Challenges in the economic evaluation of orphan drugs

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Summary: Increasing pressures on health care budgets have led to a growing interest in the use of economic evaluation in reimbursement decisions for drugs and other health technologies. Although economic evaluation methods are becoming more established internationally, doubts have been raised about their use in drugs for rare diseases (often known as ‘orphan drugs’). This paper discusses the potential deviation between social value and cost-effectiveness, the impact of rarity on the estimation of the cost-effectiveness ratio and the key questions surrounding the economics of orphan drugs.

Keywords: cost-effectiveness analysis, health policy, resource allocation.

Increasing pressures on health care budgets have led to a growing interest in the use of economic evaluation in reimbursement decisions for drugs and other health technologies. Under this approach, an assessment of value for money is undertaken by comparing the incremental costs of the new technology (with respect to relevant existing technologies) with the incremental benefits. The incremental benefits are normally defined in terms of health gain, either by use of a generic measure such as the quality-adjusted life-year (QALY), or by use of a relevant clinical outcome for the disease area concerned.

The economic evaluations do not, of themselves, determine whether a given health technology gives good value for money. This has to be judged against an external standard, such as the cost-effectiveness of interventions that are already funded in the health care system, or an explicit benchmark (or threshold) of willingness-to-pay for a unit of health gain. For example, in England and Wales, the National Institute for Health and Clinical Excellence (NICE) operates a threshold range of £20,000–£30,000 per QALY gained. Health technologies with an incremental ratio of less than £20,000 per QALY gained are highly likely to be reimbursed; those with a ratio in excess of £30,000 would require other arguments in order for them to be funded.

NICE is unusual in being so specific about its decision-making threshold. Most reimbursement agencies do not reveal their thresholds and, in the case of agencies not using a generic measure like the QALY, such thresholds would be hard to infer.

Although economic evaluation methods are becoming more established internationally, doubts have been raised about their use in drugs for rare diseases. Most of the orphan drugs appraised to date have cost-effectiveness thresholds well in excess of the ‘accepted’ level and would not be reimbursed according to conventional criteria. McCabe et al. argue that this is not an argument for treating orphan drugs any differently from pharmaceuticals in general and question whether there should be any premium for rarity. On the other hand, Drummond et al. argue that there may be more to assessing the social value of health technologies than the estimation of the incremental cost-effectiveness ratio. Therefore this paper discusses (i) the potential deviation between social value and cost-effectiveness (ii) the impact of rarity on the estimation of the cost-effectiveness ratio and (iii) the key questions surrounding the economics of orphan drugs.

Potential deviation between social value and cost-effectiveness

As mentioned above, the denominator in the cost-effectiveness ratio is usually a measure of health gain, typically the QALY. In addition, QALYs in the calculation are normally equally weighted; that is, a gain of one QALY is considered to be the same no matter to whom it accrues.

However, an analysis of decisions by the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia showed that, while decisions followed a general cost-effectiveness logic, it was clear that other factors were taken into account. George et al. give several reasons for the apparent deviation from the cost-effectiveness criterion. These include the lack or inadequacy of alternative treatments for the disease concerned, perceived need in the community, seriousness of the patient’s condition, pursuit of equity, the rule of rescue, as well as access and affordability from the patient perspective and financial implications for the government.

The extent to which these factors do, or should, impact on health care decision-making is a matter for discussion and debate. However, it is clear that most orphan drugs are for serious conditions, for which other treatments may not be available. Orphan drugs also tend to be expensive on a per patient basis, but have limited impact on the health care budget as a whole, as there are so few patients with these health conditions.
Rarity and the cost-effectiveness ratio

The most obvious impact of rarity on cost is that, because the patient population for most orphan drugs is very small, the costs of research and development (R&D) need to be recovered by charging a much higher cost per patient than for drugs with large sales potential. Although there is some evidence of a relationship between the size of the population and annual treatment cost, the pricing of all drugs (including orphan drugs) is rather opaque. Therefore, it is not surprising that decision-makers have some doubts about prices charged. The only audited public statement about the costs of R&D of an orphan drug, in the annual accounts of the Genzyme Corporation, suggests that development costs are substantial, although a little lower than the cost of a mainstream pharmaceutical (mainly because the clinical development programme involves smaller patient numbers).

The main impact of rarity on the estimation of effectiveness is that, given the small patient population, it is difficult to enrol sufficient numbers of patients in clinical studies. Also, because of small numbers, the epidemiology of rare diseases is less well understood, making the projections of long-term benefit, beyond the end of the trial, or from surrogate markers to final clinical outcomes, more speculative. This greatly increases the uncertainty facing the decision-maker when considering orphan medicines.

Key questions surrounding the economics of orphan drugs

How much efficiency is the public willing to trade for access to orphan drugs?

Given their lack of cost-effectiveness, the funding of orphan drugs can only be justified if the public is willing to give up some of the overall health gain produced by the health care system, because access to treatments for rare diseases is perceived to be a socially valuable objective. More exploration of this issue is required, either by surveying members of the public, or by using the ‘person trade-off’ (PTO) approach to estimating QALYs. This approach estimates QALYs by asking respondents how many individuals, with a given disease receiving treatment, would be equivalent to saving one healthy life.

How can social value best be introduced into the technology assessment process?

If there is, indeed, more to the assessment of social value than cost-effectiveness, these additional elements would need to be incorporated into the assessment process. A different way of weighting QALYs, either by use of the PTO approach or another set of equity weights, would be one option. The other main approach would be a structured discussion, whereby the various identified factors (for example, condition seriousness) would be discussed alongside data on cost-effectiveness.

The latter approach is already used to some extent by NICE. More research is required on the pros and cons of the different approaches to introducing the consideration of social value into the technology assessment process.

How can we ensure that the returns from investment in orphan drug development are reasonable?

The European Union, the USA and Japan have offered incentives (such as tax rebates and market exclusivity) to companies willing to invest in clinical research into treatments for rare diseases. However, these incentives are meaningless if the drugs, once developed, are not reimbursed. Therefore, there is an urgent need to harmonise incentives for research with the potential for market access. In many ways, offering incentives for R&D is like putting the cart before the horse. The appropriate way to tackle the problem is to be clearer on what, if anything, society is willing to pay for these treatments. Then manufacturers would then be able to assess whether levels of reimbursement offered provide adequate incentives for investment in the research required.

How can we ensure that funds devoted to the reimbursement of orphan drugs are used appropriately?

It was pointed out that, because of the small number of people with rare diseases, there is often more uncertainty about the clinical benefits from treatment. The best way to deal with this uncertainty is to collect more long-term data on the clinical outcomes for patients receiving treatment, through the establishment of registries. Given the small number of patients in individual countries, there would be a role for international collaboration, through organisations like the EU.

Another step towards securing value for money would be to target therapy to patients achieving substantial clinical benefit. Therefore, it may be necessary to establish stopping rules for patients failing to respond to therapy. In some cases, such stopping rules have been combined with risk-sharing schemes, whereby the manufacturer gives the payer a rebate in cases where the patient’s therapeutic response does not reach a pre-defined level. However, such schemes are not simple to devise or monitor. They do not represent a ‘magic bullet’ for payers concerned about the high cost of orphan drugs.

Conclusions

Orphan drugs present several challenges, both in the assessment of cost-effectiveness and in the development of appropriate funding mechanisms. As illustrated in this article, manufacturers and policy makers might adopt new ways of working together in order to tackle these challenges.

References


