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Commentary

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Orphan drugs revisited

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Introduction

Hughes *et al*.[1] recently discussed arguments for and against giving special funding status to orphan drugs in this journal. They concluded that there should be a uniform policy across Europe, that complete restriction was impractical, and that UK policy should aspire to the values of the EU directive. The aims of this paper are to correct some inaccuracies in the original paper, develop some of the key issues, and to draw some conclusions regarding the question 'Do drugs for exceptionally rare disease deserve special status for funding?' For ease, our paper adopts the same structure as the original.

Special status considerations

Hughes *et al*. state that a key issue is 'whether the rarity and gravity of the condition represents a rational basis for applying a different value to health gain . . .'[1]

The defining characteristic of an orphan drug is that it treats a rare disease. However, the justification for special funding frequently rests upon the 'gravity' of the condition. To examine whether orphan drug legislation accurately represents societal preferences, it would be necessary to ask whether society was willing to pay more for treatments for rare severe disorders than for more prevalent severe disorders. No study has done this.

Hughes *et al*. recount another frequently cited argument for special treatment: 'ensuring access to treatment where no other treatment exists.' Like 'gravity', this is not a defining characteristic of an orphan drug, but it is a frequently cited argument for their special status in licensing and reimbursement.[1] Not being unique to orphan drugs, it cannot be a justification for their special status.

Further, this argument contains an implicit preference for biological disease modification over health gain. In the developed world, 'no other treatment' is a substantial misrepresentation of reality; patients are not simply left with no medical treatment at all. The dichotomy is between best supportive care and disease modifying care. Best supportive care could have a greater impact upon health-related quality of life than a pharmaceutical agent. For example, £7500 per patient per year spent on home-help services could have a greater impact on the health-related quality of life of someone with multiple sclerosis than spending the same money on a disease-modifying therapy such beta interferon. If the objective of the health care system is to improve health, then health gain from best supportive care should not be valued less than health gain from disease-modifying therapy.

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It is legitimate to specify different or additional objectives. Indeed, the Department of Health requires the NHS to promote population health and innovation. Palmer and Smith[2] argue that new therapies have an option value, which should be taken into account in reimbursement decisions. Disease-modifying therapies, unlike best supportive care, offer the option of future knowledge, which may in turn, lead to a cure. Decisions not to reimburse new therapies reduce the incentives to pursue future knowledge, and thus the hope of a cure. Again, this argument is not unique to orphan drugs; there are many prevalent diseases for which there is no cure. The decision not to reimburse the latest therapy always has implications for the development of future knowledge.

Methodological issues concerning evidence on effectiveness

Hughes *et al*. repeat the generally accepted argument that it is often not possible to recruit an adequate sample size (to an RCT) to test treatments for very rare diseases.[1] Certainly, treatments for extremely rare diseases are often licensed on the basis of extremely small clinical studies. However, it is far from clear that more robust evidence could not be provided.

For example, ceredase, a treatment for Gaucher's disease, was initially licensed on the basis of a study that recruited 12 people. Within 10 years the Gaucher's Registry had approximately 3000 patients on therapy, casting doubt over the assumed difficulty in undertaking a conventional randomized controlled trial.[3]

Hughes *et al*. highlight the reliance on short-term surrogate outcomes in the evidence base for orphan drugs.[1] They propose improvements in post-marketing studies, and the development of registries to address the limitations of the evidence. However, the major uncertainty in establishing the effectiveness of orphan drugs is the natural history of the disease.[3] The opportunity to collect information on the natural history of a disease is significantly reduced once a disease-modifying therapy becomes available. Post-marketing studies cannot address this primary uncertainty in the evidence base.

Registries of all patients with the disease are required to address this uncertainty. To ensure these data are available, regulatory authorities need to require that such registries are established when a therapy is given orphan designation. This would provide evidence on the natural history of the disease at the time of licensing, so that authorities could accurately assess a therapy's effectiveness and cost-effectiveness. Such registries would also help identify subjects for recruitment to the clinical trial programme, and provide the infrastructure necessary to implement the proposed post-licensing studies.

As an aside, disease registers can be usefully contrasted with health technology registers. Many of the registers in the UK can be described as technology registers; registers of those using particular technologies, rather than all those patients with the disease. If a disease register includes both patients who are using and those not using the technology, then provided other relevant factors are included, case-control studies become possible. Given the high cost of many orphan drugs, and the uncertainty of their effectiveness compared to no treatment, it seems reasonable for funding to be conditional on entry into disease registers. The advent of electronic patient records greatly reduces the previously high cost of disease registers. NICE has recommended the development of disease registers for several new technologies.

In the absence of improvements in the quality of the evidence provided to licensing and reimbursement authorities, the weakness of the evidence does not represent an argument for excusing treatments for rare diseases from formal appraisal. The limited volume of data may be an insurmountable problem in the hypothesis-testing paradigm adopted by the regulatory authorities. However, it is not a problem in the decision-analytic paradigm adopted by reimbursement authorities.[4]

Limited budget impact

Surprisingly, Hughes *et al*. consider cost, divorced from any consideration of the opportunity cost. They observe that a drug costing £50 000 per patient per year, would only cost £2.5m a year if there were only 50 patients to be treated.[1] However, the cost should not be considered without reference to the value of what is foregone;[5] £2.5m would pay for over 520 hip replacements.[6]

Equity issues

Hughes *et al*. consider what they call 'the equity principle' and 'a rights-based approach' to health care provision. They rightly conclude that neither will favour treatments for rare conditions over more prevalent conditions. They then propose the 'rule of rescue' as the basis for the special status for orphan drugs. While acknowledging that the rule of rescue normally applies to the prevention of imminent death, they cite Hadorn to claim that it also applies

when life is not endangered.[7] Thus, they interpret the rule of rescue as a commitment to the non-abandonment of individuals when (a) there is a small number of cases; (b) the condition is severe (but not necessarily immediately life-threatening), and (c) no alternative treatments are available.

If we are to accept (a) then we accept that whereas passengers in a car that is about to explode should be saved at all costs, passengers on a jumbo jet about to explode need not be, as the numbers are large! Regarding (b), severity of the condition, the characteristic of an orphan drug is the rarity of the condition, so it makes no sense to justify special status in terms of severity. Finally, (c) implies that if there is only one way to save lives, then these lives should be saved at all costs, but if there is more than one way to save the same lives then this no longer applies, which is also absurd.

The paper gives an example of the 'rule of rescue' where children from poor countries with physical deformities are transported for treatment in rich countries. This phenomenon is also known as giving priority or special treatment to the 'identifiable victim'. If the argument for special treatment actually rests upon the identifiable individual condition, then it is important to think through the implications for the funding of other interventions, because unlike the other characteristics, identifiability is a characteristic that is amenable to individual choice and control.

Since the introduction of explicit prioritization across the NHS, some individuals have sought to overturn local commissioners' decisions using the media; the most recent example being the provision of herceptin to women with early breast cancer.[8] Their publicity has created pressure to provide a very expensive therapy whose effectiveness is highly uncertain.[9] To enshrine special status for identified individuals would create an incentive for more people to use the media to achieve 'identified individual' status and thus overturn population level prioritization decisions.

The debate around orphan drugs must recognize that the 'rule of rescue' is not in fact a rule, but rather a concept that explains the observed instinctive emotional reactions of individuals to tragic events in urgent circumstances. The process of putting a name to the sentiment and showing that it is prevalent, does not make it a valid basis for policy. For the 'rule of rescue' to be a valid basis for policy, it requires a normative justification.

Whether an affected individual is known or unknown is merely a matter of time and perspective, i.e. someone may be regarded as an unknown statistical life to one observer but will be, or become identifiable to another. From the broad societal perspective, we know that with enough information, or simply with time, those currently regarded as unknown statistical lives will become known. At this point, coherence in decision-making requires that their health be valued in the same way as currently 'known' lives. Social decision-making should reflect this broader view, and not give undue weight to values based in private perspectives and inadequate information. The alternative is that any intervention will be cost-effective, as long as those who bear the opportunity cost are unknown to us at the time we make the decision.[10]

Options for policy recommendations

Assigning equity weights

The authors propose equity weights as a means of incorporating society's preferences over prevalence into cost-effectiveness analysis. However, equity weights are a purely technical means of incorporating established social preferences into the QALY framework. Without robust evidence that society has a preference for rarity alone,[11] equity weights are irrelevant. What little evidence there is, does not support the existence of such preferences. Over 80% of the NICE Citizens Council said that rarity alone was not a reason to pay a premium price for a drug. Over 80% also said that disease severity might represent a basis for paying a premium. Only three members of the council (of 27) believed that rarity alone justified paying a premium.[12]

Risk sharing and 'no cure, no pay' schemes

Hughes *et al*. cite a number of conditional reimbursement systems that have been devised. While we broadly support such schemes, the ability to establish that the therapy has delivered the claimed health gain is dependent upon the quality of the evidence on the natural history. The use of conditional reimbursement schemes further strengthens the argument for disease registries to be established when an investigational drug receives orphan designation.

Clinical and pharmacogenetic criteria

The specification of clinical criteria beyond the limitations set out in the license may reduce the total expenditure on a specific therapy, but will not, in itself, address the challenge of the difference between the cost of the therapy and the value that society places upon the expected health gain. If the criteria for reimbursement are clinical characteristics

that are predictive of greater health gain from therapy, then there is the potential for more cost-effective use of orphan drugs. However, the knowledge of the natural history of these extremely rare conditions is such that it is often not possible to specify *a priori* criteria that are reliably predictive of enhanced or reduced health gain.[3]

The authors describe a procedure developed in Ontario, Canada, whereby a committee of medical experts decides who should receive enzyme replacement treatment for Gaucher's disease. The effectiveness of the process cannot be established, as the knowledge of the natural history of Gaucher's disease is vanishingly small, and what data there are, are inconsistent. Even though it is a monogenetic disorder, there are over 200 allele mutations, of which very few are associated with milder or more severe forms of the disease.[3] It is difficult to see how the medical experts can be confident about the health gain from therapy, as they cannot say with confidence what would happen in the absence of treatment.

Funding by research councils

There may be merit in the research councils funding research into treatments for rare diseases; the condition being that the expected return on the research investment should exceed the cost of undertaking the research. Normally, when this condition is met, we would expect the private sector to be willing to invest in such research. This said, there are reasons why the private sector may not value future benefits correctly.[10] In these circumstances, funding from the research councils may be appropriate. However, market failure of this sort is not specific to rarity, and it is thus unclear why rare diseases should have privileged access to limited research council resources.

Dedicated funding

Dedicated funding is an increasingly common financing structure, especially within the UK NHS. However, the question that faces decision makers is how much funding should dedicated to the care of a particular disease group. If the answer to this question is divorced from the value of the health gain produced, it is difficult to see how a specific allocation of resources, dedicated or otherwise, can be justified. Dedicated resources provide transparency about the implied value of health gain to the members of the population. However, it avoids the key policy question: whether funding should be dedicated to the treatment of rare diseases, or to others. Dedicated funding does not resolve the opportunity cost issue.

Conclusions

Having reviewed their paper in some detail, we are unconvinced that Hughes *et al*. have furnished any sustainable arguments for giving special status to treatments for rare diseases. Perhaps because of this, their conclusion actually contains a new argument for special status: the 'unacceptability of postcode prescribing from an equity stance'.[1]

It is timely to note that postcode prescribing is the unavoidable result of devolving reimbursement decisions to local commissioners. Different localities have different health needs, priorities and budgets, and thus make different commissioning decisions. Postcode prescribing may be a sign of effective local commissioning. What is required for this variation to be acceptable is a legitimate process such as that described by Burls *et al*.[13] Arbitrary national interventions to address legitimate variation can damage the development of local health services and the efficient use of limited resources.[13] Whether the decision is made at a local or national level, the application of consistent, sustainable principles does not lead to a special status for treatments for rare diseases. Arguing for national policies is irrelevant to making the case for special status for treatments for rare diseases.

Hughes *et al*. end their paper with the following statement: 'It is clear that a complete restriction on the funding of ultra-orphan drugs is not a practical or realistic solution'.[1] If the examination of the justifications for orphan status, and conclusions about how in principle they should be evaluated, is to be restricted to those answers which interested parties currently find to be 'practical and reasonable', then there seems little purpose in the preceding discussion.

At no point in their paper have they made a convincing argument as to why this should be the case. What little evidence there is, suggests that society does not view rarity alone as a strong reason to pay premium prices.[12] Against this background, if the value of the expected health gain from the use of orphan drugs is less than the cost of those drugs, it is legitimate and appropriate to completely restrict their funding.

Interestingly, little mention is made by Hughes *et al*., or others involved in this debate, of the prices of orphan drugs. These prices are often extraordinarily high: in many cases, orders of magnitude higher than those of any other health technology. Imatinib is priced at around £20k, and ERT at around £80k per patient per annum. Some of these prices, notably those of imatinib, have nothing to do with the costs of developing the compound.[14] Similarly, with ceredase, the first ERT, there were

plausible reasons for the extremely high initial cost, but its chemical synthesis should have reduced the cost substantially.[15]

Pricing pharmaceuticals has little to do with the market.[16] The state, through patent legislation, provides incentives for pharmaceutical research. The rules of patent protection, which are blunt and based on history rather than logic, have in many countries been altered to provide further incentives for research on rare diseases.[17,18] Contrary to expectations, some of the resulting orphan drugs have been highly profitable, due largely to their unprecedented high prices.

Given that the case for orphan drug legislation had to with countering low profitability, an argument can be made for monitoring the effect the legislation has had, not only on the development of new drugs, but also their prices. Orphan drug legislation has been one of the major changes in the patent regulation of pharmaceuticals, but one which has led to unexpected results, notably high prices. At this time, rather than considering the extension of the privileged regulatory provision of treatments for rare diseases to the reimbursement arena, there is a need to review the rationale for, and operation of, the existing legislation.

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