appeal letter*, available at: https://www.nice.org.uk/guidance/ta504/documents/appeal-letter-3 accessed 14th September 2018

[17] National Institute for Health and Care Excellence,*Mifamurtide for the treatment of osteosarcoma Technology appraisal guidance [TA235]*, available at: https://www.nice.org.uk/guidance/ta235/history accessed 14th September 2018

[18] Roche, *Leaving no-one behind: improving access to medicines for rare disease patients*, April 2018

[19] National Institute for Health and Care Excellence,*Nusinersen for treating spinal muscular atrophy ID1069*, available at: https://www.nice.org.uk/guidance/indevelopment/gid-ta10281 accessed 13th September 2018

[20] National Institute for Health and Care Excellence, *Consultation on Batch 54 draft remits and draft scopes and summary of comments and discussions at scoping workshops*, available at: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/Block-scoping-reports/batch-54-block-scoping-report.pdf accessed 13th September 2018

[21] National Institute for Health and Care Excellence, *Appraisal consultation document: Nusinersen for treating spinal muscular atrophy*, August 2018, available at: https://www.nice.org.uk/guidance/gid-ta10281/documents/appraisal-consultation-document accessed 13th September 2018

[22] Cystic Fibrosis Trust,*NICE rejects Orkambi*, June 2018, available at: https://www.cysticfibrosis.org.uk/news/nice-rejects-orkambi accessed 13th September 2018

[23] Mirror,*Thousands of patients denied 'wonder drug' for cystic fibrosis to stage protests*, June 2017 available at: https://www.mirror.co.uk/news/uk-news/thousands-patients-denied-wonder-drug-10688310 accessed 13th September 2018

[24] Pharmaphorum, *Fury as NHS rejects cystic fibrosis drug price offer*, July 2018, available at: https://pharmaphorum.com/news/fury-as-cf-drug-pricing-talks-still-deadlocked/ accessed 13th September 2018

[25] National Institute for Health and Care Excellence, *Committee Papers 2: Lumacaftor and ivacaftor combination therapy for treating cystic fibrosis homozygous for the F508del mutation [ID786]*, available at: https://www.nice.org.uk/guidance/ta398/documents/committee-papers-2 accessed 13th September 2018

[26] National Institute for Health and Care Excellence, *Lumacaftor–ivacaftor for treating cystic fibrosis homozygous for the F508del mutation*, available at: https://www.nice.org.uk/guidance/ta398/chapter/4-Committee-discussion accessed 13th December 2018

[27] Specialised Healthcare Alliance, *Spring survey results*, June 2018, available at: http://www.shca.info/perch/resources/shca-survey-results-briefing-190618.pdf accessed 13th September 2018

[28] Muscular Dystrophy UK, *Breaking news: NICE not recommending SMA treatment Spinraza on the NHS*, August 2018, available at: https://www.musculardystrophyuk.org/news/news/breaking-news-nice-not-recommending-sma-treatment-spinraza-on-the-nhs/ accessed 13th September

[29] Cystic Fibrosis Trust, *Stopping the Clock: in your region*, available at: https://www.cysticfibrosis.org.uk/the-work-we-do/campaigning-hard/stopping-the-clock/in-your-region accessed 13th September 2018

[30] Detiček A. et al (2018), 'Patient Access to Medicines for Rare Diseases in European Countries Value in Health,' Volume 21, Issue 5, May 2018, Pages 553-560

[31] Sarnola, K., Ahonen, R., Martikainen, J.E. et al. Eur J Clin Pharmacol (2018) 74: 895. https://doi.org/10.1007/s00228-018-2457-x

[32] Detiček A. et al (2018), 'Patient Access to Medicines for Rare Diseases in European Countries Value in Health,' Volume 21, Issue 5, May 2018, Pages 553-560

[33] Nicod E. et al (2017), 'HTA programme response to the challenges of dealing with orphan medicinal products: Process evaluation in selected European countries', Health Policy, http://dx.doi.org/10.1016/j.healthpol.2017.03.009

[34] Zamora et al (2017), 'Comparing Access to Orphan Medicinal Products (OMPs) in the United Kingdom and other European countries', Office of Health Economics

[35] Sarnola, K., Ahonen, R., Martikainen, J.E. et al. Eur J Clin Pharmacol (2018) 74: 895. https://doi.org/10.1007/s00228-018-2457-x

[36] Zamora et al (2017), 'Comparing Access to Orphan Medicinal Products (OMPs) in the United Kingdom and other European countries', Office of Health Economics

[37] Detiček A. et al (2018), 'Patient Access to Medicines for Rare Diseases in European Countries Value in Health,' Volume 21, Issue 5, May 2018, Pages 553-560

[38] Detiček A. et al (2018), 'Patient Access to Medicines for Rare Diseases in European Countries Value in Health,' Volume 21, Issue 5, May 2018, Pages 553-560

[39] Nicod E. et al (2017), 'HTA programme response to the challenges of dealing with orphan medicinal products: Process evaluation in selected European countries', Health Policy, http://dx.doi.org/10.1016/j.healthpol.2017.03.009

[40] Health Foundation/IPSOS MORI, *NHS at 70: Public Perceptions*, June 2018, available at: https://health.org.uk/sites/health/files/NHS%20at%2070-Public-perceptions.pdf accessed 14th September 2018

[41] Sarnola, K., Ahonen, R., Martikainen, J.E. et al. (2018), Eur J Clin Pharmacol 74: 895. https://doi.org/10.1007/s00228-018-2457-x

[42] Roche, *Leaving no-one behind: improving access to medicines for rare disease patients*, April 2018

[43] Roche, *Leaving no-one behind: improving access to medicines for rare disease patients*, April 2018

[44] All Wales Medicines Strategy Group, *Review of the process for appraising orphan and ultra-orphan medicines and medicines developed specifically for rare diseases*, July 2018 http://www.awmsg.org/docs/awmsg/awmsgdocs/AWMSG%20meetings/2018/18%20July%2018/Enc%207%20Rare%20disease%20medicines%20(RDM)%20review.pdf accessed 14th September 2018

[45] MAP BioPharma. Available at http://mapbiopharma.com/

[46] MAP BioPharma. Available at http://mapbiopharma.com/

[47] https://www.gov.scot/Publications/2016/12/9192/0

[48] MAP BioPharma. Available at http://mapbiopharma.com/

[49] MAP BioPharma. Available at http://mapbiopharma.com/

[50] Department of Health and Social Care, *NHS to save £1 billion on its medicines bill in 2019*, available at: https://www.gov.uk/government/news/nhs-to-save-1-billion-on-its-medicines-bill-in-2019 accessed 13th December 2018

[51] Department of Health and Social Care, *NICE's technology appraisal and highly specialised technology work programmes – Charging and Appeal Panels: Consultation on charging for technology appraisal and highly specialised technology recommendations and miscellaneous amendments to NICE legislation*, available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/733036/NICE_consultation_document_1.pdf accessed 14th September 2018

February 2019

MAP BioPharma Limited

www.mapbiopharma.com

enquiries@mapbiopharma.com

+44 (0) 1480 832360