

# The funding of orphan medicines in the UK

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## ABSTRACT

The increasing number of patients suffering from rare diseases is creating greater demand for treatments. This, combined with an incentivised regulatory framework, is resulting in a significant number of novel but expensive treatments coming to market. Payers are becoming concerned by the cumulative impact of these treatments and are starting to question the clinical value and justification for their high price. One of the key issues driving this is the widening gap between regulatory data requirements and the information required by payers to determine whether or not the new treatment offers value for money for the healthcare system. This paper seeks to explore the funding challenges for UK payers and highlights that the eculizumab (Soliris, Alexion) review by the National Institute for Health and Care Excellence (NICE) will provide a strong indication of how these drugs will be reviewed and funded in the future.

**Key Words:** Orphan • pharmaceuticals • market access • health technology assessment • payers • pricing • cost-effectiveness • commissioning • NHS • NICE

Regulatory incentives to develop treatment for rare diseases have increasingly motivated pharmaceutical companies to seek commercial opportunities; and there are many new therapies coming to market to treat orphan and ultra-orphan diseases. However, the high prices associated with these therapies and resulting budget impact is beginning to cause funding challenges for payers.

In the UK, treatments for rare diseases are commissioned by NHS England on the recommendations of the Rare Diseases Advisory Group (RDAG) and also now through the National Institute for Health and Care Excellence (NICE), under its Highly Specialised Technology Programme (HSTP). The first drug to go through the NICE HSTP is eculizumab (Soliris, Alexion) and in its draft recommendation, NICE has challenged the basis for the high cost of the drug.

This paper reviews the funding of orphan medicines in the UK and concludes that the Soliris review by NICE provides a strong indication of how orphan drugs are likely to be reviewed in the future.

### 'Orphan drugs': a definition

EU legislation defines an orphan drug as one that could treat a disease with a prevalence of less than 5 per 10,000 of the population. Orphan drugs can be designated by the European Medicines Agency (EMA) and, in due course, may be given marketing authorisation by the EMA. This then allows the drug to be marketed across EU countries – but this does not mean it has to be funded by healthcare organisations (EMA, 2014).

The definition of an orphan disease varies slightly between the EU and the US: in the US

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orphan diseases are those affecting fewer than 200,000 people (NICE, 2004).

The wide range of conditions that fall within the definition of ‘orphan diseases’ has led to the emergence of an informal sub-category named ‘ultra-orphan diseases’ to describe extremely rare conditions. The term has no formal legal definition but treatments for these very rare diseases have become known as ‘ultra-orphan drugs’ (NICE, 2004).

## Challenges facing payers

As the UK NHS moves into the ‘post-Nicholson’ era, confidence is fading in NHS finances. A recent report by The King’s Fund (2014) highlighted deepening pessimism about the ability of the NHS to make ends meet. Just 40% of finance directors in hospitals and other providers are confident of balancing the books in 2014/15 and, for the following financial year, the figure is significantly lower at just 16% (McKee, 2014).

Against this backdrop, payers are becoming increasingly nervous as more and more highly-priced orphan drugs come to market. There are

currently 6,000 recognised rare diseases, and Rare Disease UK estimates that 1 in 17 people will be affected by a rare disease at some point in their life – this amounts to approximately 3.5 million people in the UK (Rare Disease UK, 2014). It is clear that, even if rare diseases on their own affect a very small number of patients, when combined they are a major area of funding and represent a significant proportion of healthcare spending. Treatments for rare diseases are commissioned at a national level in the UK and the specialised commissioning budget has swollen to reflect greater demand, increasing 41% on the specialised services commissioned in 2011–12 to a figure of £12 billion in 2012–13 (Williams, 2014) (the total NHS budget for 2013/14 is £108.9 billion) (NHS Choices, 2014).

## Funding for orphan drugs in the UK

From 1 April 2013, NHS England (previously known as the NHS Commissioning Board) has had a core responsibility for all specialised services (which it refers to as ‘prescribed

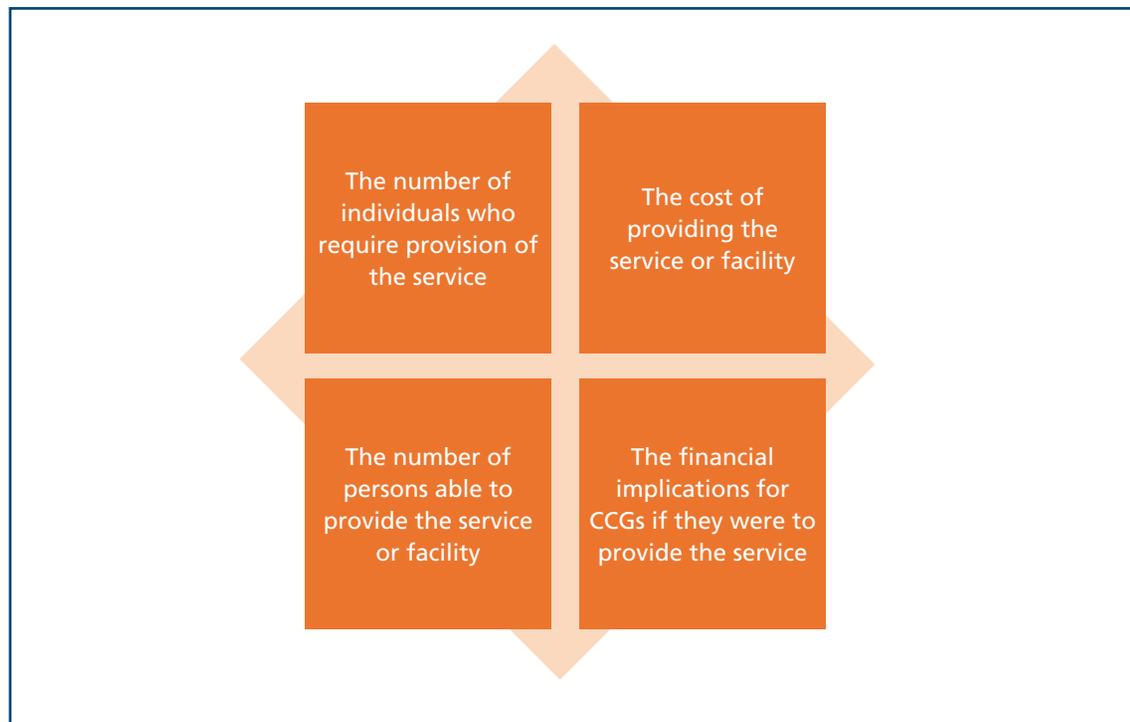


Figure 1. Factors which determine whether NHS England commissions a service (Wellards Academy, 2013)

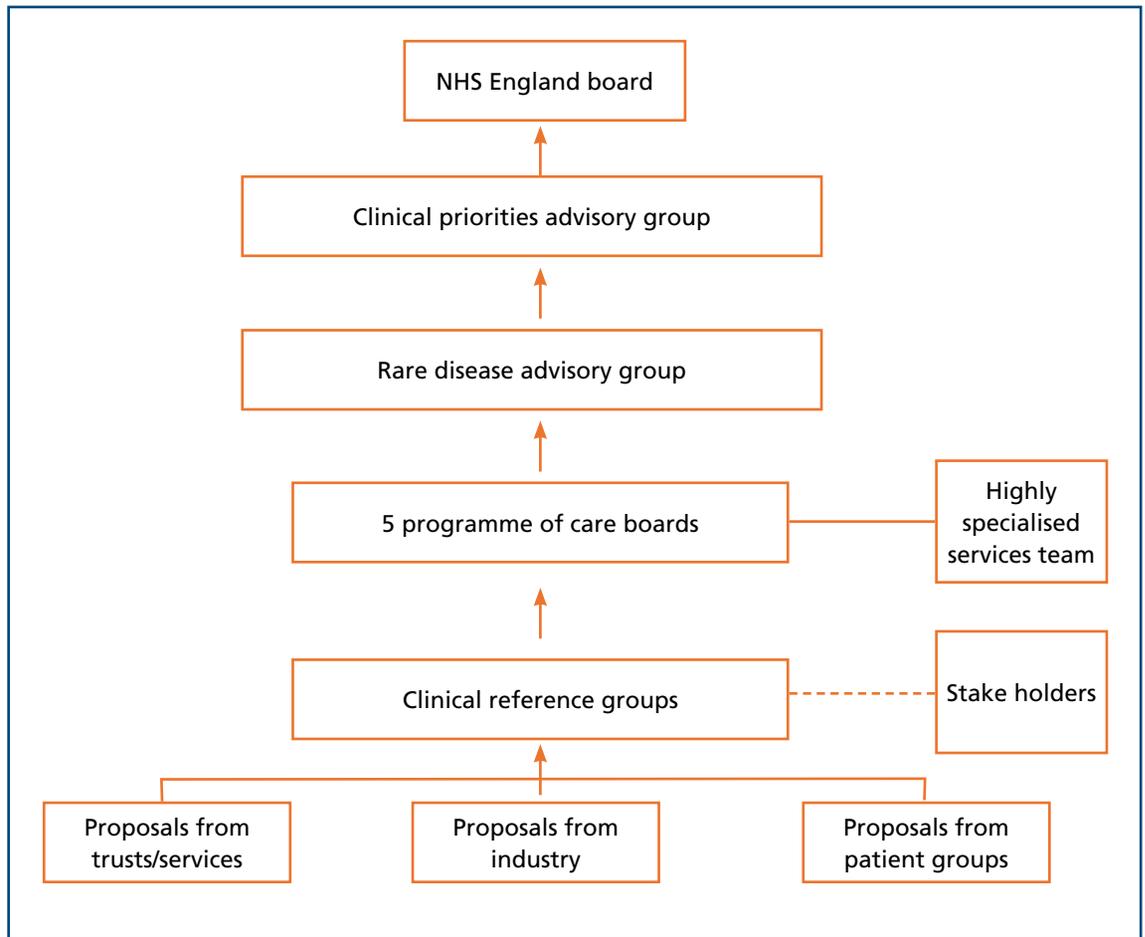


Figure 2. Rare Diseases Advisory Group in the governance structure of NHS England (NHS England, 2014a)

services’). Four factors determine whether or not NHS England commissions a service as a prescribed specialised service (see *Figure 1*). Specialised services are funded through a budget determined and held by NHS England, not through subscriptions from clinical commissioning groups (CCGs). CCGs took over from primary care trusts (PCTs) and are clinically led groups that include all of the GP groups in their geographical area.

NHS England is responsible for managing applications for funding specific patients for specialised service treatment (individual funding requests) that fall outside of nationally agreed service specifications and policies.

Individual clinical commissioning policies sit beneath service specifications and are required to ensure a consistent approach to either accessing services or receiving specific treatments for

certain conditions, based on sound clinical evidence. An agreed set of policies was published in April 2013 for the 2013/14 commissioning round (Wellards Academy, 2013).

In June 2013, NHS England published the interim specifications it had adopted. Through its 75 clinical reference groups (CRGs) it is continuing the further development of these for use in 2014/15. CRGs cover the full range of specialised services and are responsible for providing NHS England with clinical advice regarding these directly commissioned services. The CRGs are made up of clinicians, commissioners, public health experts, patients and carers, and are responsible for the delivery of key ‘products’, such as service specifications and commissioning policies, which enable NHS England to commission services from specialist providers through the contracting arrangements

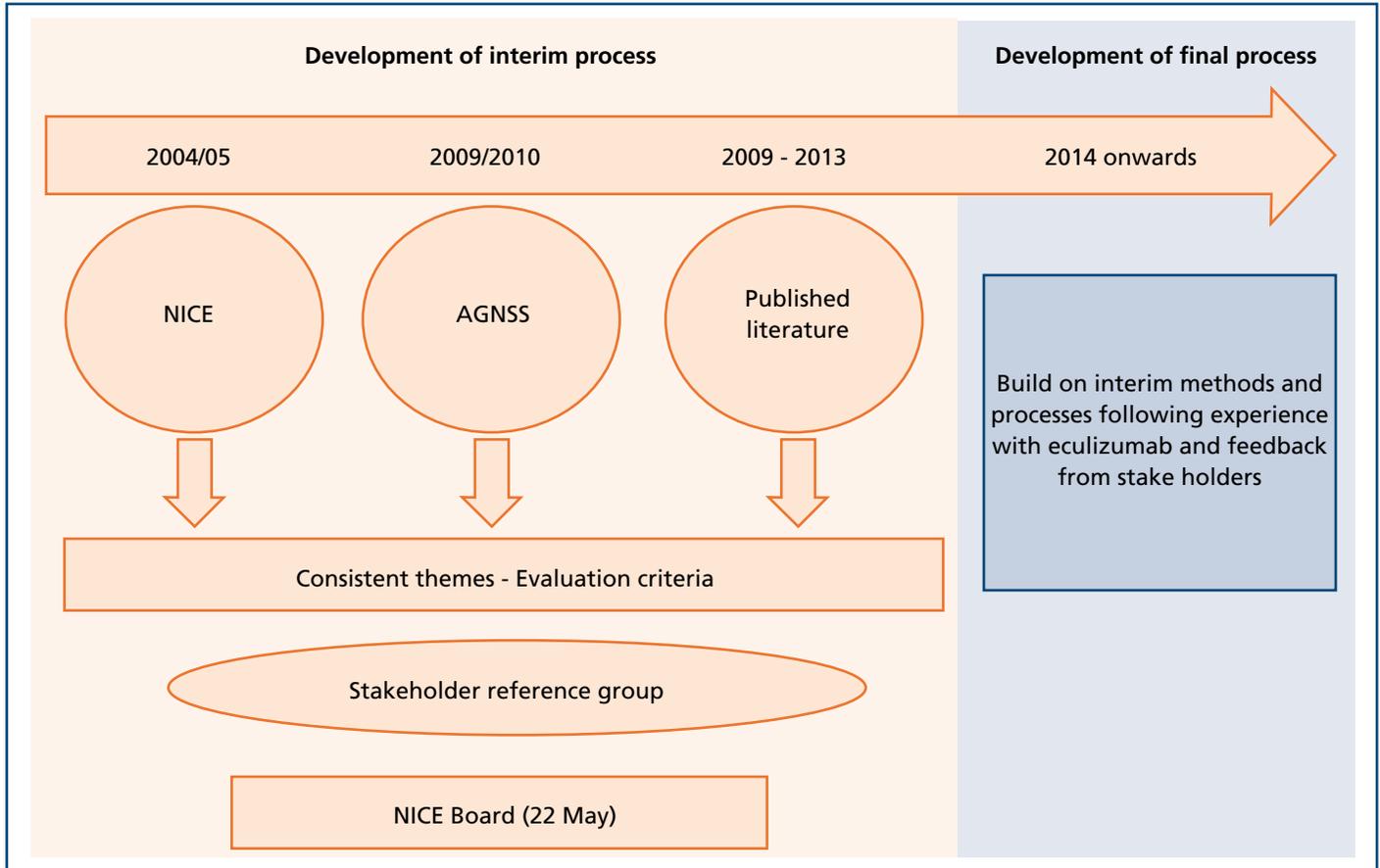


Figure 3. Method development by NICE Highly Specialised Technology Programme (NICE, 2014a)

overseen by its Area Teams (NHS England, 2014b).

## Rare Diseases Advisory Group

NHS England's RDAG (Figure 2) makes recommendations to NHS England and the devolved administrations in Scotland, Wales and Northern Ireland on developing and implementing the strategy for rare diseases and highly specialised services. The membership of the Group is broad and includes representatives from Royal Colleges, commissioners, patient, public and professional organisations. There is also representation from the devolved administrations.

Highly specialised services are defined by NHS England as conditions that, on average, affect no more than 500 patients per year. Due to the small number of patients with these conditions, they are delivered nationally through

a very small number of centres of excellence. Examples of highly specialised services include enzyme replacement therapy (ERT) and liver transplant services.

RDAG will interact with and receive recommendations from CRGs and will formulate its advice by calling on a number of evidence sources from outside the NHS, including patient groups and professional bodies.

The Group will make recommendations to the Clinical Priorities Advisory Group (CPAG) about how highly specialised services should be commissioned. This includes recommending which expert centres should be nominated to deliver highly specialised services.

## Orphan drugs and health technology assessment

Orphan medicines that were considered too specialist for NICE's work programme used to

### Box 1. NICE Highly Specialised Technology Programme topic selection prioritisation criteria (NICE, 2014a)

- 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

be assessed by the Advisory Group for National Specialised Services (AGNSS), a committee that advised government health ministers about which services should be nationally commissioned and the centres that should provide them.

AGNSS was established following the consultation 'Strengthening National Commissioning' (Department of Health, 2010) and specifically advised ministers on:

- The highly specialised services, products and health technologies that should be, or no longer be, nationally commissioned
- The centres that should be designated as providers for nationally specialised commissioned services and whether to renew or withdraw the designation at the appropriate time
- The annual budget for new and existing nationally commissioned specialised services and the contribution required from PCTs.

Under the Health and Social Care Act 2012, NICE has taken over the role of assessing very high-cost drugs for people who suffer with rare conditions from AGNSS (NICE, 2012). To take this forward, NICE has established a new programme entitled the HSTP. The programme will adhere to the general principles of NICE in that it will have topic selection, scoping, evaluation and appeal. Currently, HSTP is governed by an interim manual (NICE, 2014a), which was presented to the NICE board in May

2013, although more details, such as the topic selection process (see *Box 1*), are becoming publicly available.

The initial reaction from the pharmaceutical industry is one of scepticism. There is concern that the flexibility in the AGNSS process might be lost and that, in an area where clinical data is scarce, the true value of the treatment will not be uncovered by NICE's traditional cost-effectiveness methodology. The programme will focus on pharmaceuticals only and is looking to review three medicines per year. The first review under these new arrangements is eculizumab (Soliris, Alexion) for atypical haemolytic uremic syndrome (aHUS). NICE has requested that the manufacturer provides more information on the manufacturing, research and development costs to justify the high price of the drug. NICE has also asked the commissioners for advice regarding the likely budget impact of the drug.

What is unusual about this preliminary recommendation is that the Evaluation Committee has seemingly attacked the rationale behind the price of eculizumab, which is not NICE's traditional role – NICE's remit is to look at the clinical and cost-effectiveness of treatments, of which price is just one element. In the latest recommendation, Alexion have been asked to justify the price they've chosen.

The total cost of eculizumab per adult is estimated to be approximately £340,200 (initial and maintenance treatment) in the first year of treatment and £327,600 for one year of treatment on the recommended maintenance dose (NICE, 2014b). The draft recommendation from the NICE Appraisal Committee is effectively saying that it is not prepared to recommend a clinically effective treatment for a serious condition purely on the basis of high acquisition cost. It will be interesting to see what the final decision will be and the concern from industry is that this decision is the start of NICE's transition from a health technology assessment body to a pricing body:

***'We estimate (Soliris) would cost the NHS about £58 million in the first year, rising to over £80 million in 5 years, we need more information. Our independent***

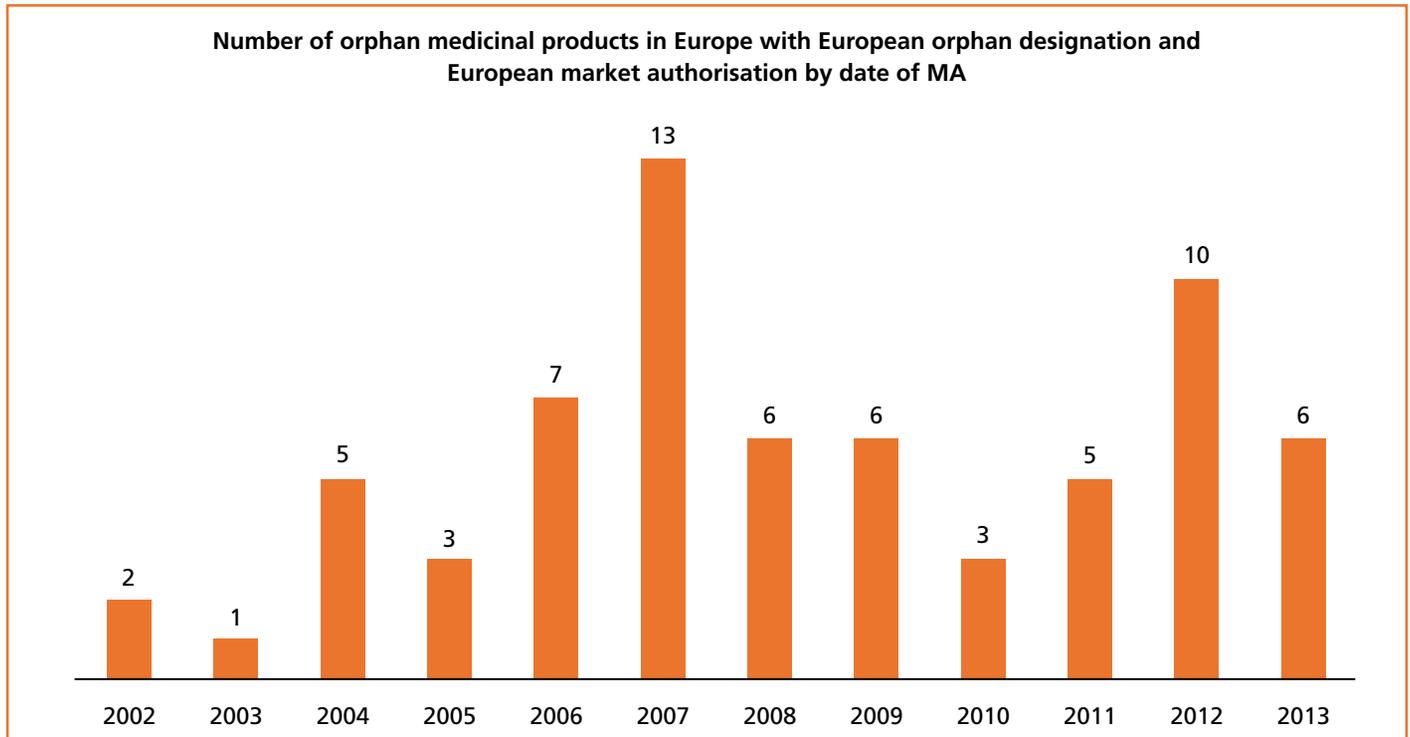


Figure 4. Orphan drugs coming to market (Orphanet, 2013)

**advisory committee has, therefore, asked for clarification from the company on aspects of the manufacturing, research and development costs of a medicinal product for the treatment of a very rare condition.’ Sir Andrew Dillon, NICE**

In Scotland, the Scottish Medicines Consortium (SMC) will continue to review orphan drugs as the organisation reviews all newly approved medicines except vaccines, branded generics, non-prescription-only medicines (POMs), blood products, plasma substitutes and diagnostic drugs. The SMC does acknowledge the challenges facing companies who develop drugs for rare disease, but still expects a full submission.

The SMC applies ‘disease modifiers’, which allow it to exercise greater flexibility in its decision-making to allow consideration of additional factors; for example, to accept either greater uncertainty in the health economic case or a higher cost per quality-adjusted life year (QALY) – these are particularly relevant when assessing orphan drugs. Scotland also has a ‘rare disease’ fund (£21 million) for orphan drugs

that are not recommended by the SMC (Scottish Government, 2014).

Finally, in Wales, the All Wales Medicines Strategy Group (AWMSG) reviews all medicines not on the NICE work programme or if NICE is going to publish guidance within 12 months of AWMSG receiving a potential submission. NICE guidance overrules AWMSG guidance if the body does proceed with a full appraisal. It will be interesting to see how the AWMSG will interact with NICE’s new HSTP; however, the statement from the Minister for Health and Social Services, Mark Drakeford, over Kalydeco (ivacaftor), has shown that the Welsh Government is not afraid to intervene in access to high-cost drugs if health technology assessment is considered a barrier to innovative treatments (Welsh Government, 2013).

## Orphan drugs: challenges beyond the UK

The environment for orphan medicines in Europe is also changing and, like their UK counterparts, European payers are becoming increasingly nervous about the number of

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orphan products coming through and the resulting impact on healthcare budgets.

However, pharmaceutical manufacturers have been encouraged to develop treatments for orphan diseases. Both the EMA and US Food and Drug Administration (FDA) provide a number of incentives to manufacturers and these include:

- Orphan drug status – grants extra market exclusivity
- High level of unmet need off-setting small patient populations
- Clinical trials can be shorter, involve fewer patients and companies can receive research and development rebates
- Greater chances of approval and shorter timelines to launch.

The impact of these incentives is shown in *Figure 4*. The irony is that, while many countries have introduced measures to encourage development of treatments for rare conditions, at the same time governments are imposing austerity measures to restrict expenditure on drugs, which has led to the reimbursement challenge. However, despite the complex discussions on clinical and cost-effectiveness of orphan medications, payer decision-making is essentially about answers to just four basic questions:

- What clinical and other benefits does a new product have over existing products and/or treatments?
- How relevant are these benefits in clinical practice?
- Can we really treat patients better with this new product?
- Do we think it is good value for money?

It is the challenge for the manufacturers of

orphan drugs to provide a robust evidence base to enable the NHS to answer these questions. There are also three key areas of concern for payers that apply universally and are amplified when considering orphan drugs.

### Regulatory vs payer requirements

One of the key problems for all payers is that the gap between regulatory and payer requirements is increasingly widening. A good example of this is the 6-minute walk test (6MWT), a benchmark for regulatory approval of ERTs. While showing that a patient can walk additional metres is a useful demonstration of clinical effect, payers are sceptical about the benefits this brings to the patient. Crucially, for payers, they need to understand the clinical value to make an assessment on whether the drug is a good use of healthcare resources.

### Anecdotal evidence

To address evidence gaps and to attempt to demonstrate the human side of orphan diseases, pharmaceutical companies often use anecdotal evidence to highlight the impact and burden of disease in patients. This is a logical step, particularly in ultra-orphan disease where the evidence base is poor; and given that large elements of the natural history might be unknown, anecdotal evidence often provides a ‘human’ perspective. However, payers react negatively to the overemphasis and reliance on anecdotal evidence, such as case studies, which leads them to believe that the drug is perhaps not as efficacious as suggested. Payers are keen to point out that patients from other disease areas outside the orphan disease space also have severe symptoms with heart-wrenching stories and that this should be acknowledged.

### Budget impact

Since the launch and funding experience with Myozyme (alglucosidase alfa), payers are becoming increasingly concerned about the uncertainty surrounding budget impact with orphan drugs. The high prices orphan drugs command ensure that the stakes are raised and errors in dosing, patient numbers

or epidemiology can have significant financial consequences for payers. Payers' biggest fear is uncertainty; and they are increasingly scrutinising manufacturer estimates and/or pushing them towards budget caps or price/volume agreements.

## Conclusion

The growing number of rare disease treatments and, more importantly, the associated high prices, is causing payers to look at new orphan drugs with increasing scepticism. As in the case of Soliris with NICE, this is leading payers to question the pricing levels for orphan drugs and whether or not these are sustainable within current healthcare budgets.

Here lies an inherent irony with orphan drugs in that, while the regulatory framework has encouraged development of treatments for rare conditions, at the same time governments are imposing austerity measures to restrict expenditure on these drugs, which has led to reimbursement challenges. As markets seek to cut healthcare costs, the cumulative effect of orphan drug spending is likely to become an area that is targeted by payers. As a result, the outcome of the Soliris review by NICE will provide a strong indication of how orphan drugs will be reviewed in the UK in the foreseeable future . [BJHCM](#)

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