

**GENETIC
ALLIANCE** UK

ACTIONFOR**ACCESS**

A report from Genetic Alliance UK for
the All Party Parliamentary Group on Rare,
Genetic and Undiagnosed Conditions



Acknowledgements

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The All Party Parliamentary Group (APPG) on Rare, Genetic and Undiagnosed Conditions aims to increase awareness of rare, genetic and undiagnosed conditions in Parliament and help to ensure that patients and families affected by these conditions have access to appropriate care and support.



Genetic Alliance UK is the national charity working to improve the lives of patients and families affected by all types of genetic conditions. We are an alliance of over 200 patient organisations. Genetic Alliance UK provides the secretariat for the APPG on Rare, Genetic and Undiagnosed Conditions.



Rare Disease UK is a multi-stakeholder campaign run by Genetic Alliance UK, working with the rare disease community and the UK's health departments to effectively implement the UK Strategy for Rare Diseases.



SWAN UK (syndromes without a name) is a patient and family support service run by Genetic Alliance UK. SWAN UK offers support and information to families of children with undiagnosed genetic conditions.

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1. Executive Summary

The All Party Parliamentary Group for Rare, Genetic and Undiagnosed Conditions has met three times to discuss access to rare disease medicines in 2016, 2017 and 2018. This report is the result of work undertaken following the 2017 meeting, which called for a new vision from the perspective of patients for access to rare disease medicines in the UK.

Around 3.5 million people in the UK will be affected by a rare disease at some point in their lives. Three quarters¹ of all rare diseases affect children, and we estimate that rare diseases are responsible for about a third of infant mortality in the UK². There are licensed medicinal products available for only a small minority of rare diseases. Despite this, it is incredibly difficult for patients to access potentially life-changing treatments.

Health technology assessment (HTA) decides whether or not medicines will be made available on the NHS. But the path between licence and HTA decision is governed by a system that is difficult to navigate. We have identified five systemic problems: fragmentation, inflexibility, challenges with capturing the value of treatments, delays and a lack of transparency. But behind these systemic problems are two fundamental problems: uncertainty and money.

Small patient populations and accelerated market authorisation means that rare disease medicines can rarely have sufficient evidence to meet the expectations of health technology assessors. This means the HTA decision for rare disease medicines is almost always limited by high uncertainty. Coupled with this uncertainty is a regular impasse between the comparatively high prices requested by pharmaceutical companies for their medicines and the availability of NHS money to pay for them. Fewer life-saving treatments are reaching rare disease patients and not only does this mean the UK is falling drastically behind other European nations in terms of treatments available, it also means patients and their families can be left in the dark, unsure of what's next.



1. Executive Summary (continued)

So how can we solve this?

Addressing the uncertainty problem: Genetic Alliance UK recommends that the UK make rare disease medicines available in the NHS as soon as they receive marketing authorisation through a period of managed access. Once introduced, evidence should be gathered from within the NHS in relation to their value for an eventual HTA. This should be on terms set as the period of evidence gathering begins. The funds to cover the costs of these medicines should be provided through flexible schemes arranged between Government and industry.

Addressing the systemic problems: Genetic Alliance UK recommends that NICE develop a single flexible approach for making decisions about access to rare disease medicines, ensuring all rare disease medicines are assessed by an appropriate pathway with realistic expectations for evidence and outcomes.

Addressing the money problem: Genetic Alliance UK calls on both industry and government to clearly explain the process for setting rare disease medicines prices, and how the price that the government can afford is set. The benefits of the recently agreed Voluntary Pricing and Access Scheme for Branded Medicines to all stakeholders should be set out. This dialogue should guide the rare disease patient community and the public to a greater understanding of reference pricing and the voluntary pricing and access scheme for branded medicines.

Many organisations, and members of Genetic Alliance UK, have been campaigning for decades for access to the treatments patients so desperately need.

Let's build on this, together, let's call for #ACTIONFORACCESS

2. Glossary

EMA

European Medicines Agency

HST

The NICE Highly Specialised Technology programme

HTA

Health technology assessment - the decision as to whether a treatment represents value for money to the NHS

HTA body

Institution responsible for delivering health technology assessment

IFR

Individual funding request

NICE

National Institute for Health and Care Excellence

PACS

Peer approved clinical system

QALY

Quality Adjusted Life Year - a measure of cost-effectiveness

Rare disease

Condition affecting fewer than 1 in 2,000 people in the UK

SMC

Scottish Medicines Consortium

STA

The NICE Single Technology Appraisal programme

VPAS

Voluntary Pricing and Access Scheme for Branded Medicines



3. Background

A rare disease is one that affects less than 5 in 10,000 of the general population. There are between 6,000 and 8,000 known rare diseases. Within the UK, approximately 3.5 million people will be affected by a rare disease at some point in their lives.

For the majority of those with a rare disease, accessing medicine is a challenge. Many conditions have no known cause/pinpointed cause. Even more, have no ongoing research into medicine/medicine in development. 95% of rare diseases have no licensed treatment. Evidently, few medicines have made it into the laboratory - but even then, this does not guarantee patient access.

Currently, 174³ medicines for rare diseases (designated 'orphan medicines') have been deemed safe for use. This is determined by a process known as market authorisation, or licensing, which weighs up the risk and benefit of the medicine. Market authorisation specifies what condition, illness or symptom (indication) the medicine is to be used for and in what dose. In practice, almost all new medicines for rare diseases (otherwise known as orphan medicines) in the UK are licensed by the European Medicines Agency (EMA).

The NHS does not reimburse/provide access to all licensed medicines. Rather, to determine which licensed medicines should be reimbursed, there is a health technology assessment (HTA) process. In part, the HTA compiles and reviews evidence (is a systematic evaluation of) about the properties, effects and impacts of a health technology. Though there are many different HTA methods in the UK, all predominantly evaluate how well a medicine works in relation to how much it costs the NHS. Other factors are taken into consideration (such as societal values, acceptability, existing treatments) and a decision is made. The outcome of the HTA is a recommendation, which can be three-fold. The medicine can be:

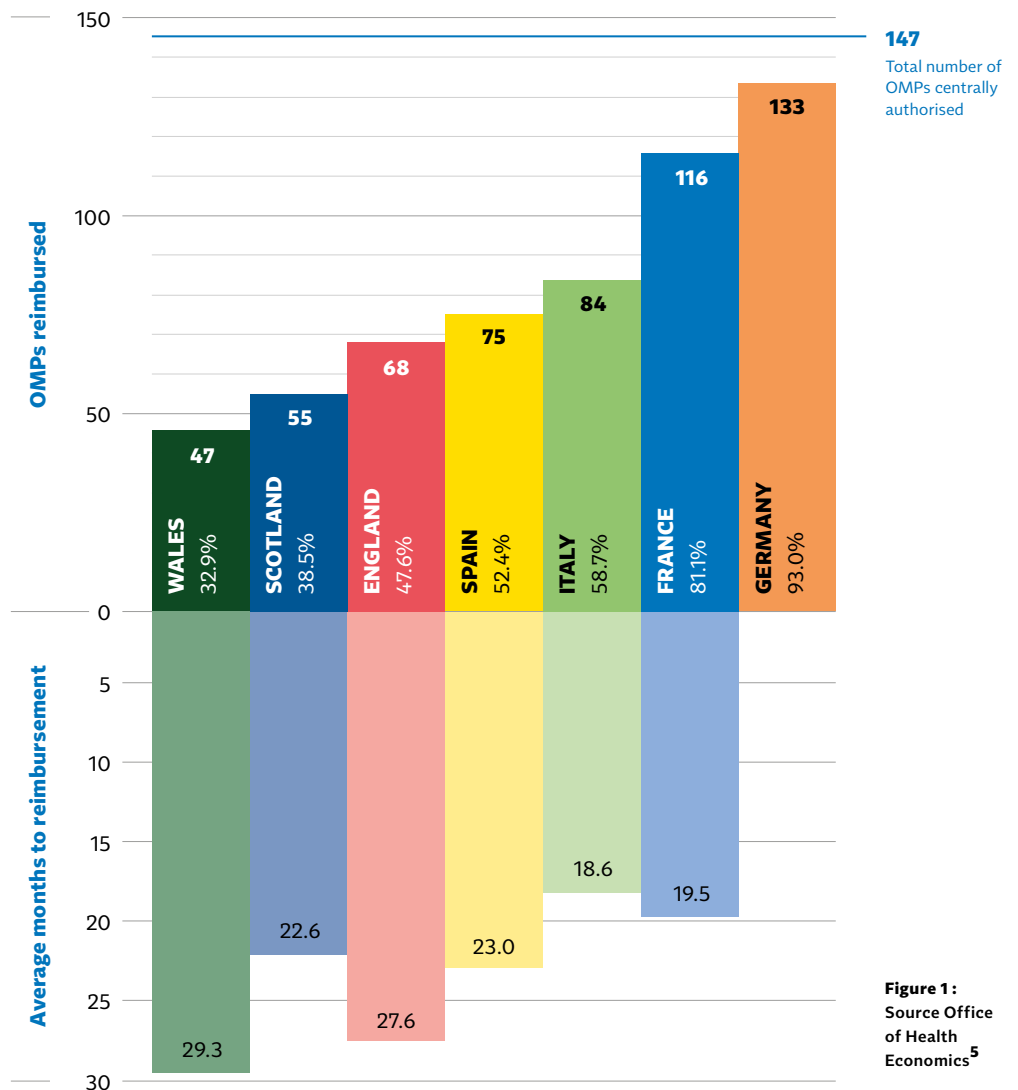
- **Recommended** (in line with its market authorisation)
- **Recommended with restrictions** (a subgroup of its market authorisation)
- Recommended only in research, with no reimbursement. This is referred to as a **managed access agreement**. It enables patients to receive new treatments while long-term data on them is still being gathered, and before final funding decisions are taken (as the end of the five years).
- **Not recommended**

Overall we are underperforming in the UK. Compared to Germany, France, Italy and Spain; England, Scotland and Wales are behind both in how many treatments for rare conditions are approved and in how long these decisions take. Of the medicines that are approved, a significant portion are recommended with restrictions. In fact, some medicines are not assessed by a HTA at all (either due to a lack of appraisal or no submission identified). In England, the main HTA body failed to appraise almost half of all orphan medicines; in Scotland, just over a third were appraised. Nowhere were all centrally authorised medicines assessed.⁴

The link between the availability of rare disease medicines, and the outcome of patients with rare diseases, is evident. Rare disease medicines can not only save lives, but be completely transformative; progressive conditions may be stopped or slowed, and patients may walk and/or see for longer. These benefits may be felt too late, or not at all, as a result of the poor HTA system in the UK.

For UK patients, failure to provide timely and equitable access to medicines has been a long-standing issue. We believe this problem cannot be pinned on any one single cause, but is a culmination of systemic and fundamental issues.

Access to rare disease medicines and average decision time (2017)



3. Background *(continued)*

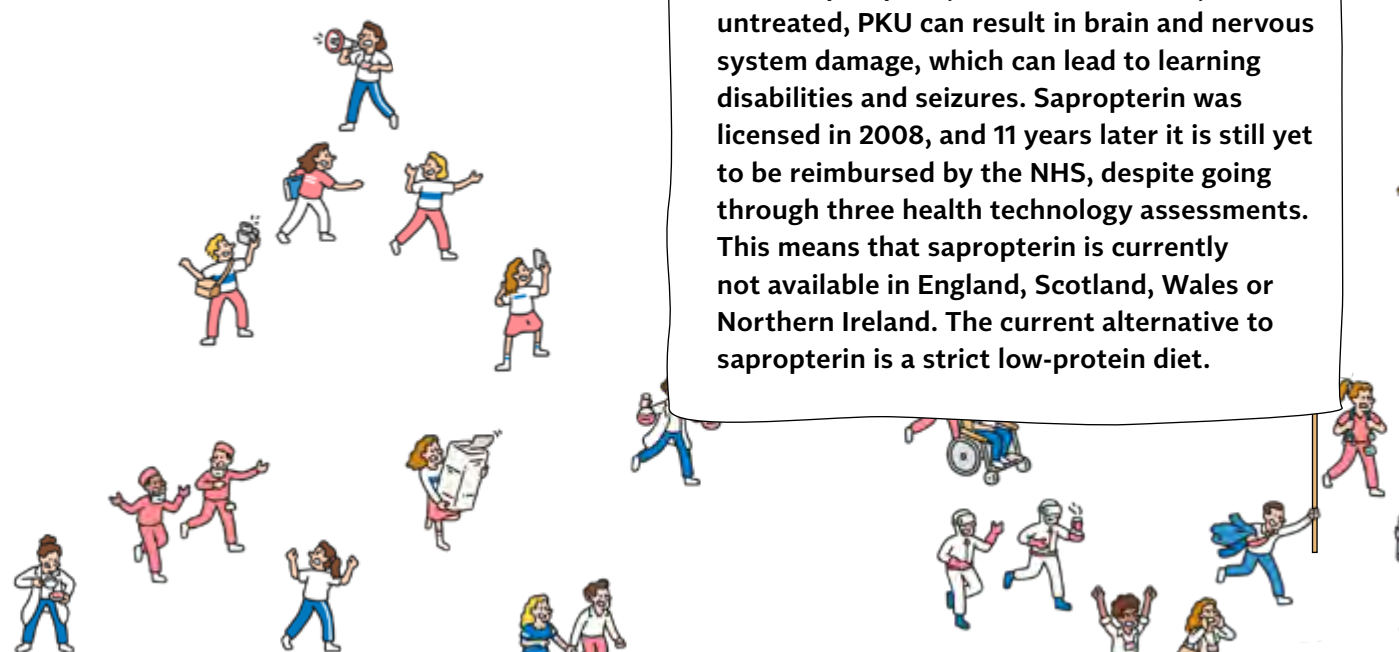
The access to rare disease medicines challenge was presented to the All Party Parliamentary Group for Rare, Genetic and Undiagnosed Conditions on 11 October 2017. Following this meeting, Genetic Alliance UK undertook to produce recommendations, led by the patient community, which would aim to solve the challenges we face in the UK. Instead of specific minor adjustments or additions to existing systems and pathways, Genetic Alliance UK has chosen to capture an overview of the situation the UK is in, and to make ambitious recommendations for a path forward. The results of this work are presented here.

The Genetic Alliance UK team has carried out more than 50 interviews and information gathering sessions with a wide range of stakeholders including patients, clinicians, academics, journalists, health department civil servants, health technology assessors, and pharmaceutical industry representatives. The findings from this work have been combined with desk research, and the two analysed in concert, enabling the construction of the overview on which we have based our recommendations.

We have also carried out a discrete choice experiment to understand the relative priorities of two key stakeholders, patients and the pharmaceutical industry. Our analysis of the problem and our recommendations have been tested in further interviews and by surveys.

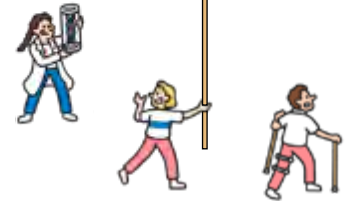
Case studies

This report uses case studies from rare disease treatments that have been assessed by UK health technology assessment bodies. Two of the treatments listed below are not yet approved for access within the NHS in England, this is despite market authorisations in 2008 and in 2018. Three of the treatments listed have now had funding approved in England, but these decisions came at least 24 months after market authorisation.



Sapropterin dihydrochloride (Kuvan) (from here on will be referred to as sapropterin), is a medicine designed to treat phenylketouria (PKU). PKU is a rare condition in which there is a build up of phenylalanine in the body. If left untreated, PKU can result in brain and nervous system damage, which can lead to learning disabilities and seizures. Sapropterin was licensed in 2008, and 11 years later it is still yet to be reimbursed by the NHS, despite going through three health technology assessments. This means that sapropterin is currently not available in England, Scotland, Wales or Northern Ireland. The current alternative to sapropterin is a strict low-protein diet.

Cerliponase alfa (Brineura) is an enzyme replacement therapy to treat Batten disease, a broad class of fatal neurodegenerative diseases. Cerliponase alfa slows disease progression, allowing children with Batten disease to maintain their sight and ability to walk for longer. Cerliponase alfa was licensed in 2017 but a deal between NHS England and Biogen was made two years later in September 2019 meaning that cerliponase alfa is now available in England only.

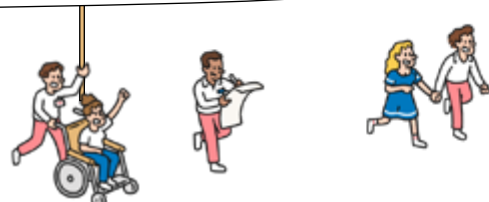


Nusinersen (Spinraza) is the first and only treatment for 5q Spinal Muscular Atrophy (SMA); a rare, genetically inherited neuromuscular condition resulting in a wide range of movement problems. Nusinersen was licensed in 2017 and is currently accessible to a portion of SMA patients in England and Scotland through a managed access agreement.



The combination treatment of **ivacaftor and lumacaftor (Orkambi)** (from here on will be referred to as ivacaftor/lumacaftor) is licensed to treat cystic fibrosis patients with an F508del mutation. Cystic fibrosis is a rare condition where thick, sticky mucus builds up in the body, most notably in the lungs and digestive system. This causes a wide range of symptoms including susceptibility to infections, reduced lung function and poor nutritional absorption. Ivacaftor/lumacaftor was licensed in 2008 for patients aged 12+ years and in 2018 for 2-12 years. Despite being recently reimbursed in Ireland and the SMC recommending ivacaftor/lumacaftor in September 2019, NICE still have not recommended this treatment for England and Wales.

Ataluren (Translarna) is a licensed medicine that slows down the progression of nonsense mutation Duchenne muscular dystrophy (nmDMD), a rare condition that causes progressive muscle weakness and disability. Ataluren allows children who are affected by the condition to maintain the ability to walk for longer. The medicine was initially selected to be evaluated through NHS England's specialised commissioning route in 2014 but legal challenges arose resulting in ataluren being assessed through the HST evaluation and a positive recommendation was made in 2016, two years after the EMA had approved the medicine. Ataluren is now available in England, Wales and Northern Ireland for patients aged two and above however, ataluren is only available for patients aged four and above in Scotland through a funding request.



4. Defining the problem

Over the course of the past six years of focused advocacy on the topic of access to rare disease medicines, Genetic Alliance UK has seen the problem of access to rare disease medicines defined and presented in many different ways. Specific processes, specific challenges, specific elements of the environment have been singled out for attention. Various commentators and stakeholders have each defined the problem, often from a particular stakeholder perspective, or less usefully from a narrow point of view formed from a specific experience.

Here we set out the perspective of patients affected by rare conditions on the definition of this problem. This categorisation of the problem is drawn from interviews with patients, health department civil servants, health technology assessors, pharmaceutical industry representatives, clinicians and academics. We have tested our definition of the problem with the membership of Genetic Alliance UK, and found that our definition encompasses all of their experiences.

4.1 Systemic issues

The focus of the vast majority of attempts to solve access to rare disease medicine issues in the UK has been on solving the inadequacies of our current policies. These issues, though frequently felt across the system, are specific to individual pathways and are the result of some flaw in the design or implementation of the specific process, some issue with how separate processes interact or some inadequacy in the implementation of the process. We have labelled these issues ‘systemic issues’ and have identified five separate broad overarching systemic issues.

4.1.1 The fragmentation problem

For a single rare disease medicine, for a single indication, there are multiple possible pathways through which it may be assessed. Despite the number of routes, there are only two pathways that are designed specifically for rare disease medicines. Both of these pathways designed for rare disease medicines are reserved for *ultra-rare* treatments and, as a result, many medicines are either assessed via routes designed for more common treatments, or not be assessed at all. Too often, rare disease medicines end up ‘falling through the gaps’.

Throughout the UK, there are seventeen possible pathways that could deliver access for a patient to rare disease medicines (as illustrated in figure 2). In England, Wales and Northern Ireland, the National Institute for Health and Care Excellence (NICE) serves as the predominant HTA body (Wales and Ireland have their own HTA bodies but typically follow the guidance of NICE). In England, NICE assesses rare disease treatments through the NICE Highly Specialised Technology (HST) route and the Standard Technology assessment (STA). NHS England currently also assesses rare disease medicines through the annual prioritisation process (although it was recently announced that NICE will appraise all new medicines as of April 2020 as part of the Voluntary Pricing and Access Scheme for Branded Medicines (VPAS) agreement ⁶). In Scotland, rare disease medicines are assessed by the Scottish Medicines Consortium (SMC); ultra-rare medicines via the ultra-orphan pathway. Each route has different entry criteria and methodologies.



Figure 2: Seventeen Pathways For Rare Disease Medicines to be Assessed

Seventeen Pathways For Rare Disease Medicines to be Assessed	
NICE	
1.	Highly Specialised Technology Programme (HST) (<i>can apply to Northern Ireland and/or Wales</i>)
2.	Single Technology Appraisal (STA) (<i>can apply to Northern Ireland and/or Wales</i>)
3.	Cancer Drugs Fund
4.	Fast Track Technology Appraisal (<i>can apply to Northern Ireland and/or Wales</i>)
5.	Accelerated Access Pathway (AAP)
NHS England	
6.	Prioritisation process via Clinical Priorities Advisory Group
7.	Individual Funding Requests
8.	Commissioning Through Evaluation Programme
Wales	
9.	All Wales Medicines Strategy Group Appraisal Process (Standard Route)
10.	Individual Patient Funding Requests
Scotland	
11.	Scottish Medicines Consortium New Product Assessment (Standard Route)
12.	Peer Approved Clinical System (PACS) (Tier 2)
13.	Ultra Orphan Medicines Pathway
14.	Peer Approved Clinical System (PACS) (Ultra Orphan)
15.	Individual Patient Treatment Requests (<i>for medicines where no submission has been made to SMC</i>)



4.1.1 The fragmentation problem (continued)

The multiple HTA bodies in England complicate and delay the HTA process. NICE has a topic selection process to determine whether it should assess a medicine, but there is no clear process in place for rejected medicines - it is therefore difficult to predict how and when a medicine will be assessed. **| This fragmentation is particularly evident in the case of sapropterin; a medicine that has already been reviewed twice by NHS England. Between the two reviews, a NICE assessment was commenced and suspended. A third NHS England review is planned for sapropterin as part of the second NHS England prioritisation process for 2019. |**

This fragmentation will be reduced in England following the VPAS agreement, as NICE have committed to assessing all new medicines by April 2020. This solution is likely to exacerbate fragmentation within NICE, where multiple assessment routes exist. The Highly Specialised Technologies pathway is most appropriate to appraise rare disease medicines but due to its strict entry criteria (Figure 3), many medicines are forced into the alternative STA pathway. This means that the tools best placed to understand the value of a rare disease medicine are woefully underused. This restrictive approach goes against the instruction from Parliament to NICE⁷ to deliver a pathway to assess technologies for rare and very rare conditions.

The STA pathway is designed for medicines to treat common conditions, so has unrealistic expectations of the evidence that might be available to demonstrate the value of rare disease medicines, meaning they are often not recommended. **| This has been the case for nusinersen as it was not eligible for the HST pathway and therefore was assessed on the STA pathway resulting in a non-recommendation. |** Consequently, rare disease treatments assessed through these pathways are often rejected, and the only remaining option for patients is to rely on gaining access on a case-by-case basis through the Independent Funding Request (IFR) process - a pathway designed for use in single, exceptional circumstances. In this manner, many rare disease medicines 'fall through the cracks'.

| Ivacaftor/lumacaftor serves as a prime example. Cystic fibrosis is considered as a larger rare condition, deemed 'rare but not rare enough' for the HST pathway. With over 3,000 people in the UK that could benefit from ivacaftor/lumacaftor (from UK Cystic Fibrosis Registry Report), the medicine was assessed by the NICE STA route. The inappropriateness of this pathway to assess the medicine was so evident that in the scoping workshop for ivacaftor/lumacaftor, the Cystic Fibrosis Trust expressed that 'this technology's appraisal via [NICE's STA] process ... will expose the technology to an arbitrary negative recommendation.' |



Figure 3: Highly Specialised Technology programme entry criteria**Highly Specialised Technology programme entry criteria**

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

Figure 4: SMC Ultra-orphan entry criteria**SMC Ultra-orphan entry criteria**

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

4.1.1 The fragmentation problem (continued)

To exacerbate matters, different assessment routes are available in each of the devolved nations, as noted in Figure 2. Across the UK, three separate decisions can be made on the same treatment, and it is frequently the case that they reach differing conclusions. For instance, the SMC appraises more rare disease medicines than NICE, but the likelihood of recommendation is higher with NICE. A quarter of SMC assessments are not recommended, compared to 9% of NICE's. This creates a 'postcode lottery', whereby a patient living on one side of the border may have access to medicines that are denied to those on the other side. **For instance, ivacaftor/lumacaftor is available to patients in Scotland but not in England. Additionally, rare disease medicines may have different inclusion criteria across the devolved nations. For example, ataluren is available for people from the age of 2 with nmDMD in England and Wales but only available from the age of 4 in Scotland.** As well as failing patient communities, this goes against one of the core aims of the UK Strategy for Rare Diseases, to promote equity of access across all four UK countries.

Figure 5: Key routes for assessing a rare disease medicine

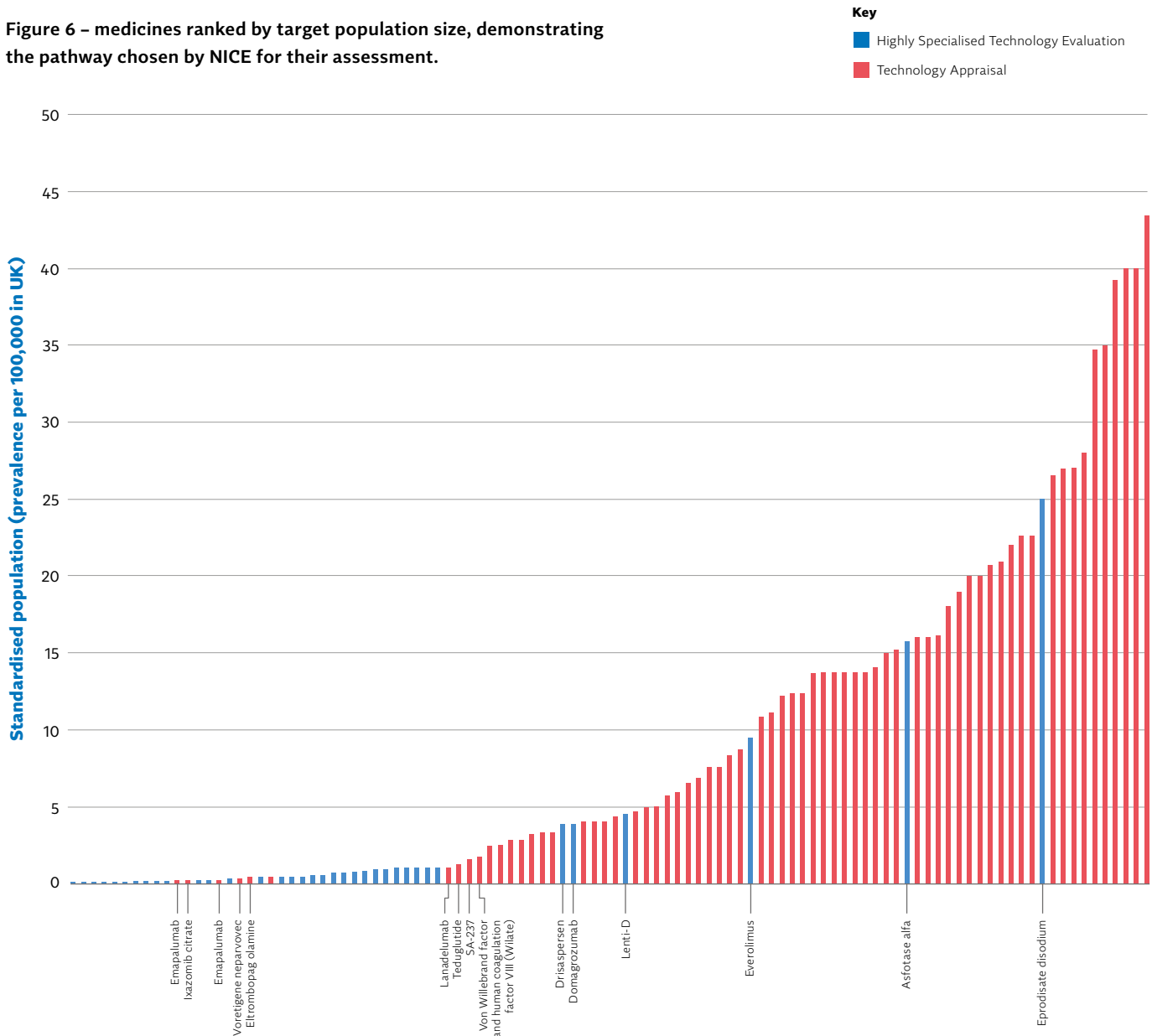
Assessment pathway	Overview
NICE NICE Highly Specialised Technology (HST)	Designed for highly specialised treatments, used for very rare conditions. Considerations made to capture non-health impacts, and patient testimonies
England, Wales and Northern Ireland	NICE HST recommendations are automatically applied in England, and will be considered by Northern Ireland (Northern Ireland Department of Health) and Wales (AWMSG)
NICE Single Technology Appraisal (STA)	Designed to appraise a single product, device or other technology, with a single indication. No extra allowances for rare disease medicines.
England, Wales and Northern Ireland	NICE STA recommendations are automatically applied in England and Wales, and will be considered in Northern Ireland (by Northern Ireland Department of Health)
England NHS England prioritisation process	A biannual process used to select medicines for reimbursement, based on a prioritisation process. Cost-effectiveness is used to base decision, and available medicines budget is taken into account. Multiple medicines are assessed together.
Wales All Wales Medicines Strategy Group evaluation	As well as advising whether NICE HST guidance should be implemented in Wales, AWMSG makes decisions on what should be routinely commissioned. AWMSG would not normally assess a treatment that NICE intend to publish a final technology appraisal on within the next 12 months.
Scotland Scottish Medicines Consortium	A biannual process used to select medicines for reimbursement, based on a prioritisation process. Cost-effectiveness is used to base decision, and available medicines budget is taken into account. Multiple medicines are assessed together.
Peer Approved Clinical System (PACS) Tier 1 / ultra-orphan pathway	Designed for ultra-orphan medicines. Higher levels of uncertainty accepted in economic case for ultra-orphan medicines, and period of data collection integrated into pathway.

4.1.2 The inflexibility problem

A fragmented system could still work well, if there were not gaps between assessment routes, or if each route was sufficiently flexible to appraise rare disease medicines. The current access system meets neither requirement. Because of this, many rare disease medicines are assessed by incompatible HTA pathways.

The most impactful piece of inflexibility in the system is the choice around which pathway NICE uses to assess rare disease medicines. The fundamental best predictor of the amount of evidence available on the value of a treatment is its target population size. The HST pathway is best suited to address the smallest population sizes, yet many treatments that have the smallest population sizes are not selected for this pathway. Figure 6 shows medicines for tiny populations being selected for the general STA pathway, and medicines for larger populations being selected for the HST pathway.

Figure 6 – medicines ranked by target population size, demonstrating the pathway chosen by NICE for their assessment.



4.1.2 The inflexibility problem (continued)

When a treatment is refused entry to the HST pathway the reason given is that the seven criteria for entry (Figure 3) are not all satisfied. This can be extremely frustrating to the patient community, as this choice drastically reduces the chance of a medicine being approved for funding. But this message is all the more frustrating as medicines have been selected for HST that do not satisfy all of the criteria. A complex treatment for ADA severe combined immunodeficiency: autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence (Strimvelis) was authorised for use through the HST programme. This is despite it not satisfying the criteria for lifelong use.

Another element of the unfairness of this is highlighted in the fact that the criteria can be interpreted differently because they are not clear. **For instance, sapropterin — which works for 20% of PKU patients (around 350 individuals) — is on the edge of the HST criteria but was allocated to a STA. However, the process was suspended to determine if a HST should be more appropriate.**

One of the most notable inflexibilities with the current system involves value for money. This is a key consideration to feed into the reimbursement decision, and is calculated by comparing a medicines benefit versus its cost (typically measured as cost per QALY, see figure 7). Each HTA route has a budget threshold in place against which to test value for money against; falling short of this threshold is grounds for rejecting a medicine. Most routes have a different threshold.

Figure 7: Cost-Effectiveness Measures

Cost-Effectiveness Measures

The Quality-Adjusted Life Year (QALY) is a measure used to quantify the effectiveness of a medicine. It captures how a medicine impacts upon quantity and quality of life. QALYs are calculated by estimating the years of life remaining for a patient following a particular treatment, and weighting each year with a quality-of-life score. There are different methods that can be used to quantify quality-of-life, but typically five dimensions are considered (known as an EQ5D measure): mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The QALY 'score' is therefore a combination of the life years gained and quality of life that a medicine generates. A year of perfect health is considered equal to 1 QALY, while death is 0 QALYs. As most medicines do not generate an additional year of perfect life, they typically have a QALY score of below 1.

QALYs are used to outline the cost-effectiveness of a medicine. The price of the medicine is divided by its QALY score to produce a cost per QALY ratio.

Though the SMC does not have a formal QALY threshold, a cost per QALY of below £30,000 is considered value for money. NICE appraisals, meanwhile, introduce a limit on the extra cost per extra QALY. For medicines to be considered cost-effective via the STA route, they must have a maximum cost effectiveness ratio of £50,000 per QALY, meaning each additional year is worth £50,000. The HST route allows for a threshold of up to £100,000 per QALY gained. Technically the threshold can reach £300,000 per QALY but in practice it is very difficult to prove the additional QALYs that warrant the higher budget. **For instance, NICE acknowledged that cerliponase alfa had very high QALY gains, above 30, yet it was still subject to the maximum threshold of £300,000. This means that despite the knowledge that this treatment would provide tremendous health benefits, it was rejected on the grounds of cost-effectiveness, emphasising the rigidity and arbitrary nature of the threshold.⁸**

These budget thresholds discriminate against rare disease medicines, which typically do not fit within these cost-effectiveness limits. For instance, we understand that none of the medicines approved by the HST route, before the threshold was introduced, would have made it through under the new rule. Consequently, few rare disease medicines are approved due to the inflexible budget thresholds within HTAs. This does not necessarily reflect upon the price of rare disease medicines. As the impact of most medicines does not extend to providing a full year of perfect health, for many the cost per QALY may be higher than the actual price of the medicine.

Other inflexibilities exist within the HTA system, such as the restrictive data collection method used in NHSE's prioritisation process. NHS England discriminates against one-off treatments, such as gene therapies, by using a five-year window to capture the benefit and cost-impact of medicines. This distorts the perception of costs. In light of a growing trend towards more high-cost one-off treatments, the impact of this unfair distortion is likely to increase.

The rigid adherence to a one medicine, one indication, approach means that medicines that could be used for more than one use must be assessed again and again for conditions that can sometimes overlap. Everolimus, a treatment for neoplasms in tuberous sclerosis complex (TSC), has been assessed twice for this condition. Once for the treatment of a form of brain tumour (SEGA), and the second time for the treatment of TSC related epilepsy, which can be caused by a SEGA. Similarly if a new branded medicine is known to be effective in addressing a rare condition it cannot be funded on an off-label basis, even for a small number of patients unless its cost is negligible.



4.1.3 The problem with capturing value

We are in an era where there are rare disease medicines that can completely transform the lives of people with rare diseases, stopping the progress of their condition, saving the life of a child or extending lives by decades. Despite this, in many cases this transformative impact is not reflected by the outcome of its HTA process. This is because, using current techniques, the full value of rare diseases medicines are often not captured. Even then, the decision does not reflect wider societal values around rare diseases, but focuses predominantly on cost-effectiveness. This puts patients in the distressing situation, whereby a treatment that could save their lives is withheld, because it does not offer value for money.

Many HTAs do not capture the full clinical picture, let alone the non-health impacts of a rare disease, such as the costs of missing work, travelling to medical appointments, or carrying out full-time caring responsibilities. There are two key reasons: the scope of the evidence base and use of QALY.

Depending on the HTA route chosen, the scope of evidence considered in the decision-making process, can be very restrictive. While the Scottish and Welsh HTA bodies have adapted their processes to incorporate testimonies from patients and clinicians, the HTA processes in England (with the exception of the HST) do not consider such a broad evidence base. The prioritisation process run by NHS England, for instance, currently only takes into consideration published, clinical data.

For instance, in the review of sapropterin, small, clinical trials run by the NHS were considered whereas registry data, collected by the National Society for Phenylketonuria on a larger scale was not taken into account. |

Furthermore, within the available evidence base, HTA decisions are primarily based around how the medicine improves a patient's quality of life and life expectancy as measured by the QALY. The tools to measure quality of life are restrictive and fail to capture the type and range of symptoms, emotions and disadvantages experienced by those with rare conditions. Differences that are important clinically and non-health impacts may therefore not be shown by cost per QALY estimates.



For instance, cerliponase alfa is a lifetime treatment that increases patient stabilisation and slows down disease progression however, the impact this treatment has on the family's health and wellbeing was not assessed. Patients with rare diseases can struggle to benefit from education and secure employment. Rare diseases also often have a disproportionate impact beyond the patient, and can place a considerable burden on caregivers. The severity of rare diseases means patients often require intensive care, usually from a family member, which reduces their ability to work.

Again, this is evident in the case of sapropterin. At the evidence review for sapropterin, representatives of the patient group felt that the information they were able to provide was misinterpreted, and the severity of the condition was not captured. Furthermore, the benefit of the medicine was not fully acknowledged; sapropterin was not deemed preferable to the existing treatment for PKU, diet-management, due to its cost (£14,000- £45,000 per patient per year). However, this comparison fails to acknowledge the wider implications of diet-management. The diet is extremely restrictive and difficult to comply with, 'with many adults going off diet resulting in devastating mental and physical disabilities', and many parents taking time off work to care for their children. Furthermore, diet-management can be more difficult for those from a lower socioeconomic background, addressing this social disparity should be factored into the assessment of the medicine, but its not.

Furthermore, even within its remit, the QALY is flawed in capturing benefit as it is skewed towards acute illnesses. Drugs that are taken for short periods of time tend to score much higher than drugs that are required for life. This means that when a medicine provides more years of life and has to be taken for life, this has a more negative effect on the QALY score compared to a medicine that may provide someone an extra few months. Ivacaftor/lumacaftor is an example of a medicine that is required for life due to the chronic condition of cystic fibrosis and the QALY assessment does not capture the benefit of the medicine.

Due to the limited evidence base, and strict quality of life measures, many HTAs do not fully capture the benefit/impact of a rare disease medicine. It can be tremendously frustrating for patients who may see a significant benefit which is not reflected in the HTA process.

Importantly, the current method of valuing benefits to patients does not reflect the wider societal attitude towards rare diseases. Even if all of the health and non-health benefits of a medicine are taken into account, the HTA decision currently boils down to cost-effectiveness. While this is beneficial from an economic perspective, this means that a medicine which has the change to revolutionise or save someone's life, may be refused. Moreover, even where there are modifiers to influence the decision-making process (e.g. a weighting is placed on unmet need) these do not adjust the process enough to align with societal values in its place. For instance, it is generally accepted that improving the health of those who are sicker is preferable to improving the health of healthier individuals. However, if more QALYs are gained by medicines which improve the health of individuals (who already have better health), then those medicines are likely to be funded. Therefore it is questionable whether it is right to be reducing a life-saving treatment to a measure of cost-effectiveness.



4.1.4 The problem with delays and pauses

Unlike some European countries, access to medicines in the UK is not immediate. Access is dependent on a health technology assessment being first conducted, and this process is typically prolonged further by delays and pauses. As a result, patients in the UK access medicines much slower than the European average.

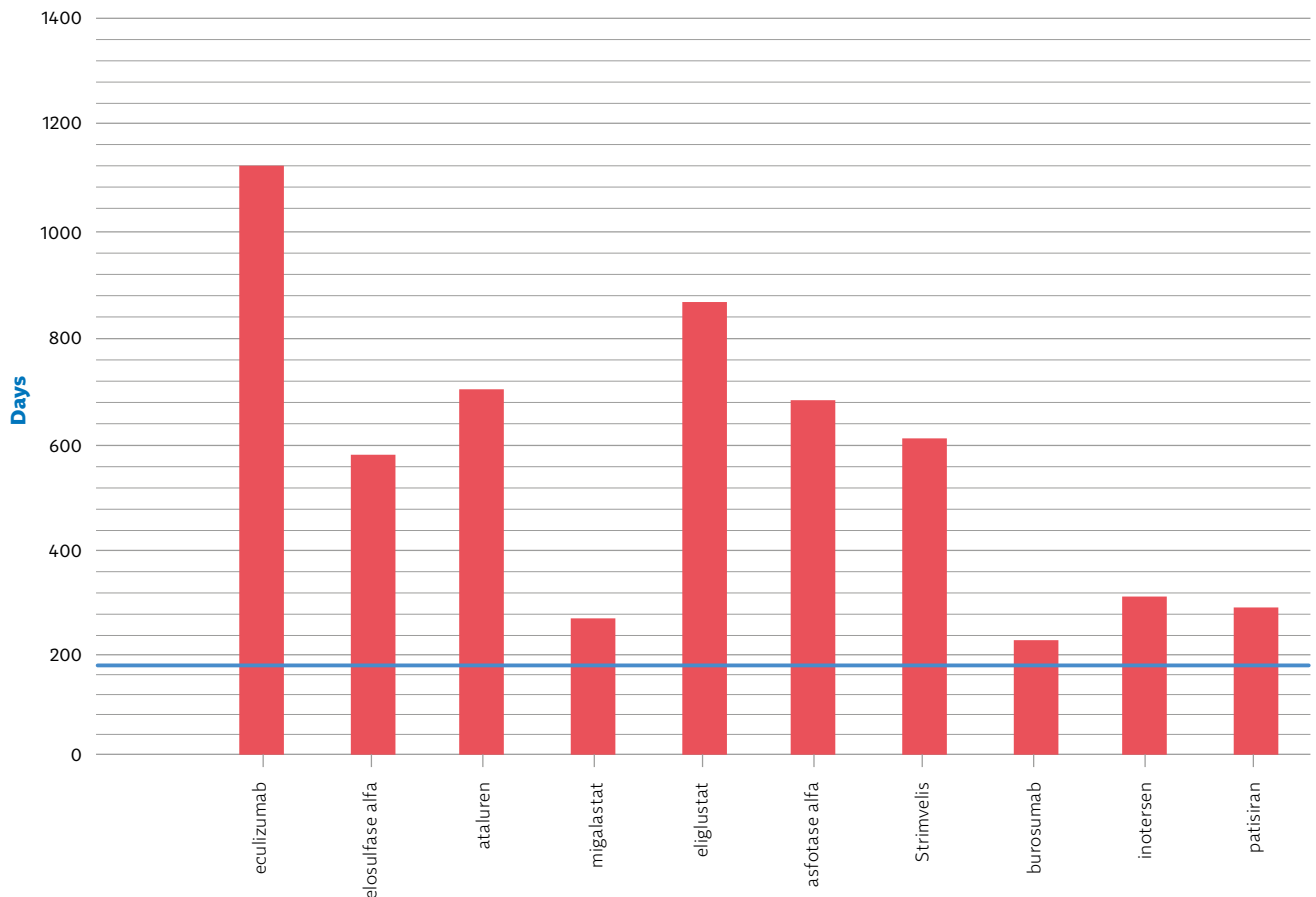
Depending on the assessment route chosen, health technology assessments in the UK can vary greatly in length to publish final guidance. For example, the NICE STA and HST pathways can take around 60 weeks and 17 weeks respectively, with no appeals. The SMC New Product Assessment can take up to five months. The ultra orphan initial assessment in Scotland takes 18 weeks, followed by an additional period of up to 3 years to allow for evidence collection (though some patients will have access during this period). The speed of the process is limited by the number of steps required to make a decision, and the resources available to do so. For instance, the NICE HST process involves just one highly specialised committee so has limited capacity to assess medicines; since the programme established in 2013, guidance has been published on eleven rare disease medicines (despite the fact that the EMA are likely to license roughly twelve per year).⁹ Meanwhile the NHS England prioritisation process is a biannual process with a long lead in process, meaning it can be months between market authorisation and the health technology assessment.

In reality, the average time between market authorisation and a reimbursement decision in the UK is 26 ½ months⁵(OHE); around two years slower than the planned timeframe for an HST. This is due to significant delays and pauses throughout the various HTA process for rare disease medicines. The two primary causes for these delays is to allow for commercial negotiations to take place, which can remain unresolved for years, or evidence to be presented to resolve uncertainty.

| Sapropterin, for instance, was licensed eleven years ago and after numerous rejections is still undergoing a HTA process. | Without a clear timeline for resolution, patients are forced to wait indefinitely for a reimbursement decision that may change their life.

In fact, the HST pathway, the one operational pathway that was designed for rare disease medicines, to which access is tightly controlled, has only once delivered a final decision faster than 250 days, when it approved access to burosumab 231 days after market authorisation. Figure 8 shows the HST process decision time against its current timelines, which estimate that a completed process should take up to 24 weeks or 168 days.

Figure 8 – Time between market authorisation and HST approval



Delays and pauses throughout the HTA process have fatal or life-changing consequences for patients. Most rare disease medicines will be licensed or funded with some kind of cut-off or limit to access relating to the progression of the condition. **For instance, ataluren for Duchenne muscular dystrophy is licensed as a treatment for those that retain the ability to walk. In the 23 months between market authorisation and NICE approval, a number of boys in Britain will have lost the ability to walk, and therefore become ineligible to access the treatment. Losing the opportunity to access a potentially life-saving treatment.**

More generally, for any progressive condition, any delay in granting access to a treatment means that patients are losing the opportunity to benefit from the treatment at all. This urgency is the reason why the European Medicines Agency (EMA) has its Priority Medicines (PRIME) initiative¹⁰ and the option to provide conditional marketing authorisation.¹¹ Where unmet health need is great, the EMA can use these options to accelerate its decision with the intention of getting life-saving treatments to patients as quickly as possible. This is undermined by the delays in HTA for rare diseases in the UK.

4.1.5 The transparency problem

The health technology assessment process is far from transparent in the UK. Due to the complexity of the system, it is often unclear why one assessment route is chosen over another, and the timeframe and outcomes of these decisions can be unpredictable. This leaves patients in the dark, not knowing if, or when, the medicine for their condition will become accessible.

It is important to select the most appropriate route for each medicine in order to avoid making inconsistent or inequitable decisions that affect patient access. Some routes have clear justifications for medicine assessment - such as the Scottish PACS tier 1 system for ultra-orphan, or PACS tier 2 for individual funding requests. Nevertheless, there is typically a lack of clarity, transparency or information on how or why one medicine evaluation approach or access route is selected over another is not available. **For example, there was no reasoning provided as to why nusinersen was assessed via the STA route over the HST. Additionally, there has been a lack of communication regarding updates of the appraisal process for long periods of time, leaving the SMA community anxiously waiting for news.**

Once a medicine has entered into a health technology assessment, its progress is not often well communicated. Timelines are not always strictly adhered to or clearly publicised. In the case of delays in particular, patients can be left with no estimation of when the process will continue. Because of the opacity around timing, many patients may have no clear understanding about where their medicine is in the process, and when they are likely to receive it, if at all. **A respondent to our survey, who is a parent of a patient with cystic fibrosis, has described feeling 'disempowered' by the lack of transparency with regards to the approval process of ivacaftor/lumacaftor and it having an effect on their mental health.**

'The process was so slow and it would stop at one point for a long time without mentioning any reason for that. It's disappointing for the desperate people like me'

Patient waiting for news



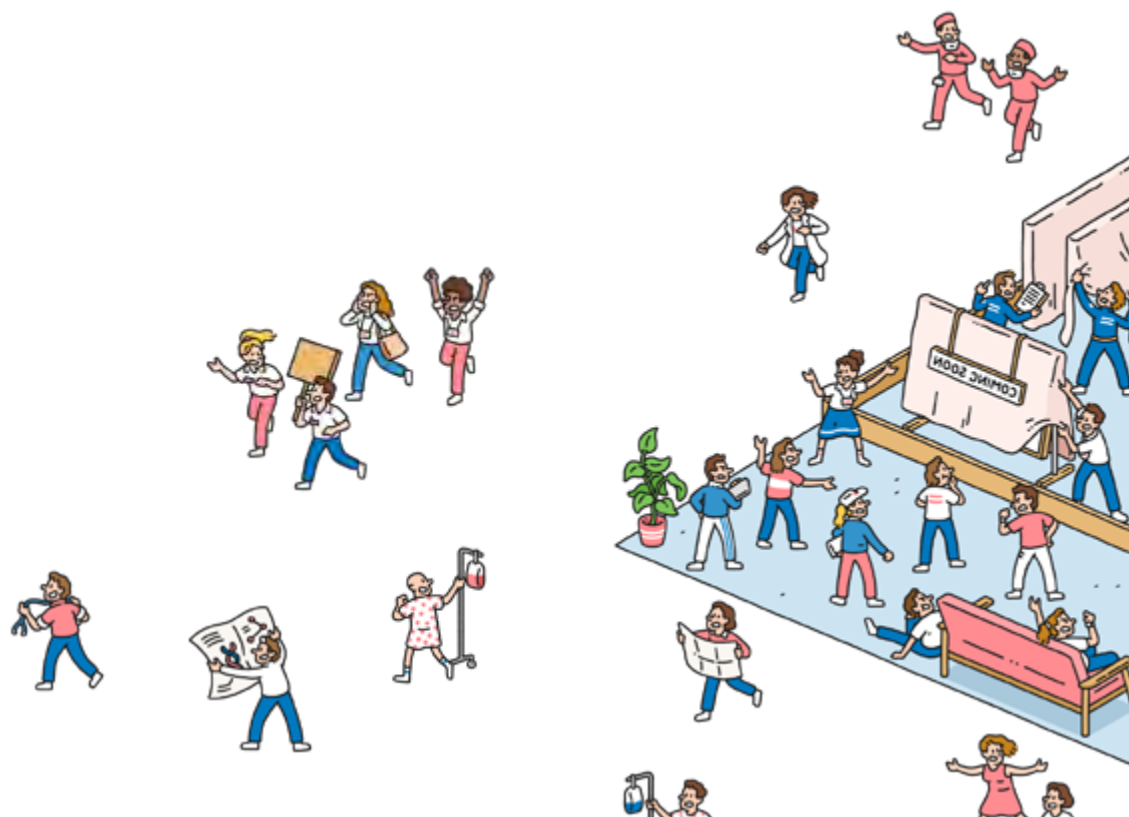
Many of the key considerations which determine the outcome of a HTA are also not communicated. While there is a need to keep certain information confidential - pricing agreements, for instance - this creates a situation where accountability is lost. When pricing deadlocks arise, it is unclear whether this is due to unrealistic demands from the pharmaceutical company, or payer, or neither. The full extent of any compromises offered by either party are also not visible to the public. Therefore, when pricing negotiations prevent access to a medicine, it is difficult to establish why.

In addition to pricing, there are other considerations in the HTA process - such as the use of evidence - which are not clearly explained. For instance, it also is not always transparent how different evidence is taken into consideration (is weighted) in HTAs to judge the value of a rare disease medicine. Because of this, the justifications

for HTA outcomes are unclear. This omission is particularly relevant when an unpredictable HTA decision is made. For example, the use of an artificial cornea to treat corneal blindness was determined by an NHS England prioritisation process to have either low benefit and medium cost, or medium benefit and high cost. This seems incongruous with the ability for the treatment to restore sight, at a cost of £3,000 for several years of sight. To compound matters, this decision was publicised on the 18th December, shortly before Christmas annual leave for most. This awkward timing made it more difficult for individuals to notice the publication and respond.

The staggered assessment of sapropterin over the course of 11 years is a clear example of why communication is so important. Initially, a draft positive recommendation was drafted for the medicine, before publishing a negative outcome. Shortly after, NHS England announced that NICE would take over appraisal of the medicine, but a delay ensued, causing NHS England to start another appraisal and cause significant confusion. Importantly, the NHS England assessments that have been conducted published no detailed justification for their negative outcomes. Therefore sapropterin may soon undergo its third NHS England assessment with no indication of how to improve upon the previous negative HTA outcomes.

When assessments bounce between different decision-makers, there is no single body responsible for ensuring that the patient community understand where they stand.



4. **Fundamental issues**

The five systemic problems of fragmentation, inflexibility, capturing the true value of medicines, delays and lack of transparency are clearly damaging the access environment in the UK now, and must be addressed. It is important to consider though, would solving these systemic problems give the UK a functioning system, with satisfactory levels of access and timely decision-making?

Despite fragmentation in the current system and the many different problems we have identified so far, most processes to decide on access to rare disease medicines in the UK follow roughly the same pathway:



Market authorisation

The rare disease medicine is granted a marketing authorisation. This is the result of a regular process with predictable timelines. For rare disease medicines currently, the authorisation is granted by the European Commission based on a decision from the European Medicines Agency (EMA). The market authorisation gives us the message that the medicine is safe enough to use and that the claimed benefits have been demonstrated. If a medicine meets a major unmet health need, the EMA's decision might be accelerated, or a decision might have been reached with a degree of uncertainty that might still need to be addressed. In all cases the EMA manages the risk of the decision by monitoring the medicine in the real world after its decision. This process is called pharmacovigilance or phase IV studies.



Health technology assessment

The medicine now arrives at the HTA bodies. At this point in time, particularly if the decision has been accelerated by the EMA, there will necessarily be less evidence to support a HTA decision than might be viewed as ideal. This is an almost universal problem with rare disease medicines.

The HTA bodies' responses to this challenge is to put the treatment through their processes regardless. Inflexibility within the system often means that a rare disease treatment is put through a pathway which has not been designed for these treatments at all. The delays start. The process might be paused to examine whether evidence can be gathered to meet the expectations, or paused because a company's estimation of the value of their treatment does not match the HTA body's assessment.



Inconclusive result

At the end of the HTA process, a predictable, almost universal result emerges: the process has found a major degree of uncertainty - the only way that a positive decision can be reached is if the confidential cost of the medicine is significantly reduced. Essentially at this point, the NHS is unwilling to pay for a treatment which may or may not deliver as predicted.



Unstructured negotiation

The next phase is for further negotiations on cost reduction between the company and the NHS. Though processes are being built for this within NHS England now, this remains an opaque process, with very little information available as to how the process occurs. Sometimes these negotiations happen before the HTA process completes within the context of appeals and sometimes they happen after a final negative decision.

| Cerliponase alfa was refused funding in February 2019, this was appealed by the Batten Disease Family Association, which was rejected in April 2019. An appeal then occurred anyway, and negotiations finally concluded with an access decision in September 2019. |

| The NICE appraisal of ivacaftor/lumacaftor ended with a negative decision in 2016, since then NHS England and Vertex have been in an unstructured negotiation phase. |

As these negotiations drag on, multiplying the expected decision-making timeframes, it is clear that there is a fundamental gap between pharmaceutical companies expectations for reimbursement and the NHS's willingness or ability to pay.



Delayed conclusion

If the patient community is fortunate, at the end of this process an agreement might be reached. We might gain access to the treatment in the NHS. However, at the end of this process, no stakeholder can be satisfied. Most importantly, patients will have been made to wait longer than they should have to access a treatment - we know that these delays mean irreversible deterioration of health or avoidable deaths. The NHS still has no evidence that the treatment it has agreed to fund has the value it expects, and companies will have given further discounts on treatments that they believe have greater value.

Some of the elements in the above process could be improved by solving some of the individual systemic problems that we have identified. But would fixing all the systemic problems fix the process?

We think the answer is no. We see time and time again HTAs in rare disease coming down to two fundamental issues: uncertainty and money. This is no surprise, as HTA is, at its most basic, an analysis of cost against effectiveness. If we have a problem with the money and uncertainty with the effectiveness, it is difficult to see how we can have a functioning decision-making process if we continue to proceed without addressing these two fundamentals.

4.2.1 The fundamental uncertainty problem

Too often, there is insufficient evidence at the time of the health technology assessment to fully determine the effectiveness of a medicine. This problem is inherent to rare disease medicines, due to small population sizes, and due to the long-term benefits that a rare disease medicine might confer, meaning that there are no instant results to measure. Yet, time after time, health technology assessments are conducted without properly managing this uncertainty.

With the exception of the SMC ultra-orphan route, in the UK health technology assessments are conducted directly after a medicine receives market authorisation (often the process is initiated before a market authorisation has been granted to ensure there is no delay). Despite efforts to encourage companies to collect a broader range of data from earlier in their studies, evidence collection usually centres around the effectiveness and safety of a medicine. Data is collected through clinical trials, and measures such as dosage and adverse events are collected. While this is sufficient to secure market authorisation, these studies are often of limited value to the health technology assessment. To demonstrate value, the efficacy and long-term benefits of the medicine must be shown, which are still not captured by many clinical trials. This problem is particularly pronounced for medicines that are subject to a fast-track market authorisation. The European Medicines Agency's PRIME scheme, for instance, speeds up the market authorisation for promising medicines targeting an unmet medical need. As many rare disease medicines fit this description, they can have fast-tracked market authorisations, further limiting time to collect evidence.

By their nature, it is difficult to collect the 'gold standard' evidence that HTA requires for rare disease medicines. Rare conditions affect small populations. This means it is difficult to enrol sufficient numbers of patients into clinical trials. There may also be limited data on quality of life. As rare disease medicines are often the first of their kind, the absence of alternatives also makes it difficult to benchmark effectiveness.

Due to the lack of available evidence at the time of the health technology assessment, it is often not possible to come to a conclusion on the effectiveness of a rare disease medicine. This leads to rejections on the reimbursement of rare disease medicines or restrictions on their use. **For instance, nusinersen is a lifetime treatment but the clinical data only represents a limited timeframe for a small number of patients. If the HTA body does not adjust its expectations to assess the benefit of this drug, it cannot reach a positive decision.** Rare disease medicines outside of cancer treatments appraised by the STA route by NICE always have restrictions applied to their recommendations.

4.2.1 The fundamental uncertainty problem (continued)

"[Ivacaftor/lumacaftor] has been penalised for a lack of long term evidence. The long term evidence that was available wasn't factored in sufficiently."

Response to Genetic Alliance UK survey

"Clinical evidence suggests that, in the short term, cerliponase alfa improves quality of life, and slows the deterioration of motor and language function. However, there is no long-term clinical evidence, so assumptions about long-term disease stabilisation and mortality are associated with substantial uncertainty."

Response to Genetic Alliance UK survey

There has not been sufficient recognition of this fundamental issue, and very little has been done to address it. HTA bodies persist in applying the same processes that lead to the same drawn-out unsatisfactory results. As we have established, most of the HTA pathways were not designed for rare disease medicines, and those that have been have extremely limiting access criteria. Essentially though, we need to recognise a simple fact: attempting to use our current HTA processes to make decisions directly after a marketing authorisation is given does not make sense. For the vast majority of treatments, there will not be sufficient evidence to make a decision with which stakeholders can be happy.

4.2.2 The fundamental money problem

We regularly face an impasse between the high prices that the pharmaceutical industry set for rare disease medicines and the availability of government money to pay for them. The opacity of both the funding systems and the pharmaceutical industry's approach to pricing makes it hard for the patient community to engage in a regular dispute that tends to leave patients most badly affected.

One simple test is to compare availability in other European countries. Under this measure the UK appears to spend less on rare disease medicines, indicated by fewer medicines available. **■ In fact, some rare disease medicines are available in almost all European countries, bar the UK; sapropterin, for instance, is available across Europe, excluding Poland and the UK. ■** We do not know whether companies are charging the UK more, or other countries are willing to pay more. Medicine availability is used as a proxy for spend because there are few other routes for us to engage in the topic.

Transparency and high prices

In the UK list prices only serve to disrupt debate around pricing and access. It is well known that the price publicly quoted for each medicine in the UK (the list, or

reference, price) is not the actual amount paid by the NHS for the medicine. Indeed the agreement on the list price is a reserved competency for the UK Government, and the amount paid, the reimbursement, is a devolved competency divided between NICE and the SMC. The difference between the medicine's list price and the amount paid can, we understand, be very large.

Companies are allowed to set their reference price freely in the UK, which is an important power to them, as it serves as a reference for other companies and other countries to base their negotiations on. Companies typically set the price a long way beyond what they might expect to be paid. In doing so, companies are better positioned to negotiate their medicine price elsewhere.

Though this situation is well understood - even by those referencing these prices - the list price remains the only public number that we the patient community, but also importantly the public and the media, can refer to to understand the face-value price of medicines. This contributes to the public perception that rare disease medicines in the UK are phenomenally overpriced (Figure 9).

Figure 9: Publicly available list prices of high cost rare disease medicines approved through NICE HST process - listed here to demonstrate the damaging effect of the extent of opacity of pharmaceutical pricing in the UK - data from NICE documents

Technology	List/reference price (£) per person, per year
Patrisan	199,587 (assuming weight of adult at 50kg)
Inotersen	308,100
Burosumab	155,584 (£2,992 for 10mg - average dose is 0.8mg/kg, average weight of 19.3kg)
Strimvelis	505,000
Asfotase alfa	366,912
Eliglustat	250,000
Migalastat	210,000
Ataluren	220,256
Elosulfase alfa	394,680
Eculizumab	333,500 (average taken between £327,000 - £340,200)

4.2.2 The fundamental money problem (continued)

We understand (though we have no concrete evidence to show this) that the list price is always heavily discounted, usually through a Patient Access Scheme¹², a UK scheme which facilitates the discounting of the list price. This discount can then be further reduced in future negotiations with the NHS.

Here we can see the two fundamental issues interacting. With the uncertainty problem unsolved HTA bodies turn to the money problem. If a medicine is not deemed cost-effective, the company is given the opportunity to discount its price to allow the medicine to be recommended. This is a crucial point in the process, yet there is not yet a published process for it, and no transparency around it. The patient community often might not know if it is happening, or how long it might take.

The exact discount amount is settled upon after a series of confidential negotiations between the company and payer. There is often a back-and-forth until a price is reached and discussions are typically drawn out due to the discrepancy between how HTA bodies and companies value their medicine. **For instance, while the price negotiation for cerliponase alfa was undergoing, children with Batten's disease were without this treatment for around three years.** Consequently, reaching an agreeable price can be near impossible, and where a price is reached, neither party may be happy; companies may believe their medicine is worth more, while the NHS may be unhappy to accept the level of risk/uncertainty. Moreover, the prices made public are inaccurate and significantly over-inflated.

A prominent case, at the time of this report being published, is that of ivacaftor/lumacaftor; a medicine designed to treat those with Cystic Fibrosis. Ivacaftor/lumacaftor was rejected for use by NICE and the SMC in 2016. It was rejected on the grounds that there was too much uncertainty around long-term value and impact (and therefore cost-effectiveness). Since then (in 2019), nearly 4 years later, ivacaftor/lumacaftor is now available more widely in Scotland only. Meanwhile, Vertex and NHS England have been locked in a, largely public, debate, in an attempt to agree on an affordable price. As well as public discussions, the Health and Social Select Committee has launched an inquiry into medicine access.

As identified in a report published by the Office of Fair Trading in 2007¹³, the UK's list price for pharmaceuticals is referenced by around 25% of the global pharmaceutical market. Since 2007 systems to increase the gap between the published price of medicines and that actually paid by the NHS have been implemented. The damage of this legacy is fictionally high prices and a lack of transparency as to the proportion of these prices that the NHS is spending on patients in need of rare disease medicines. Even in the latest agreement between the UK Government and the pharmaceutical industry 'a simple confidential discount' was stated to be the preference to manage the difference between a list price and the price paid by the NHS.

Transparency and the availability of funds for rare disease medicines

Alongside the UK's opaque processes for setting the price of medicines, we have complex schemes for managing expenditure on branded medicines. These schemes are known as the Voluntary Branded Medicines Pricing and Access scheme (VPAS) and the statutory scheme. Both the VPAS and statutory scheme are agreements set up between members of industry and the UK Government, lasting five years (2019-2024). All new rare disease medicines will be branded and therefore governed by these schemes.

Both schemes introduce a limit on the growth of spend on branded medicines. For the VPAS, sales on branded medicines are allowed to grow by 2% each year. For the Statutory scheme scheme, 1.1%. If net sales for either scheme exceeds this sales growth, the companies signed up to the scheme must pay back the excess (known as a rebate). This means that the UK Government spend on branded medicines can never grow by more than a set amount each year. For the duration of the scheme it is expected that the UK will receive rebates to account for expenditure beyond the agreed cap.

This means that these schemes ensure that there is no extra cost to the taxpayer for new medicines. The cost of new medicines will be added to the repayments by the pharmaceutical industry to the UK Government. Analyses of this system can often get bogged down in discussions of where the rebates for over-expenditure are routed within the system. (Currently English overpayments go back to the NHS¹⁴, and Scottish overpayments go to the New Medicines Fund¹⁵.) We prefer to reflect on the bigger picture: new medicines do not cost the UK Government any extra money. In fact, compared to the overall NHS budget, the proportion of Government investment that goes on branded medicines is shrinking. Over the next five years, the average growth of the overall NHS budget is predicted at 3.4% per year (following the injection of £20.5 billion by 2023/2024 ⁶), compared to the growth in branded medicines sales which is capped between 2% and 1.1% (accounting for both schemes).

Public perception of the impasse between the pharmaceutical industry and the NHS

While refusing to fund medicines that are available in other European countries, the NHS is allowed to portray itself in the media as refusing to pay for over-priced medicines¹⁷. This argument is supported by two elements of opacity around money in rare disease. On the one hand we have the reference price system, where the only price we can find is (we understand) a vastly inflated price; and on the other hand, there is very low awareness of the system which would allow the NHS to use new medicines at zero cost.

We understand that there are valid reasons to challenge pricing, and to control uptake of medicines in the NHS, however the publicly held dialogue on the pricing and purchasing of rare disease medicines does not match the policy behind it, and this is harming the public's understanding of the system.



5. Our Solution

In designing recommendations to move us towards a solution for access to rare disease medicines, we have concentrated on delivering overarching conceptual solutions to the problems we have identified. This will ensure that policy makers are always clear on what direction we should be moving in.

We have left some elements of detail to be determined in the future as part of delivering these aims and objectives. This keeps our recommendations robust with respect to upcoming changes to the policy environment.

In calling for a more flexible system, we hope to see the systemic problems solved, with a single access route managed by NICE for England, Wales, and Northern Ireland, which should be mirrored as much as possible by the SMC in providing a decision-making process for Scotland.

The chances of success of this process will be greatly increased with the launch of medicines in the NHS in advance of a HTA decision. This will allow the appropriate level of evidence to be collected for a decision to be made at an agreed time under an agreed funding arrangement.

Finally, progress towards greater transparency in pricing and funding of rare disease medicines should improve our community's ability to engage in discussions on the value, and therefore the cost, of rare disease medicines in the UK.

5.1 Addressing the uncertainty problem

The fundamental problem of uncertainty arises from insufficient evidence available at the point that the UK is currently trying to perform a HTA. With the exception of the Scottish ultra-orphan route, all HTAs for rare disease medicines begins as soon as possible after market authorisation. At this point, there is insufficient evidence to assess the value of a rare disease medicine. This is regularly demonstrated by the failure of HTA processes to end on time, and the delays, negative decisions or impasses that can arise.

To solve this, **Genetic Alliance UK recommends that the UK make rare disease medicines available in the NHS as soon as they receive marketing authorisation through a period of managed access. Once introduced, evidence should be gathered from within the NHS in relation to their value for an eventual HTA. This should be on terms set as the period of evidence gathering begins. The funds to cover the costs of these medicines should be provided through flexible schemes arranged between Government and industry.**

Where is this already done?

The SMC ultra-orphan pathway¹⁸

In the SMC ultra-orphan pathway, there is a preliminary assessment (to highlight uncertainties within the available evidence-base), followed by a period of data collection. It is only after this that a full assessment takes place and a decision is made on whether to reimburse the medicine.

Applications for this route only opened in April 2019 so it is still too early to measure the success of this pathway. The scope of access to the pathway is very narrow, only treatments for conditions with a prevalence lower than 1 in 50,000 in Scotland can be considered. This is much narrower than the definition of rare conditions which is fewer than 1 in 2,000. We believe the SMC should consider widening the scope of this pathway.

The Cancer Drugs Fund¹⁹

Though not an identical process, there are some similarities between the (new) Cancer Drugs Fund and our proposal. When NICE cannot reach a positive recommendation for a cancer treatment due to uncertainty as to its value, NICE has the option of recommending a period of managed access within the NHS, funded by the Cancer Drugs Fund, which is a pool of NHS England money. Patients can access the medicine while evidence of the value of the treatment is assessed. At the end of December 2018, 30 of the 33 treatments that entered the programme in 2016 had been funded.²⁰

Rare disease medicines in Germany²¹

In Germany rare disease medicines - those with an orphan designation and a marketing authorisation from the EMA - are considered, by definition, to bring added benefit to patients. This is logical as the orphan designation shows that it meets an unmet health need, and the market authorisation indicates that it is an effective treatment. On this basis, the treatment is delivered to patients as soon

as the marketing authorisation is granted, providing revenue for the company will be below a certain threshold.

Following access, a negotiation between the company and the payer (national association of health insurers) on price begins after 6 months, ending after 12 months, with provision for arbitration. Unlike our proposal, no extra evidence is collected during the initial period of access.

Under our proposals, patients with rare diseases will no longer have to wait on average 26 months to be able to access medicines from the point they become available in Europe, and there will no longer be patients whose condition progresses beyond the point of treatment during a HTA decision-making process in the UK.

If NICE (with their remit across England, Wales and Northern Ireland) implement such an approach, and the SMC (for Scotland) expand access to their ultra-orphan pathway, it is possible that there will be no delay to access rare disease medicines across the whole of the UK.

The Government has long promoted the NHS's suitability for the collection of data in the context of new innovative treatments²², and we believe it is well positioned to provide the infrastructure to facilitate real world evidence collection; which, as well as addressing uncertainty, would present an attractive added incentive to industry to market medicines in the UK.

Interim funding agreement

To provide funding during the period of managed access, a commercial agreement would be required between the company and payer. A suite of flexible interim funding schemes should be developed, by Government through consultation with stakeholders. This arrangement could take many forms such as:

The SMC Ultra Orphan pathway

The costs of evidence gathering is covered by the company, while the Scottish Government pays for the medicine, which is offered at a discount.

Payment by results

Definition of outcomes that would warrant payment are agreed ahead of release, and until those targets are met, the cost is carried by the company.

Incentivised UK launch

In the case that industry requires incentives to launch their products in the UK, the costs in this phase of launch could be covered by the government to attract pharmaceutical investment in the UK.

There may be concerns about the risk of ongoing treatment costs in the event of delays to the ultimate decision. In the current system, the fact that patients are made to wait to access treatments while a faulty system delivers a delayed decision, seems to be insufficient an incentive for the two parties engaged in negotiation to come to a conclusion. Under our proposals, it would no longer be patients who are most disadvantaged by a failure to reach a funding agreement.

5.1 Addressing the uncertainty problem (continued)

An agreement would be necessary at launch of a medicine. This should establish the terms of the managed access period prior to a HTA assessment, including timeframe, the methodology used to assess the medicine, and to establish the HTA body's expectations as to the quality and type of evidence to be collected.

This proposition is not without its challenges. For instance, there are many rare disease medicines which might not demonstrate their full benefit for a number of years; others have health outcomes that are difficult to define as clear end-points. The setting of the terms of a managed access period, and funding, could be difficult. Yet, any added time between market authorisation and HTA assessment means added data to improve the quality of the decision. This data will not only come from within the UK but providing the company invests in data collection, could come from around the world.

Uncertainty is inherent to rare disease medicines. The current urgency to perform a HTA comes from a need to get valuable treatments to patients. Our proposal to deliver rare disease treatments to patients at the point of marketing authorisation through managed access means patients get the treatments they need without delay, while providing the necessary evidence and time to make an appropriate HTA decision.



5.2 Addressing the systemic problems

There are two decision-making processes in the UK that have been designed to work for rare disease medicines. Of these, only one has existed long enough to make recommendations. As of 1 October 2019, this process, the NICE Highly Specialised Technology programme had made 10 decisions. All positive. Of more than 185 orphan medicinal products licenced in the EU³, the UK has managed to assess just 10 with a tool designed for the process.

It is clear from our work though, that within this process, NICE does actually have the tools to make effective decisions about access to rare disease medicines. The problem has been the narrow scope within which NICE is willing to apply the tool. This narrow scope is quite different to the scope that Parliament defined when it instructed NICE to deliver the HST pathway. The original instruction was to provide a pathway for assessing highly specialised technologies for rare and ultra-rare conditions⁷. The effect of the narrow scope of entry to the HST programme has been to only satisfy the latter part of this instruction.

To unlock this potential, **Genetic Alliance UK recommends that NICE develop a single flexible approach for making decisions about access to rare disease medicines, ensuring all rare disease medicines are assessed by an appropriate pathway with realistic expectations for evidence and outcomes.**

Towards a single system for rare disease decision-making in the UK

During the timescale of this project, two major policy developments occurred which provided opportunities for a progression towards a single system for decision-making on rare disease.

The Voluntary scheme for branded medicines pricing and access (VPAS) as discussed previously contains an agreement that NICE will assess all new medicines by April 2020. This creates the policy opportunity that there would be a single decision-maker for access to rare disease medicines in England, Wales and Northern Ireland. If NICE can solve the systemic issues we have identified, by following the recommendations here, then a great deal of progress will have been made. Scotland would then remain as the single country of the UK which follows a different decision-making pathway.

The second major policy development, announced at the beginning of our work on this project was the Scottish Government's announcement to deliver an ultra-orphan process for extremely rare disease medicines. This pathway and method was a strong influence on our findings and recommendations with respect to 'Addressing the uncertainty problem' and our proposal for a period of managed access in advance of a HTA.

It was therefore felt that progress towards a single system - the original aim of this work could begin with progress towards two single systems. On the one hand, England, Wales and Northern Ireland could be governed by NICE, implementing a new approach for rare disease medicines. On the other hand, Scotland will be delivering an approach that matches much of the methodology recommended here, albeit in a narrow scope. Greater harmony and collaboration between the two systems can drive better results and track the pathway towards a more unified approach.

5.2 Addressing the
systemic problems
(continued)

A new flexible approach for NICE

Within the category of rare diseases, there is a spectrum of variation; some affect only a handful of patients, while others can affect up to 30,000 people in the UK. Some are progressive conditions which affect patients over a period of decades, others are faster acting. Some are multisystem disorders with a broad constellation of symptoms, others might be very narrow in their impact. These impacts might be straightforward to measure clinically, or may impact other parts of a patient or families lives.

Rare disease medicines exist over a similar spectrum of variation. To provide an appropriate assessment of these medicines it is necessary for the HTA process to adopt sufficient flexibility to match the spectrum of rare disease medicines.

NICE has already shown a degree of flexibility. As aforementioned, the budget threshold operates on a sliding scale (cost per QALY), and this threshold is higher for rare disease medicines. The HST and ultra-orphan route also allow for more leniency in terms of evidence requirements.

We propose a formalised, consistent approach to incorporating flexibility into the HTA system to be delivered at the beginning of a period of managed access. This procedure can establish the expectations of the evaluation committee with respect to the various domains of evidence on which it wishes to base its decision. This can also establish the threshold at which the treatment will be considered to be cost effective.

Flexibility would be incorporated into this route in the form of a 'sliding scale' whereby the terms of a medicine assessment would differ depending on a number of criteria such as its population size, level of unmet need, where the benefit is felt and how easy it is to demonstrate for example. Evidence requirements for medicines targeting smaller populations would be more lenient than those for larger populations. A clear justification would be required for where each medicine sits on the scale. Using this approach no medicines would 'fall through the gaps'.

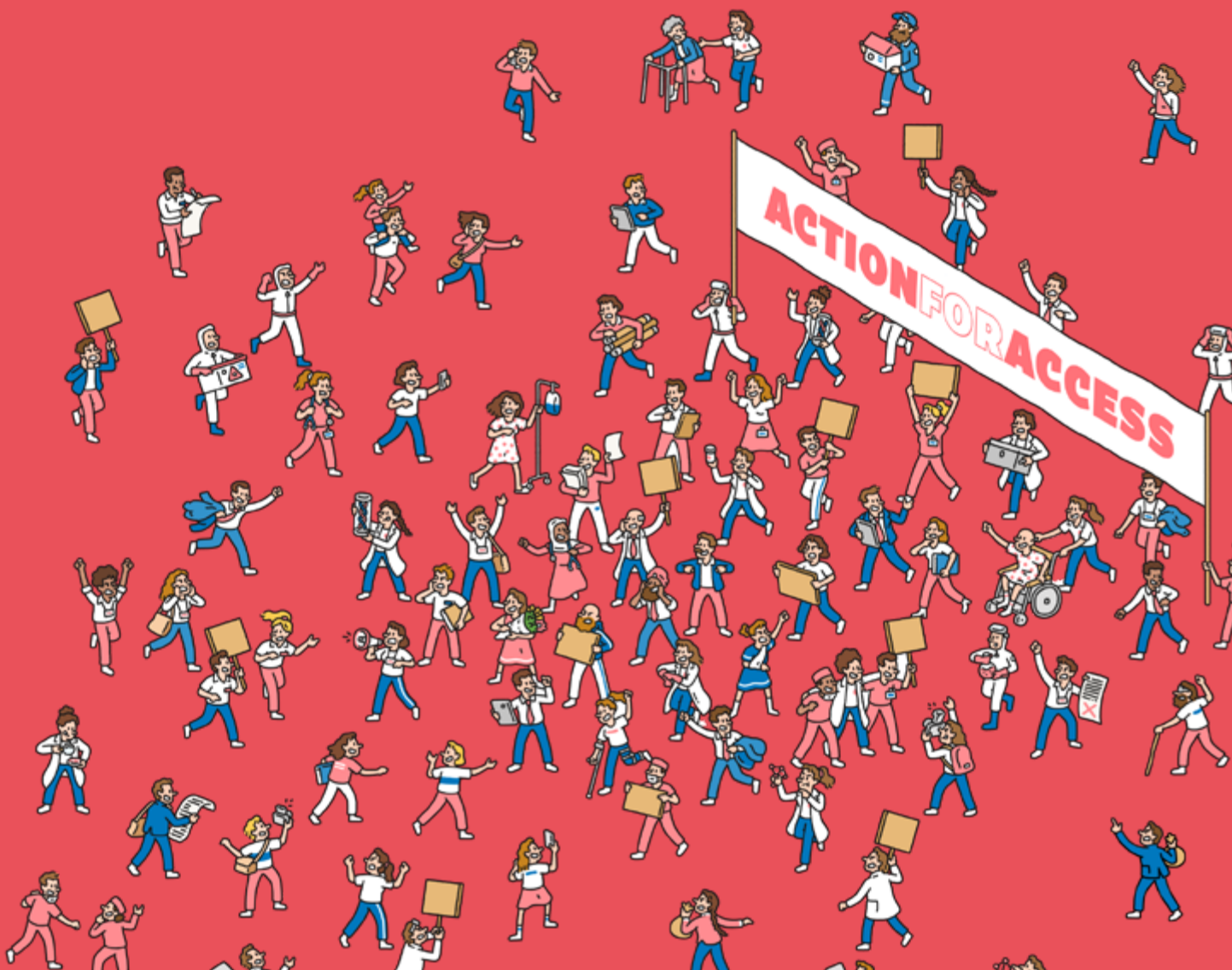
This process to define the terms of the HTA would establish at the beginning of the period of managed access, exactly what the evidence gaps are for the specific treatment, and how these evidence gaps should be filled. With realistic expectations for evidence, and an approach to deliver it, the ultimate decision-making process at the end of the period of managed access should face fewer challenges than exist within the current system.

Solving the transparency issues

The lack of transparency that our community must face currently is to some extent the product of other flaws in the system. As responsibility for decision-making passes between two bodies, it is not clear whose responsibility it is to communicate the change to patients. With a single-system, as prescribed by VPAS, this issue is resolved. The pauses and delays during which communication is scarce are the result of the application of inappropriate decision-making processes to rare disease medicines about which there is a degree of uncertainty.

While patients and families are waiting for access to a treatment, transparency is a more important issue, as they are waiting for communication on a grave decision - with managed access in advance of a HTA, this urgency is reduced.

Essentially though, it is unacceptable for a Government decision-making body to fail to communicate effectively with a population affected by their decisions. People living with rare diseases in the UK have a right to expect better.



5.3 Addressing the money problem

The money problem is created by two issues that are in tension:

- Pharmaceutical companies' public prices are deliberately higher than they need to be, for purposes related to price-setting around the world. These are then discounted confidentially. The UK public sees the higher public prices.
- The UK has already agreed its total spend on branded medicines until 2024 - all new medicines approved by NICE will be covered by this expenditure. This means that new medicines cannot take up further NHS resources.

The combination of these two facts leave the rare disease patient community in a very challenging situation - we are told prices are actually much lower than publicly stated, but have no evidence for this, and we are told that the NHS cannot afford many new medicines, when the cost to the taxpayer will be nothing.

This situation is needlessly complex and opaque. **Genetic Alliance UK calls on both industry and government to explain clearly what the process for setting rare disease medicines prices is, and how the price that the government can afford is set. The benefits of the recently agreed Voluntary Pricing and Access Scheme for Branded Medicines (VPAS) to all stakeholders should be set out. This dialogue should guide the rare disease patient community and the public to a greater understanding of reference pricing and the VPAS.**

The system should be made far more transparent so that the conversation around medicines funding is democratised. A comprehensive understanding of the influences on medicines pricing would help to redress the dichotomies in the current system, and reduce the pricing impasses that we currently face with each medicine appraisal.

It was not possible for us to make more robust or specific recommendations about how to address 'the money problem,' specifically because of the opacity within the current system. We recognise that there is unlikely ever to be complete transparency in this area, but believe the complexity and opacity of the current situation is a major contributing factor to the challenges the UK is currently facing.

Industry's role

We believe industry should consider carefully the impact of 'reference' pricing on public and patient perceptions of rare disease medicines, and consider approaches that might engender greater public confidence in the pricing and the value of their products.

Clear, open and comprehensible communication about the nature of the pharmaceutical industry will help bring understanding. It is a global industry, with responsibility to owners and share-holders. This is the nature of the overarching system that delivers pharmaceutical innovation. There are reasons for confidential pricing, and these should be clearly communicated.

Different products bring different costs to companies, both in development and in manufacturing and supply. Greater transparency and discussion of these elements of the system should help the patient community and the public understand some elements of the system we depend on for cures and treatments.

Industry's messages on these topics should bear scrutiny, and companies should be prepared to answer questions about pricing strategy in a straightforward manner.

Governments' role

We believe Government should better explain the benefit of the VPAS agreement. Awareness of this agreement should be greater. Within communities waiting for access to rare disease medicine it is surprisingly low. The agreement is, at the same time a number of things:

- It is a landmark agreement with industry that secures access to innovative medicines at a planned, low, rate of investment, which manages tax-payers expenditure on branded pharmaceuticals in a responsible manner;
- It is a policy tool that can allow the NHS to access new medicines without additional budget allocations, ensuring that the pharmaceutical industry cover the cost of new medicines;
- It is an indication that Government does not plan to invest in innovative therapies at the same rate as it invests in the NHS overall.

Some of these can appear contradictory. To those waiting for a funding agreement for a new medicine, these could be extremely frustrating. With greater knowledge of this policy, among the rare disease patient community and among the public, we might be able to move the conversation past the sometimes faulty perception of the impasse between the NHS and the pharmaceutical industry.

With greater knowledge of this system, the NHS should then be clearer and more specific as to why prices are too high. We understand that there are reasons, but the current message does not ring true when considered against this policy, especially when a majority of EU countries have reached a funding arrangement for a particular medicine.

Possibilities in the future

If we can move past the NHS vs the pharmaceutical industry position that we appear to have stalled in, it might be possible in the future for us to revisit 'the money problem' and deliver some more constructive recommendations. It may also be possible for us to consider the UK's proportion of investment in pharmaceuticals.



6. Next Steps

We have presented here a three pillar approach to moving the dialogue on access to rare disease medicines forward. Genetic Alliance UK is committed to this approach, and would welcome support and alignment from other stakeholders. We will continue the Action for Access campaign, and will seek opportunities to deliver our vision for the future of access to rare disease medicines.

The NICE Methods Review poses an immediate opportunity, though its scope currently appears to be too narrow to effectively address all elements of our recommendations.

We believe the definition of the problems presented here, and the recommendations for the future are adaptable and will support individual access to rare disease challenges within the UK. We intend to provide a service to Genetic Alliance UK members who would like to incorporate this work into their own campaigning.

The messages presented here will be kept up to date on the Genetic Alliance UK website, where we will host news of progress of the campaign.

We will receive the recommendations of the All Party Parliamentary Group for Rare, Genetic and Undiagnosed Conditions, and take them forward.

We will take our findings to the Cross Party Groups for Rare, Genetic and Undiagnosed Conditions in Wales and Scotland, and take forward their recommendations.

We welcome opportunities to further disseminate this work.

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