Special status for orphan drugs in health care decision making processes: a wise move?

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Appraising orphan drugs: a discussion paper

Section 1: Background

It is generally acknowledged that the increasing cost of pharmaceutical therapies is a substantial challenge to the sustainability of existing models of health care financing. Within the portfolio of all pharmaceutical products there are a category of therapies; so called 'orphan drugs',[1] whose acquisition costs are so great that provision of treatment for even a few patients can represent a threat to the financial stability of health care payer such as a Primary Care Trust.

Historically, such therapies have been rare, and health care systems have developed special measures to absorb the costs at the national level.[2 3] A number of independent processes can be observed which in combination suggest that such *ad hoc* management strategies will not be sustainable in the medium to long term. Firstly, the changes in the legislative frameworks which govern drug development and market authorisation have led to an unprecedented increase in the volume of orphan drugs that are entering the market.[4] Secondly, the state of medical science has developed to the point where therapies can be developed for many orphan conditions which were previously considered untreatable. Finally, developments in genomics and proteanomics may lead to the separation of single highly prevalent diseases, such as cardiovascular disease, into a large number of constituent conditions, each of which may meet the definition of an 'orphan' disease.

Against these developments it seems timely to consider how licensing and reimbursement authorities should consider treatments for rare diseases. The objective of this paper is to assess the arguments advanced to support the contention that treatments for orphan diseases (orphan drugs) should be treated differently from drugs for more prevalent conditions in (a) the research, development and licensing processes and (b) the reimbursement procedures post licensing.

The remainder of this paper is structured as follows. In Section 2 we briefly describe what is meant by orphan drugs, and the benefits of orphan drug classification in the research, development, and reimbursement in different countries; and the rationale provided for these advantages in the relevant legislation and elsewhere in the literature. In Section 3 we briefly review arguments relating to the application of standard appraisal methods to orphan drugs. In Section 4 we consider arguments relating to the cost of production, as the basis for treating orphan drugs as a special case. Section 5 reviews the valuation of health arguments for treating orphan drugs as a special case. Section 6, the final section attempts to summarise the state of knowledge regarding orphan drugs and identifies research necessary to advance our understanding.

Section 2:What are orphan drugs?

The idea underlying the concept of orphan drugs is that some diseases are so rare that there is no incentive for pharmaceutical companies to develop treatments. To this degree, the precise prevalence threshold for orphan disease designation varies between legislative jurisdictions. (See Table 1).

Orphan drugs are in fact a specific example of the broader category of non-commercial drugs. Non-commercial drugs are treatments or therapies that will not be produced under normal commercial conditions. For example, the disease might be highly prevalent, but the health care systems which treat people with the disease might not be able to afford modern medicines. There are a number of other factors that may make a therapy non-commercial including the cost of production and the scale of health benefit compared to existing treatments.

Whilst each orphan disease may be relatively rare, there are in fact a large number of orphan diseases. The United States NIH Office of Rare Diseases identifies over 6000 orphan diseases. Over 200 treatments for rare diseases have been approved by the US Federal Drug Administration (FDA),[5] and the National Institute for Clinical Excellence (NICE) has already undertaken 15

orphan drug appraisals, over ten per cent of the total appraisals to date.[6 7] In so doing they have applied the same methods and decision criteria as in all other appraisals. However, NICE recently proposed a sub-classification of 'Ultra-Orphan Drugs'.[6] These are products for the treatments of conditions with a prevalence of less than 1 in 50,000 population. This is consistent with the prevalence criteria used by the National Specialist Commissioning Advisory Group.[8]

The first legislation to specify orphan drugs as a special case was the 1983 Orphan Drugs Act in the United States of America (USA).[9] The preamble to the legislation included the following statement:

> "Because so few individuals are affected by any one rare disease or condition, a pharmaceutical company which develops an orphan drug may expect the drug to generate relatively small sales in comparison to the cost of developing the drug and consequently incur financial loss.
>
> There is reason to believe that some promising drugs will not be developed unless changes are made in the applicable federal laws to reduce the costs of developing such drugs and to provide financial incentives to develop such drugs; and it is in the public interest to provide such changes and incentives for the development of orphan drugs." [9]

The stated rationale, in the United States, for changes in the commercial and legal environment in which orphan drugs are developed is that the development of treatments for rare conditions is in the public interest. The European Union legislation proffers a different rationale:

> " Some conditions occur so infrequently that the cost of developing and bringing to market a medicinal product to diagnose, prevent or treat the condition would not be recovered by the expected sales of the medicinal product; the

> pharmaceutical industry would be unwilling to develop the medicinal product under normal market conditions… patients suffering from rare conditions should be entitled to the same quality of treatment as other patients…"[10]

In this case the rationale is equality of treatment; people with rare diseases should be entitled to the same quality of treatment as people with more prevalent diseases; i.e. it is an equity argument.

The specific support provided to the orphan drug research and development process varies across jurisdictions, but generally there is a combination of public funding for basic science, tax incentives for the research and development, extended patent protection and market exclusivity for a number of years.

Whilst these regulations have been very effective to date, the implementation of reimbursement processes such as the NICE Appraisal Programme, almost certainly has implications for the development of orphan drugs.

Standard Appraisal Methods and Reimbursement for Orphan Drugs

As health systems have increasingly separated licensing from reimbursement decisions, some special reimbursement schemes have been implemented. In the UK most orphan drugs are reimbursed through the normal channels; i.e. where NICE has recommended their use, reimbursement is mandatory; otherwise the reimbursement decision is made by the local health commissioner; i.e. the Primary Care Trust. The only exception to this is the treatments for multiple sclerosis, where a special risk sharing scheme was established by the Department of Health to manage reimbursement after NICE decided that they did not represent a cost effective use of NHS resources given the currently available evidence. [11]. By contrast, in Australia and the Netherlands special funds for reimbursing orphan drugs have been, or are in the process of being established.[3] In the USA the reimbursement of

orphan drugs depends upon the health insurance coverage of the individual, although there are a number of charitable foundations that assist people in obtaining reimbursement.

The UK approach leaves local health commissioners exposed to a risk of catastrophic expenditures. Many promising orphan drugs are associated with diseases that have a genetic basis. This is particularly true for the ultra-orphan diseases, such as Gauchers, Fabrys and MPS1. In such circumstances, if a local health commissioner has one case, they are likely to have multiple cases. If the cost of treatment for these patients is to be covered from standard drug budget, it will have significant implications for the scale of health care provided to the rest of the community. The effect of this is that there is substantial variation in the reimbursement of orphan drugs across local health commissioners in the UK; i.e postcode prescribing.

NICE was established, in large part, to attempt to put an end to postcode prescribing.[12] Therefore it seems reasonable for NICE to be responsible for establishing a national policy for the reimbursement of orphan drugs.

It has been suggested that the evidence base for orphan drugs, especially ultra-orphan drugs is too sparse for the application of standard appraisal processes. This is conditioned upon the misconception that appraisals require estimates of efficacy or effectiveness of a therapy based upon randomised controlled trials. A review of the most recent Guide to the Methods of Technology Appraisal issued by NICE makes clear that this is not the case.[13]

Appraisal consists of two stages; the estimation of the costs and effects of the new therapy, followed by a judgement on whether the current evidence base is sufficient to support a decision.

To estimate the costs and effects it is necessary to synthesise available evidence from a variety of sources, including, but not limited to, RCTs, observational studies and expert judgement.[13] The synthesis must capture the uncertainty in the estimates of costs and effects. The synthesised evidence on

costs and effects is then combined in a formal decision framework to produce an estimate of the incremental cost-effectiveness of the new therapy compared to current practice; including the uncertainty surrounding the decision; i.e. what is the risk that the decision implied by the analysis will prove to be wrong; because, for example, a therapy is reimbursed but proves not to be cost effective in practice.

The decision maker must then consider the consequences of the decision uncertainty; i.e. if the decision proves to be wrong, how much will society lose. This can be formally measured and it is largely a function of the size of the population to be treated. In the case of orphan drugs, the appraisal framework will accept a higher risk of making the wrong decision, because all other things being equal, the cost of a wrong decision will be less than the cost of a wrong decision in a highly prevalent disease area. Thus, the appraisal framework not only 'copes' with the lower levels of evidence available for orphan drugs, it actually supports the use of lower evidential standards for orphan drugs.

The key conclusion of this section is that the existing methods of appraisal can provide estimates of costs and effects even in the case of ultra orphan diseases and there is no technical reason why treatments of these diseases should not be dealt with within existing processes and using existing methods. Therefore the argument to offer special status to orphan drugs is not a technical one about methods, but is about values. There are two possible value issues which could justify special status: the costs of production for orphan drugs or the valuation of the benefits of orphan drugs. It is these issues that we consider in the next two sections.

Section 4: The cost of production of orphan drugs

There is a fundamental question to consider:

> "Should government encourage the private sector, by providing subsidies from public funds, to invest in the development of therapies where the cost of production exceeds the value we place on the health gain produced?"

It is not immediately obvious that the answer to this question should be 'yes'. In which case, why should we be having this discussion at all? Surely the private sector can fully anticipate the future benefits and returns to developing treatments for rare disease and their investment decisions should fully account for all future benefits? We can only justify having this discussion if there is market failure; i.e. although society values the health gain sufficiently highly, the free market processes do not lead to the development of the treatments.

There are two sources of market failure, which are cited as reasons for the public sector to intervene. Firstly, the private sector may have a higher opportunity cost of capital than the society's marginal time preference due to corporation tax and risk premiums. Secondly, investment which generates the possibility of future new and valuable therapies may have public good characteristics so that the private sector is reluctant to invest because the longer term benefits and returns maybe recouped by others (free rider problem). In these situations the public sector should and does intervene to attempt to correct this failure: the public sector supports much fundamental research directly through grants to academic research institutions; provides tax incentives for research and development; and the legislative framework and patent law protects intellectual property rights.

It has been argued that developing orphan drugs are much more expensive, per head of population, than drugs for prevalent conditions.[14] It is far from clear that this is necessarily true. Given the substantially lower standard of evidence required for licensing of orphan drugs, and the frequency with which the public sector has funded much of the basic research; it is difficult to believe that the greater case finding costs associated with research on rare

diseases are sufficient to make these drugs especially expensive to develop. Whilst some orphan drugs are produced using recombinant technologies, which are more expensive than traditional small molecule chemical production technologies; this is not a function of the rarity of the disease. Many more prevalent treatments use recombinant technologies.

It could be argued that existing measures of benefit are insufficient. However, even if that is true, there is no reason to believe that the effects of market failure and poor incentives are restricted to rare diseases. If there are reasons for further intervention then presumably those reasons apply to all investments in research and development not just rare disease. Therefore, the arguments based on innovation, cost of production and market failure cannot provide justification for the special status for treatments for rare diseases.

Section 5: Valuation of the benefits from Orphan Drugs

If the costs of production and value of innovation cannot justify special status then the argument must rest on the valuation of the benefits. There are three ways in which special status may be justified: because of the concept of clinical need; because the measures of health benefits currently used don't pick up all the aspects of health outcome that are valuable to patients and to society; and because there is some equity principle that implies treatments would be adopted for rare diseases even if the costs were considerable. We deal with each in turn.

Definitions of clinical need

The value we place on a health care intervention depends upon what we consider is the objective of the health care system. NICE has implicitly adopted the view that the objective of the NHS is the maximisation of health gain from the expenditure of its budget. This objective is consistent with the view that need can be regarded as the capacity to benefit from an intervention

and every individual's heath gain is valued equally i.e. an individual cannot need health care if it has no impact upon either their health related quality of life and/or their life expectancy. It is this view of need and the implicit view of equity that is embedded in cost-effectiveness analysis. Therefore the justification of special treatment of rare diseases could be based on alternative views of need, such as that of 'clinical need' that seems to be reflected in the EU statement about equal access to quality care.

Alternative ideas of equity in health care include equality of health outcome; equality of resource use and the expenditure of resources in proportion to the severity of the individual's ill health. It is valuable to reflect upon the affect of adopting the different objectives.

If the objective is for all people to achieve the same health outcome, assuming that we continue in a world where it is impossible to return some people to full health, decision makers may in fact expend resources reducing the health of many. More pragmatically, if the system only intervenes in cases where the individual has fallen below the target level of health, there would be huge variations in the return on health expenditure, as some individuals would have easily remedied maladies; whilst others with incurable disabilities might consume all available resources in the pursuit the unachievable. It is also interesting to consider how the target health outcome would be established. Logically the only health outcome we can all be confident of achieving is death.

If we cannot achieve equality of health outcome, equality of resource use should certainly be possible. Again it would be necessary to accept huge variations on the health gain from the expenditure across individuals, as some individuals would gain substantially from health care, whilst others, either because their untreated condition was very close to full health or the nature of their ill health was incurable, would gain very little. Presumably, individuals in full health would be excused from their responsibilities to consume health care. If there were geographical variations in the distribution of healthy people; would the unspent surplus be allocated equally across the nation or

would it be allocated equally across the unhealthy individuals in the same commissioning area? It is important to note that under this strategy no one would be left without treatment.

What would be the implications of expending resources in proportion to the severity of the ill-health? First, obviously many people with minor ailments would go without treatment in order to ensure that treatment was provided to those who are severely ill. This might be a good thing. However, there would be variations in the return on the investment. In some cases; e.g. heart transplant, where the untreated condition is severe and the treated condition remarkably good, it would be high. In other cases, where the condition is severe but essentially untreatable, e.g. terminal cancer, the return would be low. The people left untreated under this strategy would be those with the least disabling illnesses.

We have highlighted the variation in the return on the expenditure in each of the above because it indicates that a reallocation of the resources could lead to more health gain for another individual than the health lost as a result of the reallocation. Whilst mainstream welfare economics does not support such interpersonal comparisons and trade-offs, these are the very essence of health care resource allocation decisions.

In its rawest form, maximisation of health gain will leave some individuals without treatment. These will be the individuals with the least ability to benefit from the consumption of those resources. To allocate resources to them would lead to other individuals baring greater losses of health.

Whatever view is taken of the appropriateness or not of alternative definitions of need and the implication they have for the objectives of health care what is clear is that they are not specific to rare diseases. Citing alternative objectives or definitions of need to justify special status would have implication across the health care system and would lead to different resource allocation patterns across all disease areas, not just orphan diseases. In fact there is no reason to believe that orphan diseases would be particularly

advantaged or disadvantaged by alternative objectives and definitions of need..

Measuring Health Gain

A central challenge in operationalising the maximisation of health gain objective is measuring health gain. It is beyond argument that the current measures of health gain are severely limited and some of these limitations are clearly important in considering the value of the benefits from orphan drugs.

For the overwhelming majority of (ultra) orphan conditions there is no alternative disease modifying therapy. It has been argued that society values the hope offered by the availability of an orphan drug, and that refusing to fund such drugs not only removes the hope for the current generation but impacts upon the hope for future generations as companies will not embark upon the research and development processes that the level of reimbursement available is too low to cover the sunk R&D costs.. To pay more for a current therapy than we value its health gain requires that this generation accepts lower health gain to give hope of more health gain to future generations. Presumably other non-drug interventions, such as physio-therapy and home aids, will receive less funding in order to pay for the drugs. It should be noted that whilst ultra orphan diseases frequently have no alternative therapy, there are in many other conditions for which there are no treatments. Thus, this argument is not specific to the appraisal of orphan drugs.

Society appears to value identified lives much more highly than statistical lives. This is frequently demonstrated through the media coverage when the NHS refuses to fund extremely expensive and/or unproven treatments for named individuals. [15] This is obviously a germaine consideration in the appraisal of treatments where all the people could be comfortably gathered in an average sized meeting room, and even more so, when the disease has a genetic basis. However, the named individual criterion is not limited to rare

conditions and to institutionalise special provisions under these circumstances could have significant unintended effects by creating strong incentives for individuals to publicise their health care requirements.

Most importantly however, all of these are empirical questions that apply to orphan drugs and other indications as well. We can find out whether society wishes decision makers to give special weight in each of these circumstances and, in principle, how big that special weight should be.

Equity

Research on the incorporation of equity considerations in to the measurement of health gain is on-going.[16] However, to date none have examined the question at issue in the orphan drug debate:

> "Should we value the health gain to two individuals differently because one individual has a common disorder, whilst the other has a rare disorder?"

Consider the following:

2 Individuals; p, q (prevalence of 1 per 20,000 and 1 per 4,000 respectively)
Same characteristics; prognosis without treatment and capacity to benefit.

Is it acceptable that p does not get treatment?

Cost of treating p=10; Cost of treating q=1. Budget = 10.

The choice is between treating 1p or 10q.

If you choose to treat p, you must value p *at least* 10 times higher than q.

What is the combination of #q and #p, that makes you indifferent between the two alternatives. [*]

In summary, the general issues around the valuation of benefits from health care are not specific to orphan diseases. If these arguments were invoked to support the special treatment of orphan drugs, they would have implications for the appraisal of many other therapies. The only issue that is specific to orphan drugs is whether there is a rarity premium and if so, how big is it.

Discussion

In this paper we have argued that the existing evaluation and appraisal framework can estimate cost effectiveness and assess whether the evidence is sufficient to support a decision, *without any special arrangements for orphan or ultra orphan drugs.* We have also argued that the special issues in the cost of production for orphan drugs do not provide a justification of special treatments in the appraisal process. Different concepts of need are not specific to orphan status, nor are limitations in the measurement of health gain. We have identified only one candidate justification for the special treatment of orphan drugs in the appraisal process, which we have described as the 'Rarity Premium'. This is the degree to which society values health gain to people with rare diseases more highly than health gain to people with more prevalent diseases.

Beyond the absence of strong reasons to treat orphan drugs differently in the appraisal process, the attribution of special status to orphan drugs may have significant implications.

If there is a group of therapies that are not subject reimbursement criteria, then there will be a strong incentive for the producers of therapies to reclassify

[*] #=number; strictly the premium is not when you cannot choose, but when you are equally happy for q or p to be treated.

the indications of their drugs to meet the definition of this category. Similarly, there will be an incentive to use pharmacogenomics and proteanomics to disaggregate prevalent diseases into multiple rare diseases, and license therapies for each one independently.

Associated with this second point, but not confined to it, is the issue of treatments with multiple indications. The return on the investment in the research and development of a therapy comes from the portfolio of indications. Orphan drug legislation implicitly assumes that the therapy has a single indication only. Where a therapy has one indication that is rare and one that is prevalent, the incentive will be to introduce a therapy for the rare indication first, even though greater health gain may be available from other indication. Even when all the indications are for rare diseases, the total size of the population to be treated may be sufficient to lead to provision. Special reimbursement arrangements would lead to excessive profits in these circumstances.

If the special licensing/reimbursement arrangements establish a lower standard of evidence hurdle, there is a risk that the orphan drug category becomes a 'retirement home' for therapies that have failed to clear the more robust evidential hurdles in other indications. It may be that the future lies in *different* evidential hurdles, which do not require large numbers of patients, rather than *lower* evidential hurdles.

Given all these concerns about establishing a special status for orphan diseases, is there a constructive way forward? It is important that analysts and decision makers alike recognise that the instinct to say 'yes' to the provision of treatment is real, and to identify the underlying values that drive this instinct. Once these values have been identified, it will be possible to apply them consistently to all appraisals, not just those for rare diseases.

Where claims are made for a higher valuation of benefit, its existence and its magnitude must be established empirically. Claims do not represent evidence and are not a sufficient basis on which to allocate limited resources. Equally,

the wider research, development and appraisal processes, within which such claims sit, should be an explicit and transparent decision framework.

The orphan drug legislation was enacted to address a very real concern that people with unpleasant, even life threatening diseases were be left without treatment because of the limitations of the market mechanism. However, the legislation has had some undesirable effects, creating some undesirable incentives. The establishment of reimbursement mechanisms has brought some of these issues into sharp relief and as a result hard decisions about what society is and is not willing to pay for from the health care budget can no longer be avoided. We believe that the application of the decision analytic methods described in the NICE Methods of Health Technology Appraisal,[13] will allow the creation of an explicit, transparent and consistent decision framework for both orphan and non-orphan drugs; which is we believe, essential for legitimate social decision making.

Table 1: Definitions of orphan diseases

Country	Number of affected individuals	Prevalence (per 10,000 population)
United States of America	**<200,000**	**7.5**
Japan	**<50,000**	**4.0**
Australia	**<2,000**	**1.1**
European Union	**<215,000**	**5.0**
UK Ultra-Orphan	**<1000**	**0.18**

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