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Assessing the economic challenges posed by orphan drugs: A response to McCabe et al.

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To the Editor:

In their comment on our study, McCabe et al. make several points, with which some we agree and some we do not. Here, we respond to the most pertinent issues, using the same twelve headings.

(i) Patients suffering from rare conditions should be entitled to the same opportunity of receiving treatments as other patients with more frequently occurring disorders.

We agree with McCabe et al. when they say "to what degree the access to and funding of orphan drugs by different health systems is consistent with the values of societies they serve, is an empirical question that would benefit from carefully designed research." This was the main point of our study. The standard methods of HTA, in particular the economic evaluation component, suggest a given set of value judgments, which may or may not reflect societal values. In economics terms, the question is how much efficiency (in terms of maximizing health gain from the healthcare budget) is society willing to trade for more equity (in giving therapy to those currently denied access). However, it is important to remember that HTA comprises not only economics considerations, but also social and ethical components.

McCabe et al. argue that we engage in "fetishization," first, by focusing on pharmacological treatment and, second,

that equity in treatment by disease was never an objective of healthcare provision generally or OD policy in particular.

On the first issue, of course any treatment (pharmacological or nonpharmacological) that materially improves the length or quality of life should be considered. The problem is that, historically, such treatments did not exist for most of the diseases currently treated by ODs.This was the critical element explicitly addressed in OD legislation. For example, the criteria for OD status in Europe under Article 3, section 1(a) of the EU regulations (No. 141/2000) requires that the medicinal product must be "intended for diagnosis, prevention, or treatment of a life-threatening or chronically debilitating condition" and in section (b) that "there exists no satisfactory method of diagnosis, prevention or treatment . . . . or if such method exists, that the medicinal product will be of significant benefit to those affected by that condition" (3).

McCabe et al. point out that "best supportive care" is always an option. However, it is not true that there is always a satisfactory option. In a review of the first 5 years of the EU regulation No. 141/2000, there were 268 products that met the orphan designation criteria and 22 received market authorization during that time. These twenty-two products were authorized for twenty different life-threatening or chronically debilitating rare diseases where, before the authorization of these products, in eight of twenty diseases there were no satisfactory treatments and in all the cases the approved products brought significant benefit to patients over what was previously available. This finding was noted by the Commission to be a benefit unto itself, pointing to a difference in the perceived benefit of a new treatment when the comparator is no satisfactory treatment, as opposed to one when the comparator is an acceptable treatment (2).

With regard to access to therapy, we agree that every healthcare system has to make its own decisions and that variation across systems will be present. However, we do not agree that "equity of treatment by disease has never been stated as an objective of health care provision." At the EU level, the OD legislation (Regulation (EC) No. 141/2000) states in section (2) of the preamble that "patients suffering from rare conditions should be entitled to the same quality of treatment as other patients"(3). At the national level, in 2004 a *French National Plan for Rare Diseases 2005–2008: Ensuring equity in the access to diagnosis, treatment and the provision of care* was developed. This plan explicitly calls for "coherence between regulatory, patient care and reimbursement by the national health insurance to ensure the availability and reimbursement of orphan drugs" (5).

It seems a bit of a stretch to claim that merely having the therapy on the market constitutes equality of opportunity for people suffering from rare diseases, in situations where the cost of obtaining the therapy is well beyond their means. Under this definition of equity, we all have equal access to a Ferrari!

(ii) Because of rarity, the development costs have to be recouped from sales to a limited number of patients worldwide, with consequent high acquisition costs per patient.

McCabe et al. question our data, which came from an official report commissioned by the European Union and point out that "the private sector will set price at the level they think the market will bear." We agree that commercial considerations will feature in drug pricing decisions and that prices of drugs may not necessarily reflect the costs of development and production. However, covering costs is a critical element of developing and providing sustainable treatment for patients with rare diseases.

We acknowledge that the cost of developing drugs, including ODs, is not well documented. The cost of developing an OD is likely to be lower than that of drugs in general, as the Phase III of clinical development is likely to be less extensive. Nevertheless, the cost will still be substantial. In their annual report of 2006, Genzyme stated that the 20 April 2007 development cost of Myozyme for Pompe disease was $500 million. Setting aside any question of profit, it is obvious that to recoup this expenditure, the price per patient will be higher if there are 10,000 patients in total, as opposed to 10 million.

(iii) Because of the small number of patients suffering from rare diseases, it is often difficult to enroll sufficient patients into a standard randomized controlled trial.

We agree with McCabe et al. that the feasibility of providing high-quality evidence should be addressed on a case by case basis. We were merely pointing to the difficulties and also suggested some other ways forward.

(iv) If standard HTA procedures were to be applied to ODs, virtually none of them would be "cost-effective."

McCabe et al. state that "if this is true, it is not because ODs fail to meet some arbitrary standard of evidence but because the societal valuations of the benefits that they provide do not exceed the costs at current prices".

The standard approaches to economic evaluation equate "societal valuation" with health gain measured in (equally weighted) quality-adjusted life-years. Our point is that this measure does not encompass all the values that society may wish to take into account when allocating scarce resources. The social value of equity is manifest in OD legislation, as noted previously. Furthermore, in several countries, there is revealed willingness to pay for OD treatments that are many times greater than commonly accepted incremental cost-effectiveness ratios. We need an approach to HTA that adequately reflects all the relevant values. However, we do agree with the point that regulatory frameworks need to provide incentives to undertake research and development in areas that are likely to lead to socially valuable technologies.

(v) When considering the opportunity cost of ODs, it is important to consider also the magnitude of the budget impact they present.

McCabe et al. are correct in saying that the opportunity cost of any intervention is the value of the next best intervention forgone. So the question we would need to pose to members of society is, what amount of health gain (if any) would they be willing to give up to give people suffering from severe diseases where small numbers of patients resulted in high costs of treatment access to that treatment. Our point was that, if society placed any value on access to effective treatment (an empirical issue), the amount given up in other services may not be great, given the small numbers of individuals with these conditions.

(vi) The legitimacy for the availability of ODs, therefore, rests on whether the standard methods of HTA adequately reflect societal preferences.

We agree with McCabe et al. that it is not the methods of HTA but the societal preferences embedded in the measurement and valuation of health outcomes for rare and common diseases on which the debate turns. The difficulty, as McCabe et al. point out, is that "the most commonly cited reasons for additional value are not specific to rarity so cannot legitimize special status."

In a study examining the consistency of decision making by the Pharmaceutical Benefits Advisory Committee in Australia, George et al. give several reasons, including the scientific rigor of the evidence, the lack or inadequacy of alternative treatments currently available, the perceived need in the community, and the seriousness of the intended indication. They also mention other possible objectives such as equity, the rule of rescue, access and affordability from the patient perspective, and financial implications for government (4).

We agree that many of these reasons are not specific to ODs. However, ODs do present with many of these characteristics in a very intensive form. Possibly, new methods of HTA could be developed to take account of all these factors, in which case all technologies could be handled by the same procedures.

(vii) ODs are almost always for serious conditions and they represent the only therapeutic options.

Perhaps we should have said "always," rather than "almost always," because we have not heard of campaigns for the funding of therapies for rare diseases that have trivial health consequences.

McCabe et al. are willing to consider that the seriousness of the condition and the lack of other therapeutic options (where this is really the case) may well be legitimate concerns. Therefore, because these issues are not adequately dealt with by the standard methods of HTA, the societal value of treating all serious conditions, rare or not rare, may be misrepresented.

(viii) Of twenty-seven Council members (of the NICE Citizen's Council), overall, twenty took a decision that there should be a different way to assess value.

The figures we reported are consistent with those given by McCabe et al. As we clearly state, four of twenty-seven Council members thought that patients with a rare disease should be treated as a matter of principle, provided that the treatment works.

There is clearly much more agreement about issues such as severity of the condition and treatment of life-threatening diseases than there is about giving a special status to rare diseases. Whether or not society would be willing to pay a "rarity premium," is an empirical matter that we believe should be explored. Clearly, several "rarity premiums" are currently paid; for example, in investing resources to save the lives of those lost at sea, or to provide air ambulances for those in urgent need of health care in remote locations. Obviously, these policies would need to be debated also. As we have said above, it all depends on whether society is willing to trade any efficiency for equity and how equality of access is defined.

(ix) It does not make much sense (in terms of efficiency) for the public system to fund or subsidize R&D on ODs and later not reimburse the resulting innovations.

McCabe et al. agree but draw different conclusions. They state that "incentives offered and the price signals given by reimbursement authorities should logically follow from what is of social value—not the other way around." We agree, providing we can have an adequate exploration of what constitutes social value.

(x) Research is required into whether the traditional way of financing clinical research into medicine for rare diseases is sustainable in the long run.

No major disagreement here. If society does not think that there is any value in treating these serious, but rare, diseases, then there is no point in doing the research.

(xi) What level in the healthcare system should budgets be set.

No major disagreement here either. This is a practical issue that only needs to be addressed if society thinks that there is value in treating rate diseases.

(xii) How can funding schemes be developed so as to allow access to ODs, yet provide assurances to payers that funds are not being wasted?

McCabe et al. question why there should be special measures to ensure that funds are not being wasted. We were not arguing for special measures, merely recognizing that the problems surrounding "condition reimbursement," where technologies are reimbursed subject to a requirement that additional research is conducted, are far from resolved.

Also, we do have doubts about the practicalities of undertaking randomized controlled trials in some circumstances. Therefore, we will need to address the issue of providing unbiased estimates of the magnitude of effect in the presence of unknown confounders. This is an issue well-known

to economists working on the evaluation of social programs, where it is difficult to conduct experiments (1).

Finally, McCabe et al. accuse us of making two "extraordinary omissions." The first relates to the price of ODs, which they claim we have not questioned sufficiently deeply. Of course, the main focus of our study was on the current application of HTA to ODs. However, we agree that it is reasonable to ask whether the profit of companies whose portfolio focuses on ODs is higher than average, or in any sense "excessive." However, this determination would require careful study and not just the presentation of a few figures by McCabe et al. In addition, in our study, we discuss other methods by which society might fund the development of ODs. These alternatives may be less open to possible exploitation by industry.

The other "extraordinary omission," according to McCabe et al., was our failure to mention the possibility that, due to advances in genetics, many more diseases will be classified as orphan or rare. Although surely we cannot be expected to deal with all the world's problems in a single study, there are clear lessons from the current debate that may inform how we approach the human genome project, which is currently consuming large amounts of public and private funding.

If the main output of this research is to provide small improvements in outcome by individualizing treatment in situations where there is already an effective therapy available, this may not be as much societal value as providing effective therapies where none currently exist. Presumably, the main lesson is from the current debate that society needs to be clear on what it values and what it does not.

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