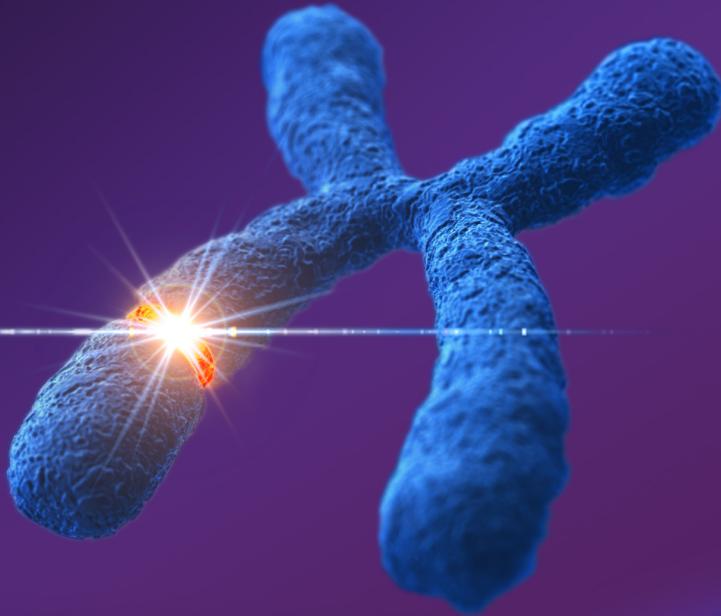


Very rare diseases, complex issues

Future evaluation of ultra-orphan medicines in the UK



Executive Summary

This publication primarily focuses upon the new evaluation framework for ultra-orphan medicines in England at a critical time in the development of this framework. It also comes ahead of the full formal consultation on the methodology and processes behind such evaluations to be held in 2014 by the National Institute for Health and Care Excellence (NICE). It builds upon engagement activities undertaken in the past year with policymakers, academia, industry, patient groups and medical research charities during the development of the interim evaluation framework.

There is a clear justification for the unique characteristics inherent in the research, development and delivery of ultra-orphan medicines to be recognised. The equitable treatment of patients with very rare diseases and conditions depends upon all stakeholders working together to create a landscape that ensures access to clinically effective treatments. This paper highlights some of the core issues of debate and demonstrates the wider future implications that the evaluation of ultra-orphan medicines may have.

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Recommendations

The BioIndustry Association (BIA) can make the following specific recommendations, the detail of which is provided throughout this publication:

Consideration should be given to the incentives to develop orphan and ultra-orphan medicines and avoid the outcome whereby clinically effective medicines have been developed but patients cannot access them. Governments have recognised the societal need to provide equal opportunity for treatments and have sought to incentivise the research and development of orphan and ultra-orphan medicines. Such incentives are undermined if these principles are not recognised and adopted further down the development and regulatory process.

Ultra-orphan medicines require a separate evaluation framework. There is a clear and justifiable need for this because of the unique characteristics and challenges involved with evaluating medicines for very rare conditions. The independent research released in this document would appear to demonstrate political support for this.

The new validated NICE framework should build upon the validated Advisory Group for National Specialised Services (AGNSS) framework. The creation of this framework involved a wide range of stakeholders and careful analysis. NICE should be expected to build upon this expertise. In some areas this is clearly already happening.

There is a need to ensure integrated implementation and service delivery. There is a further need to closely align the evaluation and service delivery elements of ultra-orphan medicines recognising that the functions are now split between NICE and NHS England whereas under the AGNSS framework they were considered together.

Introduction

Being rare is becoming increasingly common. Of course, the research and development of new treatments and medicines for rare and very rare diseases (orphan and ultra-orphan medicines) is vitally important for the thousands of patients who suffer from such conditions and the trend of increasing specialisation of treatments is set to continue as we stand on the cusp of personalised medicine.

The research and development endeavour brings together committed public funders, academia, medical research charities and both large and small companies seeking ways to address the underlying causes of rare and very rare diseases and radically improve patient outcomes. It is a painstaking and expensive exercise with each new medicine targeting extremely small patient populations. For ultra-orphan drugs this typically relates to less than 1 in 50,000 people, which equates to just 1,200 citizens in the UK. Further detail on the distinction between orphan and ultra-orphan diseases is given on page nine.

Numerous reports, both governmental and other, have demonstrated the need to treat very rare diseases equitably with more general conditions, such as diabetes and asthma. Recognising this, the European Union incentivises the development of orphan and ultra-orphan products and requires Member States to develop national rare disease plans. Yet all healthcare systems across the world struggle to identify the appropriate balance to ensure equitability of access and treatment. Arguably nowhere is this plainer than in the evaluation structures put in place to assess new treatments for rare and very rare diseases. Here the balance is more challenging between ensuring access to treatments for patients who might have no other treatment options and delivering value for money for the tax payer.

Against this background, the assessment and evaluation of orphan and ultra-orphan medicines in the UK has encountered a sustained period of flux. Until recently, the task in England was undertaken by AGNSS which was also responsible for arranging service delivery and national budgeting for these very rare (ultra orphan) conditions. However, following the Health & Social Care Act 2012, AGNSS was disbanded with the responsibility for evaluation passing to NICE, with a Ministerial statement that they utilise the framework developed by AGNSS.

Recent reviews of how both the Scottish Medicines Consortium (SMC) and the All Wales Medicines Strategy Group (AWMSG) assess very rare medicines are seeing the emergence of separate evaluation processes for ultra-orphan medicines. Following these reviews there is recognition that different factors need to be taken into account in order to ensure that access to orphan medicines is improved.

This report primarily focuses upon this evaluation structure for ultra-orphan medicines in England, now referred to by NICE as highly-specialised technologies (HSTs). It provides a timeline of recent developments, an overview of some of the key issues worthy of consideration going forward and looks ahead to the establishment of the new process. The report is intended to be succinct, drawing together various issues into one document. It does not purport to be exhaustive in nature in what is a highly complex area. Where possible, readers are signposted to sources of other information that may prove helpful.

Timeline

Below is a brief timeline highlighting some of the key events of relevance to this report and the recent history of the evaluation of HSTs in the UK.

NHS Commissioning & Planning

Health Technology Assessments (HTA)

1983: Supra Regional Services Advisory Group

1996: National Specialised Commissioning Advisory Group (NSCAG)

2006: Carter Review of Specialised Commissioning

2007: National Commissioning Group (NCG)

2010: Advisory Group for National Specialised Services (AGNSS) created

2012: Health & Social Care Act

2013: NHS England commissions specialised and highly-specialised diseases

1999: National Institute for Clinical Excellence (NICE) established

2004: NICE Citizens Council advise NHS to consider paying for ultra-orphan medicines

2010: AGNSS develops ethical decision-making framework to assess ultra-orphan medicines

2012: Moratorium on AGNSS assessing new ultra-orphan medicines

2013: Assessment of ultra-orphan drugs transferred to NICE

2014: NICE Interim process to assess 'highly specialised technologies' (HSTs)

2014: NICE consultation on final HST process

The political barometer

The evaluation of orphan and ultra-orphan medicines and patient access to innovative new treatments are clearly topics of importance to policymakers and the constituents they represent. The level of understanding and engagement from Members of Parliament into NICE's new HST evaluation procedure ensures the topic remains subject to appropriate scrutiny.

Similar levels of political scrutiny into the evaluation of orphan and ultra-orphan medicines have taken place in Scotland, with the Health & Sport Committee's inquiry into access to newly licensed medicines stimulating the review into the workings of the SMC for end of life and very rare diseases¹.

The BIA commissioned independent research of Members of Parliament to ascertain the views of UK parliamentarians on a number of questions related to the issue of rare and very rare diseases, their evaluation and their cost (see table on opposite page).

The research² has found that:

- **68%** of MPs agree or strongly agree that access to treatments on the NHS for very rare diseases should be based on clinical need and not the NHS's ability to pay.
- **63%** of MPs disagree that there should be a maximum price per patient for treating people with very rare and complex diseases.
- **Almost half** (49%) of MPs who expressed a preference said that NICE should not apply its standard mathematical methodology to evaluating very rare diseases, while just over a fifth (22%) agreed that it should.

I'm not sure if 'standard' NICE methodology is appropriate for something which is by definition unusual but I don't think we can afford to ring-fence rarer conditions or write a blank cheque that we will fund their treatment without limit according to need.

Liberal Democrat

More assistance needs to be given to research which is highlighting ways of treating rare diseases. In the long term this is very cost effective.

Conservative

Medical treatment, whatever the condition, must be on medical need not ability to pay or cost

Other Party

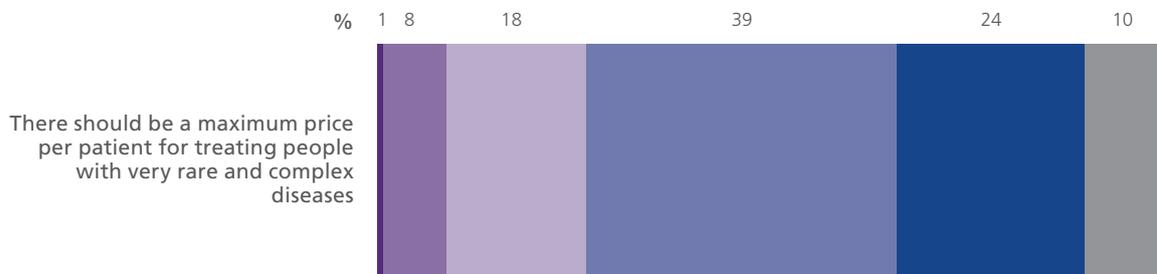
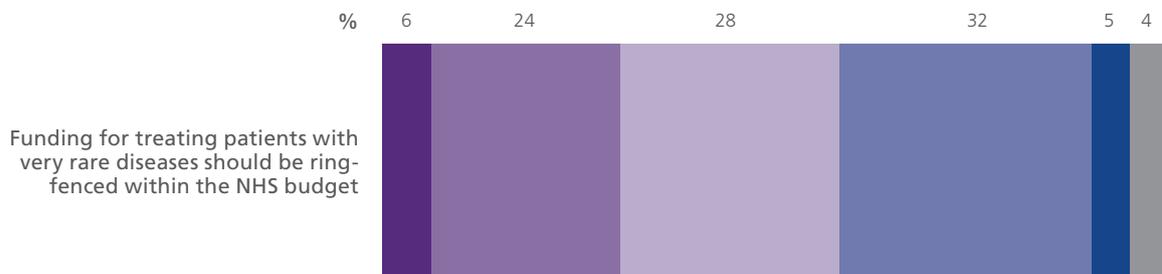
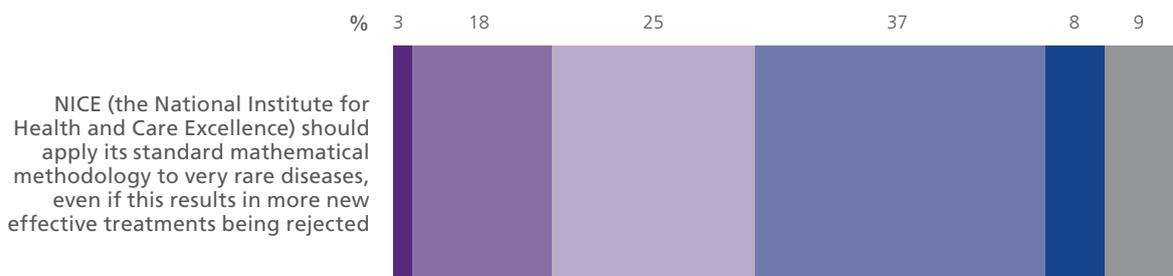
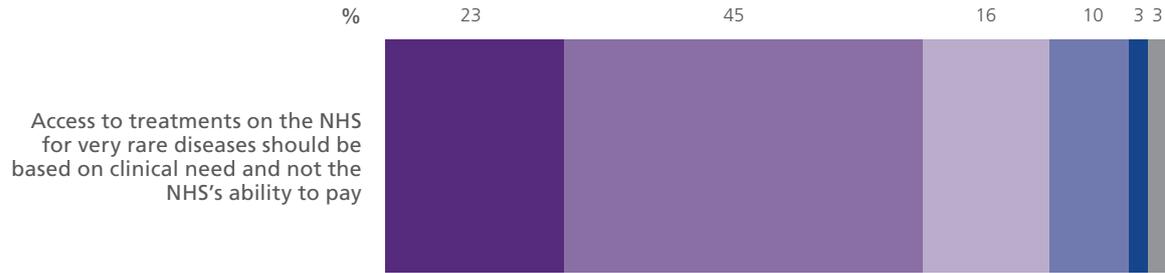
I think it is effectiveness not price that should be the criterion"

Labour

In general, because of the large costs of development, the rarer the disease the higher the price for new treatments and technologies which aim to improve both life expectancy and clinical outcomes for patients with that disease. Very rare diseases tend to affect about one in 50,000 individuals.

To what extent do you agree or disagree with each of these statements?

■ Strongly agree
 ■ Agree
 ■ Neither agree nor disagree
 ■ Disagree
 ■ Strongly disagree
 ■ Don't know



Very rare diseases, complex issues: Future evaluation of ultra-orphan medicines in the UK

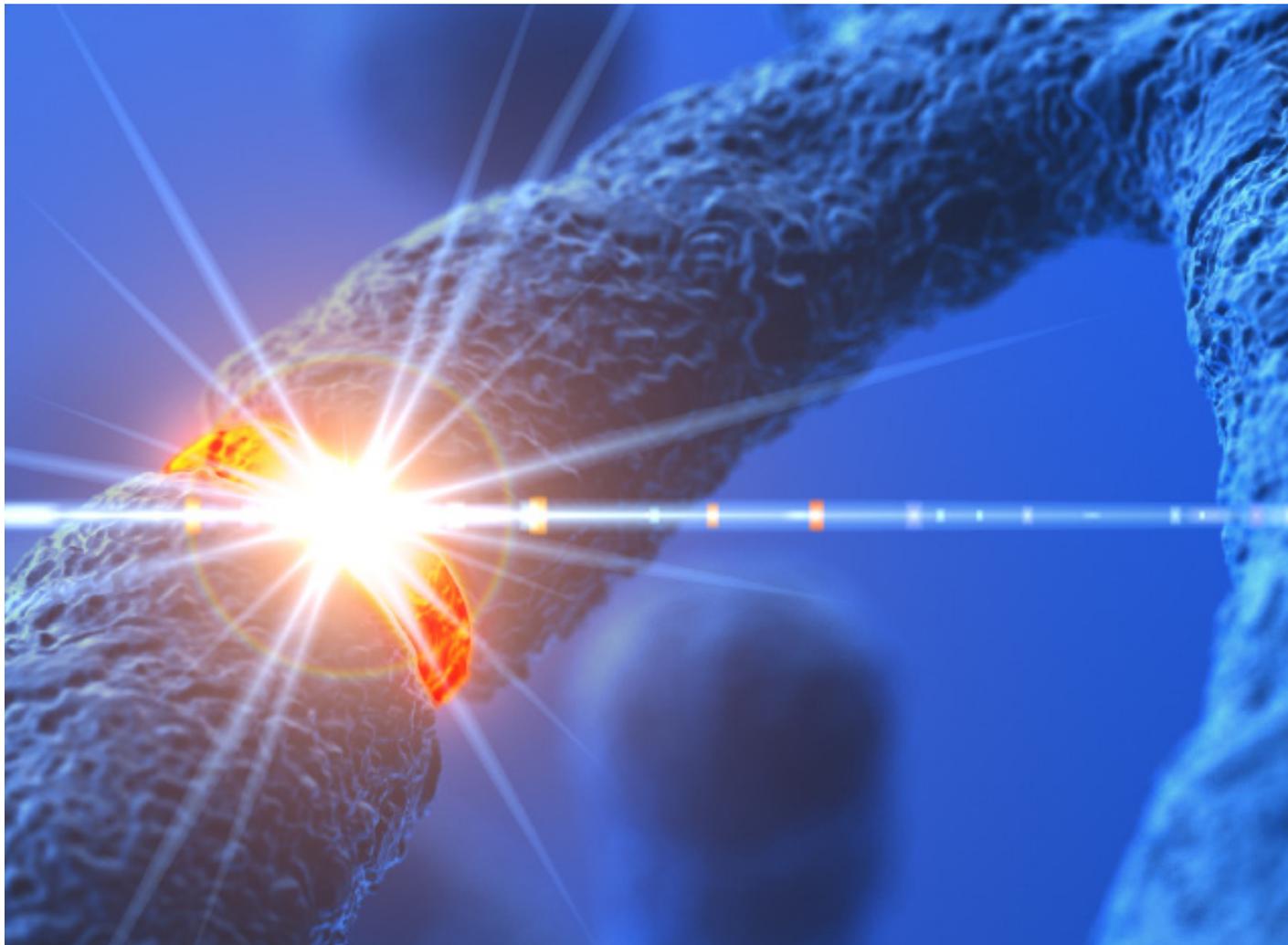
The results of this research tend to show the awareness amongst politicians of the uniqueness of orphan and ultra-orphan conditions and the special characteristics which should be considered when seeking to ensure equitable patient access to novel medical treatments.

It is difficult to draw specific recommendations from such research, but clearly there is a desire for equity across all patients in the UK irrespective of the commonality of their disease or condition. In a £113bn budget the total costs of these treatments is necessarily small, in the region of £500m, so the question for the NHS, or more correctly NICE, is whether these treatments represent value for money?

Following the strong support for access based on clinical need, MPs were also clear that the NHS should not seek to impose a maximum price per patient for treating very rare and complex diseases. This is consistent with the moral and political imperative 'to do something' if 'something can be done' to save a person's life. This is more commonly referred to as the 'Rule of Rescue' and is considered further on page 14.

Further, the survey results suggest that Members of Parliament understand that orphan and ultra-orphan treatments will likely be more expensive than medicines for common conditions and should, on balance, be subject to a separate review process. This is consistent with the direction of travel that NICE is following with the creation of the separate HST process.

However, it is also clear that there is not a strong appetite for the ring fencing of funds with a dedicated focus on rare diseases (albeit that similar funds currently exist elsewhere, such as in Scotland). This could represent the same preference for equity across therapeutic areas and a desire to achieve consistency of access within a single budget.



Rare vs common, or both?

Discussion and disagreement over the allocation of healthcare resources are as old as the NHS itself. But as the NHS struggles with financial pressures at the same time as it emerges from one of the deepest reorganisations in its history, decisions about where and how increasingly limited budgets are spent will become more acute.

From a policy perspective high-cost, low-volume orphan and ultra-orphan medicines can only realistically be funded by collectivist healthcare systems, such as the NHS, through the centralisation of taxpayer funds³. Given the increasing pressures on healthcare budgets, many healthcare systems, including the NHS, have begun to use health technology assessment (HTA), including economic evaluation, to assist in decisions concerning the reimbursement of drugs.

In assessing the cost-effectiveness of orphan and ultra-orphan medicines the utilitarian view in health economics values health gain for both common and very rare diseases equally⁴. This is because health economics is not just about looking at the costs and benefits of a new drug, treatment or service but also, in a world of limited budgets, the consequences of approving one treatment in terms of what cannot then be provided for other patients. The so called opportunity cost. However, this view rests on the assumption that resources in the NHS are both fixed and finite, when the £2.2 bn NHS underspend which was returned to HM Treasury suggests they might not be⁵.

Although the NHS is currently experiencing a sustained period of financial pressure the previous decade saw NHS finances double in real terms⁶. Despite this, clinically effective treatments for both orphan and ultra-orphan diseases were being turned down because of fixed and limited NHS budgets. Following a series of legal challenges from patient associations, AGNSS was created to align clinical and financial decision making in one group focussed on the needs of patients with very rare diseases. Subsequently, AGNSS developed a Multi-Criteria Decision Analysis (MCDA) approach⁷ to assessment of high-cost, low volume treatments and technologies. This MCDA framework only considered treatments and technologies which were clinically distinct and were for a population of no more than 500 patients in England – i.e. ultra-orphan.

Following the creation of NHS England and the transferring of the evaluation framework from AGNSS to NICE, the debate around affordability, equitability and value of rare vs common has honed into view once more.

Recommendation: The new validated NICE framework should build upon the validated Advisory Group for National Specialised Services (AGNSS) framework. The creation of this framework involved a wide range of stakeholders and careful analysis. NICE should be expected to build upon this expertise. In some areas this is clearly already happening.

Is it right to prioritise rare against common?

Should the NHS treat condition A or condition B, or both?

| Maximising Health Gain for £100,000 | |
|--|--|
| Very rare condition A | Common condition B |
| Treatment for A = £100,000 per patient per year | Treatment for B = £10,000 per patient per year |
| 1 patient per year treated | 10 patients per year treated |
| Economic theory: treating condition A means health gain for this patient more valuable | Economic theory: treating condition B maximises the health gain for a limited budget |
| Equity principles suggest that society should treat both | |

Very rare diseases, complex issues: Future evaluation of ultra-orphan medicines in the UK

As has been noted earlier, EU legislation put in place at the turn of the century provides incentives to license drugs for rare diseases. However, these incentives have been questioned as placing more value on health gain in very rare than in common disease⁸. Of course, on the face of it that criticism would appear to be true, but the rationale behind the EU incentives for orphan medicines have always been explicit and clear, “patients suffering from rare conditions should be entitled to the same quality of treatment as other patients”⁹. The reason for the EU policy is to achieve equity, not maximize overall health gain.

It is the principle of equity that has stood behind the creation of the NHS: good healthcare should be available to all, regardless of wealth. More recently, the NHS Constitution has attempted to make explicit the guiding principles for the NHS¹⁰. The seven principles in the constitution include a focus on equity, but also a reminder that health resources are finite.

A societal commitment exists for all patients in the NHS. However, questions are being asked whether this commitment to make treatments equally available to both patients with common and rare disease is being slowly eroded¹¹. The concern is that the UK’s fiscal position will see NHS coverage retreat from ultra-orphan medicines based on affordability grounds. History tells us that when NHS finances are tight, treatments for those with very rare and complex conditions tend to suffer. However, it is the very essence of the NHS that everyone counts and no-one should be left behind, simply because they are unlucky enough to have a very rare or complex genetic disease.

Incentives for orphan drug development

Over a period of time, a consensus emerged in many different countries that action was required to address the gap that emerged in commercial drug development for rare and very rare diseases. Orphan drug legislation in the United States, Singapore, Japan, Australia and the European Union encourages the development of orphan drugs through a range of incentives.

All share the common underlying principle of equity in access to treatment — patients suffering from rare conditions should be entitled to the same opportunity of receiving treatment as other patients with more frequently occurring disorders. In the EU the incentives include reduced marketing authorisation fees, protocol assistance and protection from market competition in some circumstances once the medicine is authorised.

These incentives have resulted in an increased number of drugs developed and brought to market. But real success of the orphan drug policies can only be demonstrated if patients with rare diseases have either increased life expectancy or improved quality of life, and preferably both.

The current situation, where companies are given incentives to develop orphan drugs, yet, access to the drugs is limited by financial and reimbursement constraints, is inefficient from a societal perspective and unacceptable both to patients and to industry. If incentives are to be given to develop treatments for rare and very rare diseases, then ideally these need to extend beyond market exclusivity into patient access and reimbursement. At the very least reimbursement should not undermine the principle of equal opportunity for treatment.

Recommendation: Consideration should be given to the incentives to develop orphan and ultra-orphan medicines and avoid the outcome whereby clinically effective medicines have been developed but patients cannot access them. Governments have recognised the societal need to provide equal opportunity for treatments and have sought to incentivise the research and development of orphan and ultra-orphan medicines. Such incentives are undermined if these principles are not recognised and adopted further down the development and regulatory process.

The distinction between orphan and ultra-orphan

Although a consensus has been reached for action to incentivise commercial drug development for rare and very rare diseases, the resulting orphan drug legislation has not developed in a uniform fashion across the globe. The major, and most significant, difference, is that there is no uniform definition for an 'orphan disease'. In the United States, an orphan disease is one where the prevalence is less than 7.5 cases per 10,000 population, whereas an orphan disease in Australia has a prevalence of less than 1.1 cases per 10,000. In the European Union orphan diseases are defined as having a prevalence of less than 5 cases per 10,000 population.

| Country or Region | Legislative Framework | Prevalence for orphan status (cases per 10,000 population) |
|-------------------|-----------------------------|--|
| USA | Orphan Drug Act 1983 | 7.5 |
| Europe | Regulation 141/2000 | 5 |
| Japan | Orphan Drug Regulation 1993 | 4 |
| Australia | Orphan Drug Policy 1998 | 1.1 |

The consequence of this inconsistent definition is that there will be different approaches to market exclusivity, assessment and access for the same diseases in separate parts of the world. Whereas legislation and regulation respects geo-political boundaries, patient expectations, information and communication technology and patient associations do not.

In the UK, NICE and the All Wales Medicines Strategy Group (AWMSG), have for some time used the informal term 'ultra-orphan' medicines to describe medicines for the treatment of very rare diseases with a prevalence of no more than 1 in 50,000, equating to less than 0.2 cases per 10,000 population^{12,13}. This definition has also been adopted by the Scottish Medicines Consortium (SMC), following its recent review into access to newly licensed medicines.

| Disease type | Prevalence | UK Incidence (est) |
|-------------------------------------|----------------------------|-----------------------|
| Orphan diseases | 1-5 per 10,000 population | |
| Narcolepsy | 2.5 per 10,000 | 25,000 |
| Cystic Fibrosis | 1.26 per 10,000 | 9,000 |
| Pancreatic cancer | 1.2 per 10,000 | 8,500 |
| Mesothelioma | 0.3 per 10,000 | 2,500 |
| Ultra-orphan diseases | ≤0.2 per 10,000 population | |
| Gaucher disease type 1 | 0.1 per 10,000 | 325 |
| Mucopolysaccharidosis type 1 | 0.1 per 10,000 | unknown |
| Atypical haemolytic uremic syndrome | 0.1 per 10,000 | 194 |
| Fabry disease | 0.022 per 10,000 | 150 (England / Wales) |
| Niemann-Pick disease type B | 0.04 per 10,000 | 25 known cases |
| Cystic Fibrosis (G551D mutation) | Unknown | 320 (England) |

The above table¹⁴ provides a snapshot of some of the diseases recognised as orphan or ultra-orphan, highlighting the difference in prevalence and UK incidence for illustrative purposes only. The majority of patients who rely on orphan and ultra-orphan drugs live with rare and complex diseases for which no alternative treatment exists. The world of orphan and ultra-orphan diseases is diverse, with some rare cancers being classed as orphan diseases as well as complex genetic conditions.

Why do we need a separate HTA process for very rare diseases?

Some say it is not possible to generate sufficient evidence for evaluation assessment on interventions for rare and very rare diseases because of low study power and uncertainty about the end points which demonstrate benefit to the patient and value to the tax payer. Small numbers as used in trials for very rare diseases increase the chance of ‘false negatives’ (wrongly concluding that the drug doesn’t have the desired effect, also known as a Type 2 error) which make it difficult to undertake cost-effective analyses that produce certain results.

Indeed, the new NICE HST process will admit evidence from a variety of sources to be considered in the evaluation process, including anecdotal evidence from expert clinicians. The result of accepting a broader evidence base into the evaluation process is that the subsequent decision on funding must reflect the amount and quality of the evidence – i.e. there will be a considerable level of uncertainty around the estimate of cost effectiveness.

As HTA matures as a discipline other sources of evidence are emerging which could help in the evaluation of very rare diseases. However, until new sources of evidence can introduce greater certainty into the evaluation process for very rare diseases, a long-standing question has been whether the evaluation for ultra-orphan medicines, and indeed orphan medicines, can be conducted in the same framework as for common ones.

Due to the nature of the evidence base in treatments for ultra-orphan diseases (small clinical trials, which run the risk of Type 2 error) there is a need for a more holistic approach to their evaluation, as with the AGNSS MCDA approach. This is because ultra-orphan medicines could never meet the conventional NICE threshold due to their pricing structure. Ultra-orphan treatments have relatively high prices – typically £100,000’s per patient per year – as the costs of development have to be recouped from a smaller treatment population.

If there were a single assessment process for all medicines it would likely be faced with the prospect of approving a treatment for a very rare disease with a highly uncertain cost per QALY of £500,000 whereas rejecting a treatment for a more common condition when the cost per QALY was certain at £31,000. Both decisions could be said to be correct, but it would be difficult to maintain public confidence in a single framework which delivered such seemingly different results. The creation of a separate process for ultra-orphan medicines is a pragmatic rather than technical solution.

In a personalised medicine world, regulators and health payors have a natural and understandable concern that a single product with multiple uses in several different – but all rare – indications could have severe cost implications (see topic selection discussion below). However, as the above commentary attempts to illustrate, ultra-orphan medicines require a separate evaluation structure to better ensure equity of access to treatment.

Recommendation: Ultra-orphan medicines require a separate evaluation framework.

There is a clear and justifiable need for this because of the unique characteristics and challenges involved with evaluating medicines for very rare conditions. The independent research released in this document would appear to demonstrate political support for this.

Topic selection

Topic selection refers to the way in which products are chosen, through “horizon scanning” of the drug development pipeline, as potentially suitable or otherwise for evaluation under the HST programme. NICE have outlined the criteria for topic selection as follows:

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

Determining the applicability of a product to the new HST programme, will be an important component of the new regime. Should the technology not be considered suitable, other approaches to ensure patient access to clinically effective and approved treatments may be adopted. These range from a full standard NICE appraisal to a series of Individual Funding Requests by clinicians and hospitals to NHS England (and ultimately, in some incidences, evaluation by the Clinical Priorities Advisory Group).

Given the different potential outcomes flowing from topic selection criteria, and the need for industry and patients to work within a predictable and transparent system, this issue deserves greater focus. Moreover, the necessarily close working relationship required between NICE and NHS England with regards very rare conditions highlights the need for co-ordinated processes now that evaluation and service delivery elements are managed by different organisations.

Recommendation: There is a need to ensure integrated implementation

and service delivery.

There is a need to closely align the evaluation and service delivery elements of ultra-orphan medicines recognising that the functions are now split between NICE and NHS England whereas under the AGNSS framework they were considered together.

A window into the world of personalised medicine?

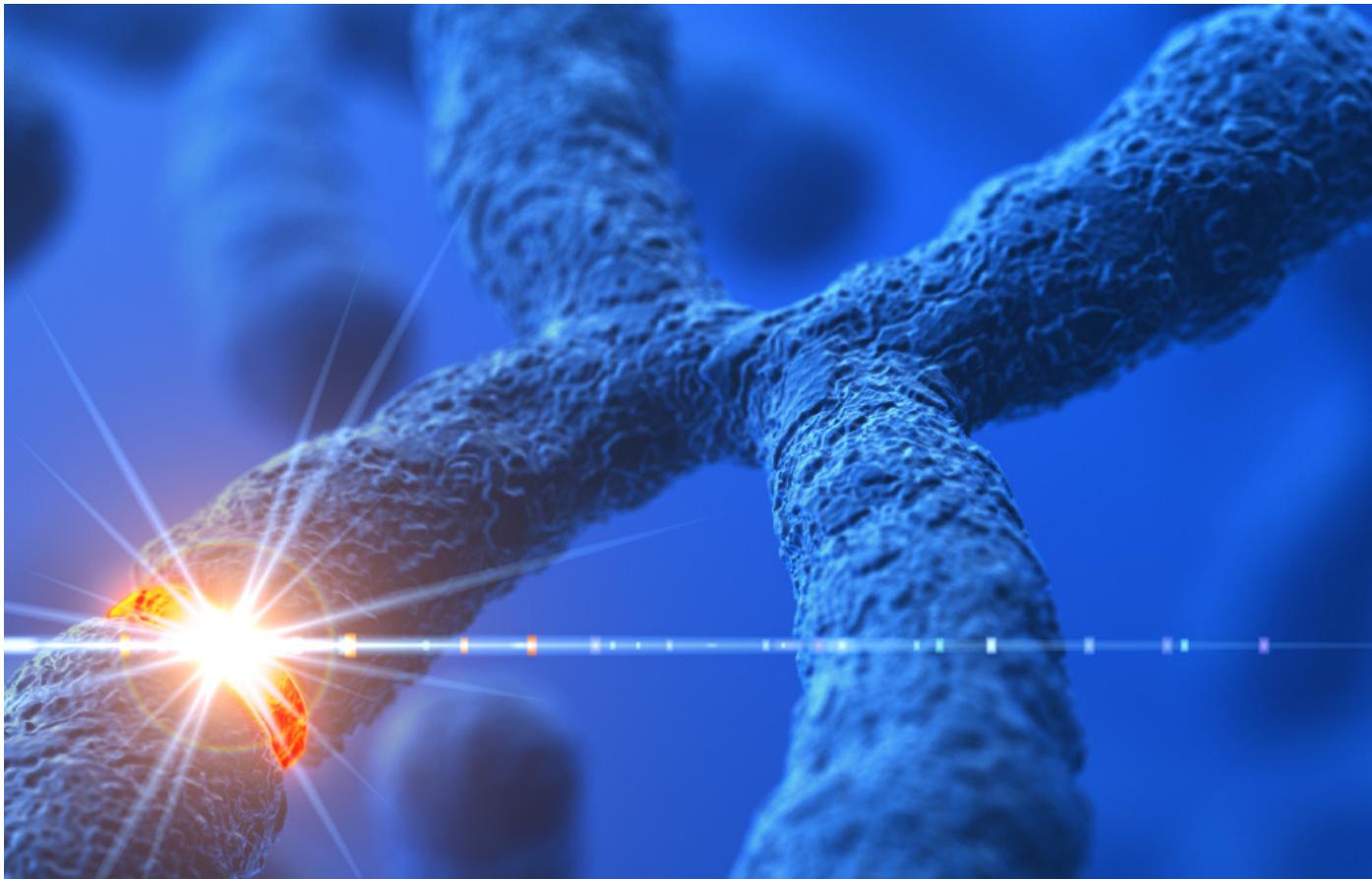
Topic selection for HSTs is particularly interesting given its wider ramifications for drug evaluation. The way it is ultimately handled for ultra-orphan drugs provides a window into the world of a more personalised medicine approach to drug development where increasingly products will be developed for specific sub-sets of larger patient populations.

Each of these patient sub-sets may be extremely small – perhaps of a similar size to a HST – although a single product, perhaps in combination with others, may be suitable for more than one sub-set. The overall number of patients may therefore grow to a larger population as more indications are granted Marketing Approval.

In these cases, which will become increasingly likely as personalised medicines targeting specific biomarkers and genetic mutations are developed, how should they be treated by the HST process? Budget holders may understandably be nervous of the financial implications of this new wave of personalised medicines and the issue was commented upon at length during the BIA led roundtable discussion (see page 17). One can see, referring to the bullet points above, that criteria have been established to take account of these issues, including reference to a need for the technology to be clinically distinct and that it is to be used exclusively for that purpose. The impact this will have on eligibility of innovative new products will need to be monitored. And for those that ‘fall out’ of this process, yet are not suitable for full NICE assessment, what is the appropriate mechanism going forward?

In this context, the Kalydeco case study (on the following page) is particularly relevant. The product, as the case study explains, was subsequently subject to a more bespoke evaluation procedure, coming as it did in between the disbandment of AGNSS but before the NICE HST route was formally taken forward.

In this way HSTs have significant relevance to the future of drug assessment more generally and this issue is likely to continue to pose challenging questions.



Case study: Kalydeco

Cystic fibrosis is a complex and multi-system disease that causes the internal organs, particularly the lungs and digestive system, to produce thick sticky mucus that eventually leads to death from respiratory failure. In 2012 the median age at death for cystic fibrosis patients was 28 years.

A newly developed product by Vertex, Kalydeco (ivacaftor), is the first in a new class of personalised medicines that treats the root causes of cystic fibrosis by targeting a defect in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

In July 2012 Kalydeco received marketing authorisation for the treatment of cystic fibrosis in patients aged six years and older who have a copy of the G551D mutation in the CFTR gene. This mutation is very rare, affecting just 4% of cystic fibrosis patients, and NHS England estimates that only 320 people in England meet these criteria.

As Kalydeco is a personalised medicine for a very rare genetic subset of a more common disease, neither NICE nor the AGNSS considered appraising this new medicine to be within their approach to drug development. There was also significant uncertainty about how Kalydeco could be commissioned to prevent inequality across the country.

However, in August 2012 the Yorkshire and Humber office of the North of England Specialised Commissioning Group, which is the national commissioning lead for cystic fibrosis, commissioned a clinical and cost-effectiveness evaluation on behalf of the four Specialised Commissioning Groups in England.

The draft evaluation report was discussed with the Cystic Fibrosis Clinical Reference Group (CRG) before the final report and the CRG's recommendations were presented to the Clinical Priorities Advisory Group (CPAG) in September 2012. CPAG accepted Kalydeco's clinical-effectiveness, but deferred making a final decision for a month to allow for further discussions with Vertex.

Following these discussions CPAG announced in December 2012 that Kalydeco would be provided to all clinically appropriate patients with G551D from January 2013.

Vertex welcomed the speed and flexibility with which the NHS conducted a rigorous and collaborative appraisal process and made a final commissioning decision, which has previously taken over a year for medicines for very rare diseases.

NICE and NHS England should ensure that the process followed to appraise Kalydeco informs the Highly Specialised Technology programme and the Rare Diseases Advisory Group's work so that future medicines for very rare diseases can be robustly appraised within a similar time frame.

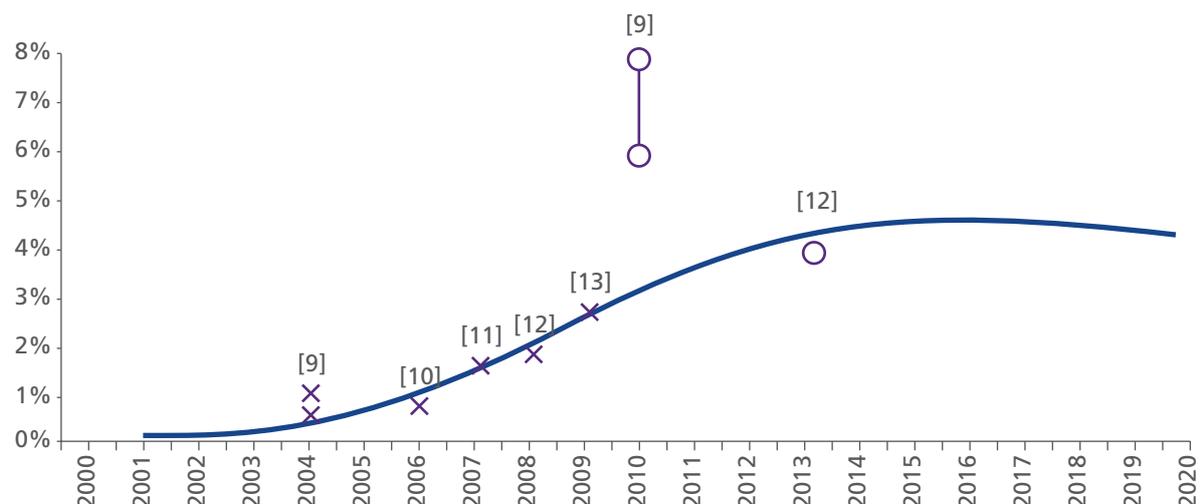
The future costs of rare and complex diseases

Incentives in EU orphan drug legislation have seen an increased number of orphan and ultra-orphan drugs brought to market. While this is, of course, of great benefit to patients, it also raises challenges for future public policy in terms of the impact on healthcare budgets. And if the promise of personalised medicine holds true, will paying for new and costly personalised treatments bankrupt healthcare systems in the future?

There are a range of different assessments of what expenditure on orphan drugs, including ultra-orphan, will be in the future. In 2004, early analysis for European Commission predicted orphan drugs would be 6-8% of total pharmaceutical budget by 2010 – [range 9 on the graph below]. So far, this has proven not to be the case, but healthcare systems have seen the share of the pharmaceutical budget taken up by orphan and ultra-orphan diseases grow from 0% in 2000 to 3.3% by 2010.

Future estimates suggest that this share is predicted to increase from 3.3% in 2010 to a peak of 4.6% in 2016, after which it is expected to level off through 2020 at 4-5%. These are only predictions, however. From a public policy perspective, the NHS sees hospital specialised drugs budgets increasing at the highest rate compared to all other areas of NHS spending, so controlling costs of highly-specialised treatments will undoubtedly be an evolving area of healthcare policy.

Projected budget impact of orphan diseases as percentage of total pharmaceutical spend (2000 – 2020)¹⁵



- **Will there ever be a maximum price of care per patient in very rare diseases?**

Perhaps the most striking result in the research of MPs' views is the overwhelming majority who said there should not be a maximum price per patient for treating patients with very rare and complex diseases. This aligns with the societal commitment for all patients treated by the NHS to be able to benefit equally from available treatment options, including those with very rare diseases, who might be said to require rescue.

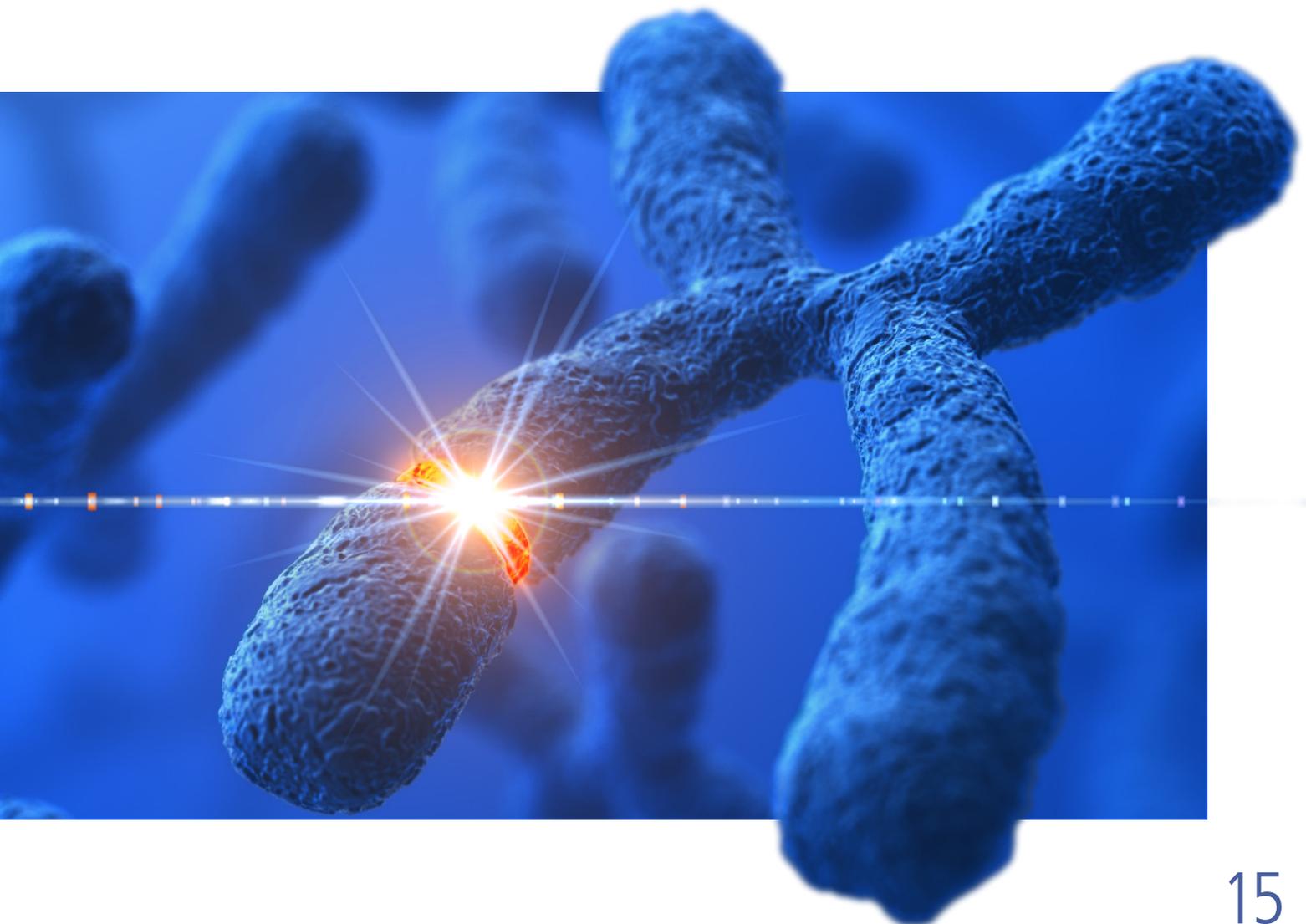
The 'rule of rescue' is generally considered to mean the sense of immediate duty that people feel towards those who present themselves, usually to a health service, with a serious and life threatening condition. It is a useful concept and the analogy of the Chilean mine workers trapped underground is a particularly helpful analogy for the use of high-cost, low volume medicines. On a strict cost-effectiveness analysis it is doubtful that the rescue of the Chilean mineworkers would have been 'approved' if it had been a pre-planned exercise, but the moral case for action at the time was unimpeachable.

Very rare diseases, complex issues: Future evaluation of ultra-orphan medicines in the UK

In Australia, the Pharmaceutical Benefits Advisory Committee (PBAC) can resort to the “rule of rescue” in exceptional circumstances¹⁶. This rule might influence a decision, which would be negative due to a high relative cost per QALY and other relevant criteria, if a number of conditions are met: (i) there are no other realistic treatment options for that condition; (ii) the medical condition is a serious, disabling or life-threatening condition; (iii) the medical condition applies to only a small number of patients; and (iv) the proposed drug provides a worthwhile clinical improvement sufficient to qualify as a rescue from the medical condition. This mechanism is used sparingly (around four times a year) but creates a pragmatic framework to define the circumstances under which the treatment could be used.

Of course, different countries have different measures of value when it comes to assessing pharmaceuticals and determining priority areas for public spending. In the UK, the assessment is dominated by the utilitarian approach and the law of opportunity costs which means that in a world of finite resources, helping one person means that someone else cannot be helped. However, most people would agree that individuals in desperate and exceptional circumstances should sometimes receive greater help and prioritisation than was justified by a purely utilitarian approach.

The NICE Citizen Council has previously considered the “rule of rescue”, but there is no defined framework for its use. At the time, a majority of the Council said that it should not be rejected completely and it should be applied in certain exceptional cases. However, as personalised medicine and scientific innovation develop, society will be faced with assessing and paying for medicines to treat ever smaller patient populations, perhaps for just a handful of patients, but the costs of developing these treatments will remain relatively high. In these circumstances it is likely that a different framework of assessment will be required when making decisions on reimbursement and prices of new medicines and examples from other countries might prove useful.



Endnotes

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The BIA organised a roundtable event in the House of Commons, kindly hosted by Andrew Miller MP, Chair of the House of Commons Science and Technology Committee, which brought together key stakeholders to discuss "Rare diseases, complex issues" on 22 October 2013. A list of the attendees at that discussion is below:

| Name | Position | Affiliation |
|---------------------------|--|---------------------------------------|
| Mark Barrett | Managing Director UK & Ireland | Alexion |
| Steve Bates | Chief Executive Officer | BioIndustry Association |
| Paul Catchpole | Value and Access Director | ABPI |
| Janis Clayton | VP and General Manager | Shire UK |
| Tanya Collin-Histed | Chief Executive | Gauchers Association |
| Rt Hon Stephen Dorrell MP | Member of Parliament for Charnwood | House of Commons |
| Kate Eden | Director, Public Affairs | Shire |
| Henry Featherstone | Director of Public Affairs | Genzyme (UK & Ireland) |
| Josie Godfrey | Associate Director, HST programme | NICE |
| John Ivory | Business Unit Director | Genzyme (UK & Ireland) |
| Alastair Kent | Director / Chair | Genetic Alliance UK / Rare Disease UK |
| Simon Lem | Managing Director UK | Vertex |
| Fiona Marley | Assistant Head of Specialised Commissioning | NHS England |
| Brendan Martin | General Manager | Genzyme (UK & Ireland) |
| Robert Meadowcroft | Chief Executive | Muscular Dystrophy Campaign |
| Andrew Miller MP | Member of Parliament for Ellesmere Port and Neston | House of Commons |
| Fiona Pearce | Technical Adviser to the HST programme | NICE |
| Antonis Pappasolomontos | Head of Public Affairs and Policy | BioIndustry Association |
| Mark Samuels | Managing Director, NOCRI | NIHR |
| Lord Turnberg | Chair, APPG for Medical Research | House of Lords |
| Clare Whelan OBE DL | Head of Office, Rt Hon Stephen Dorrell MP | House of Commons |
| Andrew Wilkinson | | Specialised Healthcare Alliance |
| Len Woodward | Trustee | aHUSUK |
| Iain Wright MP | Member of Parliament for Hartlepool | House of Commons |

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