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Drugs for exceptionally rare diseases: a commentary on Hughes et al

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Abstract

Recently in this journal, Hughes and colleagues discussed special funding status to ultra-orphan drugs. They concluded that there should be a uniform policy for the provision of orphan drugs across Europe; that complete restriction was impractical, and that UK policy should aspire to the values of the EU directive on orphan drugs. We critically assess these arguments, demonstrating that they failed to justify special status for treatments for rare diseases.

Introduction

Hughes et al. in discussing arguments for and against giving special funding status to ultra-orphan drugs,[1] concluded that there should be a uniform policy across Europe; complete restriction was impractical; UK policy should aspire to the values of the EU directive.

The aims of this paper are to correct the 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 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 simply not 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; £7,500 per patient per year spent on home helps 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.

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] It is undoubtedly true that 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 Gauchers Disease was initially licensed on the basis of a study which recruited 12 people. Within ten years the Gauchers Registry had approximately 3000 patients on therapy; casting doubt over the assumed difficulty in undertaking a conventional randomised controlled trial.[3]

Hughes et al highlight the reliance on short-term surrogate outcomes in the evidence base for ultra-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 ultra 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.[1*]

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. 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 £2.5 million 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] £2.5 million 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 ultra-orphan drugs. Whilst 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 prioritisation 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 prioritisation decisions.

The debate around ultra orphan drugs must recognise 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 NICE's 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 3 members of the council (out 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. Whilst broadly supporting such schemes, we note that 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

Whilst the specification of clinical criteria beyond the limitations set out in the license may reduce the total expenditure on a specific therapy – it 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 ultra-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 Gauchers Disease. The effectiveness of the process cannot be established, as the knowledge of the natural history of Gauchers Disease is vanishingly small; and what data there is, is inconsistent. Even though it is a monogenetic disorder there are over 200 allele mutations; of which very few have been shown to be associated with milder or more severe forms of the disease.[3] It is difficult to see how the medical experts can be confident as to 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 in to 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 therefore it is not clear 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 which is whether funding should be dedicated to the treatment of rare diseases, or others; i.e the opportunity cost issue is not resolved by dedicated funding.

Conclusions

Having reviewed their paper in some detail; we are left 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. [14] Arbitrary national interventions to address legitimate variation can damage the development of local health services and the efficient use of limited resources. [14] 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 seem 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 ultra-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 ultra orphan drugs. These prices are often extraordinarily high, in many cases higher by orders of magnitude than any other health technology. Imatinib is priced at around £20k and ERT at around £80k per patient per annum. We know that some of these prices, notably imatinib have nothing to do with the costs of developing the compound.[15] Similarly, with ceredase, the first ERT, there were plausible reasons for the extremely high initial cost, however its chemical synthesis should have reduced the cost substantially.[16]

Pricing pharmaceuticals has little to do with the market.[17] 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. [18] [19] Contrary to expectations, some of the orphan drugs that resulted have been highly profitable, due largely to their unprecedentedly 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.

Footnote:

* 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 ultra 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

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