Orphan drugs and the NHS: should we value rarity?

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The growing number and costs of drugs for rare diseases are straining healthcare budgets. Decisions on funding these treatments need to be made on a sound basis

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Cost effectiveness plays an important part in current decisions about the funding of health technologies. Drugs for rare disease (orphan drugs) are often expensive to produce and, by definition, will benefit only small numbers of patients. Several countries have put measures in place to safeguard research and development of orphan drugs, but few get close to meeting the cost effectiveness criteria for funding by healthcare providers. We examine the justifications for special status for rare diseases and ask whether the cost effectiveness of drugs for rare or very rare diseases should be treated differently from that of other drugs and interventions.

Current practice

The citizen's council of the National Institute for Health and Clinical Excellence (NICE) was recently asked to consider whether the NHS should be prepared to pay premium prices for drugs to treat patients with very rare diseases.[1] It recommended that the NHS should consider paying premium prices based on three criteria: the severity of the disease, evidence of health gain, and whether the disease is life threatening.[1] The decision by the Department of Health to ring fence funding for enzyme replacement therapy for lysosomal disorders, with expected annual costs above £100 000 ($180 000, €150 000) per patient for life, suggests that central government also currently believes that premium prices should be paid.[2]

NICE has conducted a feasibility study to explore whether its current processes and methods of technology appraisal can be applied to the appraisal of ultra-orphan drugs (those for diseases with a prevalence of 0.18/10 000 or less).[3] It has not yet stated whether it will recommend that treatments for very rare diseases should have special status during appraisal.

To date, the institute has evaluated only one ultra-orphan drug, imatinib for gastrointestinal stromal tumours. The estimated cost per quality adjusted life year was £30 000, and its use was approved.[4] Other ultra-orphan drugs may also not require special status to be considered cost effective (for example, anegralide for essential thrombocytopenia). However, these are likely to be the exception rather than the rule (table 1). The four biotech therapies licensed for the treatment of ultra-orphan diseases in the UK cost over £58 000 per person a year. The four ultra-orphan products in clinical development are also biotech products and likely to have similar price tags. These prices make it impossible for these treatments to meet conventional criteria for cost effectiveness.[5]

Orphan status

Several jurisdictions have established regulations for orphan drugs. The United States was the first to do so, through the 1983 US Orphan Drugs Act.[6] The European Union did not establish orphan drugs status

Special status for drugs for rare diseases such as neurofibromatosis may be unsustainable

until 2000. The precise prevalence threshold varies widely, with the United States having the most generous and Australia the least. (table 2).

The justifications for providing special status to orphan drugs are ambiguous and differ between jurisdictions. The US Orphan Drugs Act states: "Some promising drugs will not be developed and it is in the public interest to provide such changes and incentives for the development of orphan drugs."[6] This suggests that the justification for special status is based on the cost of production and the value of innovation. The European Union legislation provides a subtly different but equally ambiguous rationale: "Patients suffering from rare conditions should be entitled to the same quality of treatment as other patients."[7] In this case the rationale seems to be equity.

A range of special measures are in place to support research and development of orphan drugs. These generally include public funding for basic science, tax incentives, extended patent protection, and market exclusivity.[6 7] The issue faced by bodies such as NICE is whether a similar special status should be enshrined in decisions about allocating resources.

Estimating cost effectiveness

The evidence base for orphan drugs is suggested to be too sparse to allow estimates of cost effectiveness.[3]

A figure showing orphan drugs appraised by NICE is on bmj.com

However, estimates for all drugs and interventions synthesise evidence from a variety of sources, including randomised controlled trials, observational studies, and expert judgment. The resulting decision on funding must reflect the amount and quality of the evidence so that the decision is made in knowledge of the uncertainty around the estimate of cost effectiveness. Thus, even when the central estimate of the cost effectiveness is below the threshold for funding, if there is a large amount of uncertainty, the decision maker may still choose not to fund and await more evidence to reduce the uncertainty. The methods currently used by NICE are well suited to this.[5] The institute has already appraised drugs for 15 rare diseases using the same methods and decision criteria as for other appraisals (see bmj.com).[5]

The level of evidence required to support a decision to adopt a technology should depend on the consequences of the uncertainty—that is, if an uncertain decision proves to be wrong, how much will society lose in terms of resources and health outcomes forgone? The expected cost of uncertainty is largely determined by the number of patients affected. Therefore the existing framework of evaluation and appraisal will accept a lower level of evidence for orphan drugs because the cost of uncertainty will be lower. Existing methods not only cope with the lower levels of evidence available for orphan drugs, they support the use of lower evidential standards for orphan drugs.[8]

Cost of production and value of innovation

The justification for special status for orphan drugs is often couched in terms of the costs of developing a drug for a rare disease relative to the small market and consequently the high costs of treatment for each patient.[6 7 9] The real costs faced by the pharmaceutical industry are open to argument, but the fundamental question is whether society should subsidise the private sector to invest in the development of technologies when the cost to society exceeds the value it places on the health gain produced. If the answer is no, then the costs of production cannot justify any special treatment.

However, this analysis requires the private sector to fully anticipate all the future benefits and returns from developing treatments for rare diseases. The private sector may not fully account for these in its investment decisions if it discounts the future benefits more highly than society (because of taxation and risk), or if it fears that the longer term benefits and returns may be recouped by others. In these situations the public sector should and does intervene through directly funding research, tax incentives, and patent law to protect intellectual property rights.[6 7] Existing measures may be inadequate, but even if that is true, poor incentives are not restricted to rare diseases. Any reasons for further intervention would apply to all investments in research and development. Therefore, the arguments based on the value of innovation or the cost of production cannot provide justification for special status.

Valuation of benefits

The argument must therefore rest on the way the immediate benefits from the treatment of rare diseases

Table 1 Examples of ultra-orphan drugs

Condition	Drug	Status	Annual cost/ patient (£)
Congenital sucrase isomaltase deficiency	Sacrosidase	Licensed	3 800
Essential thrombocytopenia	Anagrelide	Licensed	4 295
Gastrointestinal stromal tumours	Imatinib	Licensed	28 500
Gaucher's disease	Miglustat	Licensed	58 400
Gaucher's disease	Imiglucerase	Licensed	70 100
Fabry's disease	Agalsidase	Licensed	109 600
Mucopolysaccharidosis 1	Laronidase	Licensed	311 000
Hereditary tyrosinaemia (type 1)	Orfadin (organic chemical)	Licensed	Unknown
Hunter syndrome	Idursulfas	Early clinical trials	Unknown
Mucopolysaccharidosis VI	Aryplase	Licence applied for	Unknown
Niemann-Pick's disease	OGT 923	Early clinical trials	Unknown

are measured and valued. The value placed on an intervention depends on the objective of the healthcare system. The often cited objective of maximising health gains is consistent with the view that clinical need can be regarded as the capacity to benefit from an intervention and that every individual's heath gain is valued equally. This view of need, and the implicit view of equity, is embedded in cost effectiveness analysis.[5] But it is not consistent with the European Union's legislation stating that all patients should have equal access to the same quality of care.[7] If the objective is to maximise health outcomes, the cost effectiveness of drugs for rare diseases should be treated in the same way as that of other technologies.

A range of alternative objectives and equity principles are possible. These include equality of health outcomes, equality of resource use, or allocation of resources in proportion to the severity of the individual's ill health. However, adopting a different objective, or view of need and equity will have profound implications for allocation of resources throughout the healthcare system, not just for the treatment of rare diseases. Moreover, these competing concepts of equity are not specific to rare diseases and cannot justify their special treatment. Indeed, rare diseases may not be particularly advantaged or disadvantaged by alternative objectives and principles of equity.

Measurement and valuation of health gain

Measuring improvements in health outcome, in a manner which adequately captures all the effects valued by the patient, is challenging. Quality adjusted life years may not capture all that is valued in some circumstances. For example, it has been argued that treatment should be valued independently of any improvements in health when no other active treatment is available,[10] when an intervention may arrest a disease process or preserve life for a time, or when prognosis is particularly poor.[9 11-14] Another argument is that the valuation of health outcome

Table 2 Definitions of orphan diseases

Country	No of affected individuals	Prevalence (per 10 000 population)
United States	<200 000	7.5
Japan	<50 000	4.0
Australia	<2 000	1.1
European Union	<215 000	5.0
United Kingdom (ultra-orphan)	<1000	0.18

Summary points

The appraisal framework already supports the use of lower evidential standards for orphan drugs

The costs of production and the value of innovation cannot justify special treatment for orphan drugs

Arguments about the measurement and valuation of health outcomes apply equally to orphan drugs and drugs for more common conditions

Valuing health outcome more highly for rare conditions is incompatible with other equity principles and theories of justice

The cost effectiveness of orphan drugs should be treated in the same way as for other technologies

should reflect the fact that known lives tend to be valued more highly than unknown statistical lives.[15] This may be particularly relevant to diseases with a strong genetic component, when people who will develop the disease can be identified. Many rare diseases reflect some of these issues, but they are also relevant to more common diseases and so cannot justify special status. The appropriate response to these issues is to conduct the methodological and empirical work required to improve our measurement and valuation of outcome across diseases, whether rare or common.

Equity and rarity

The justification for special status for rare diseases must rest on the question: should we value the health gain to two individuals differently because one individual has a common disorder and the other has a rare disorder?

Consider two groups of people who have similar diseases (J and K). J is a rare disease (1 per 10 000) and K a more common disease (1 per 1000). Imagine these people have the same personal characteristics, the same prognosis without treatment, and the same capacity to benefit from the treatments. Is it acceptable that people with J do not get treatment simply because they have a rare disease? Most would say not. However, now imagine that the cost of the orphan drug for J is higher than the treatment for K. Suppose the cost of treating one case of J is £1000, the cost of treating one case of K is £100, and the budget is £1000. Then the real choice posed by orphan status is between treating 1 person with J or 10 people with K. To argue that the patient with J should get treatment implies that that health gain of people with J should be valued 10 times higher than that of people with K. The idea that decisions should be made based on valuing health outcome more highly for no other reason than rarity of the condition seems unsustainable and incompatible with other equity principles and theories of justice. Why should a person's health be valued less simply because the condition is not rare?

Sustainability

There seem to be no sustainable reasons why the cost effectiveness of drugs for rare diseases should be

judged differently from that of other healthcare technologies. While orphan drugs were rare, healthcare systems were able to deal with them in an ad hoc manner. But there are now over 6000 orphan diseases with over 200 treatments approved by the US Food and Drugs Administration and 64 trials currently sponsored by the US Office of Orphan Products Development.[16] Genomics is expected to disaggregate currently prevalent diseases into many genetically defined distinct conditions. Orphan status is thus likely to become increasingly common.

Orphan status is maintained for drugs with multiple indications (M Hafner, Royal College of Physicians conference on managing rare diseases, London, 5 October 2004). This enables companies to take a strategic approach to the development process in order to extract the maximum amount of public financing and minimise the financial risk. Given the commercial imperative to maximise revenue and minimise costs, it is reasonable to expect further growth in the number of rare diseases and orphan drugs. The pharmaceutical industry already seems to have identified the strategic opportunity that the licensing legislation for orphan drugs represents.[17] Any special status granted to orphan drugs in decisions about allocating resources is also likely to be fully exploited.

Special status for orphan drugs in resource allocation will avoid difficult and unpopular decisions, but it may impose substantial and increasing costs on the healthcare system. The costs will be borne by other, unknown patients, with more common diseases who will be unable to access effective and cost effective treatment as a result.

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Commissioning for rare diseases: view from the frontline

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Deciding whether to fund treatments that do good one by one tends to lead to a positive decision. However, this can cause wider harmful effects, as West Midlands' experience in the funding of enzyme replacement therapy for lysosomal storage diseases shows

Orphan drugs tend to be expensive for two reasons. Firstly, development and production costs need to be offset in low volume sales, and, secondly, the monopoly position of manufacturers (entrenched within legislation to provide an incentive to develop treatments for rare conditions) permits large profit margins. Historically, the NHS has paid for expensive orphan drugs. It could do so because treatments for these diseases were so rare that the effect on health services was negligible. This policy is increasingly being questioned. As more and more expensive orphan drugs come on to the market, the impact on other health services is becoming substantial. In addition, since the establishment of the National Institute for Clinical Excellence (NICE) in 1999, the idea that technologies should reach minimum standards of cost effectiveness has become widely accepted.

However, efficiency is not the only principle in resource allocation: we also value equity and caring. Indeed, the abrogation of the principle of efficiency (by more generous reimbursement of treatments for rare diseases) is usually defended on such grounds. However, as we move towards more explicitness in decision making, which requires us to show that principles are being applied consistently, incoherence and tensions within the equity argument have begun to surface. McCabe and colleagues cite various reasons given in support of a more generous reimbursement policy for orphan drugs and refute each on theoretical grounds.[1] We approach the issue from a different perspective, that of the frontline commissioner. We tell the story of what happened during 2002-5, when commissioners responsible for health services in the West Midlands tried to approach such decisions in an explicit, justifiable manner.

The context

In England, primary care trusts are responsible for securing health services for their local populations. For high cost, low volume activities, trusts are expected to collaborate with neighbouring trusts to commission specialised services.[2] Services covering populations of 3-6 million are commissioned regionally, whereas services with a national caseload under 400 tend to be commissioned nationally through the National Specialist Commissioning Advisory Group.[3]

The question

The decision facing West Midlands concerned enzyme replacement therapy for lysosomal storage diseases. These are a group of rare inherited deficiencies in enzymes that degrade cellular material. Treatment aims to replace the deficient enzyme, thereby preventing accumulation of material and consequent ill health.

In 2001, the West Midlands was funding enzyme replacement therapy for Gaucher's disease, the only lysosomal storage disease that had a specific treatment at the time. In 2002, a new enzyme was licensed for Fabry's disease, and primary care trusts needed to decide whether to fund it. No comprehensive framework for making such decisions was in place.

Although the evidence supporting enzyme replacement therapy is thin, this was not the main issue. Even if the drugs were 100% effective, the question remained whether they produced enough benefit to justify their cost, given other claims on resources. Over 5000 diseases are classified as rare in

Spleen of patient with Gaucher's disease: enzyme replacement therapy can prevent accumulation of glucocerebroside

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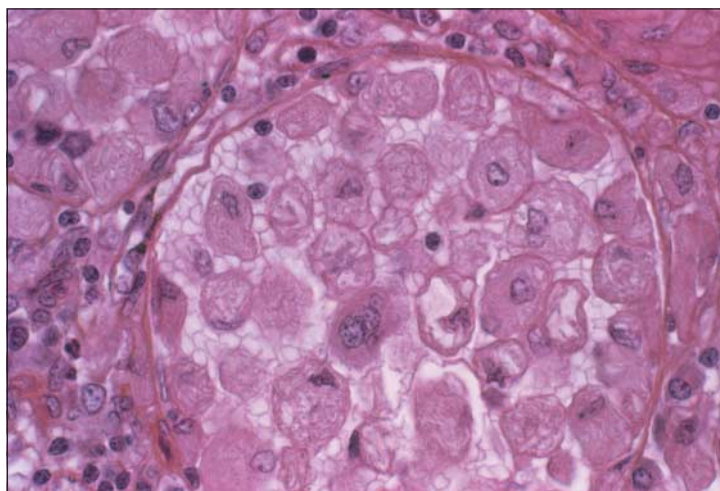Amanda Burls
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