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COMMENTARY

Toward a Functional Definition of a "Rare Disease" for Regulatory Authorities and Funding Agencies

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ABSTRACT

Background: The designation of a disease as "rare" is associated with some substantial benefits for companies involved in new drug development, including expedited review by regulatory authorities and relaxed criteria for reimbursement. How "rare disease" is defined therefore has major financial implications, both for pharmaceutical companies and for insurers or public drug reimbursement programs. All existing definitions are based, somewhat arbitrarily, on disease incidence or prevalence. **Objectives:** What is proposed here is a functional definition of rare based on an assessment of the feasibility of measuring the efficacy of a new treatment in conventional randomized controlled trials, to inform regulatory authorities and funding agencies charged with assessing new therapies being considered for public funding. **Methods:** It involves a five-step process, involving significant negotiations between patient advocacy groups, pharmaceutical companies, physicians, and public drug reimbursement programs, designed to establish the feasibility of carrying out a randomized controlled trial with sufficient statistical power to show a clinically significant treatment effect. **Results and Conclusions:** The steps are as follows: 1) identification of a specific disease, including appropriate genetic definition; 2) identification of clinically relevant outcomes to evaluate efficacy; 3) establishment of the inherent variability of measurements of clinically relevant outcomes; 4) calculation of the sample size required to assess the efficacy of a new treatment with acceptable statistical power; and 5) estimation of the difficulty of recruiting an adequate sample size given the estimated prevalence or incidence of the disorder in the population and the inclusion criteria to be used.

Keywords: drug development, orphan drugs, rare disease, drug reimbursement.

Introduction

Evaluation of new treatments for rare diseases is inherently difficult [1,2]. In 1983, the United States enacted orphan drug legislation with the specific aim to encourage the development of new therapies for diseases that are so rare that the likelihood of a pharmaceutical company recovering the costs of research and development through sales was small [3]. This allowed for various measures, including research and development grants, provision of expedited review, and market exclusivity for a period of 7 years after approval, facilitating the development of new drugs for the treatment of rare diseases to achieve profitability for the manufacturer. Through such measures, the goal of profitability for the manufacturer has been reached for some drugs for rare diseases [4], albeit with significant challenges remaining for the third-party payers who bear the high costs of such drugs often without adequate information about value for money [5]. Under the provisions of the U.S. Orphan Drug Act, *rare* was defined as a disease affecting fewer than 200,000 Americans. The rationale for choosing this threshold for defining "rare" remains uncertain and relates to incentives for development and not to decisions relating to reimbursement.

Pressure on public payers in particular to provide reimbursement for new, potentially life-saving therapies for rare diseases in the absence of unambiguous evidence of effectiveness, coupled with the societal commitment to fairness in decision making concerning reimbursement, has led to strategies that target treatment with the greatest potential for benefit for those potentially with the most to gain [6]. Because drugs for rare diseases are often extremely expensive, the incremental cost per outcome achieved, a routine measure for assessing cost-effectiveness, often exceeds thresholds thought to be reasonable for health care interventions [7,8]. The development of "rare disease" policies in this context is stimulated by a drive to deal with problems of reimbursement as the main obstacle to access to treatment, rather than as a stimulus to industry to develop new

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therapies to treat rare conditions (see http://www.ema.europa.eu). Central to the decision making around providing access to these very expensive therapies was the commitment to some assurance that the therapies are, in fact, effective. This is recognized to be difficult for rare diseases, and each jurisdiction involved in policy development generally based entry into a special access process on a definition of rare [9,10].

The rationale for selecting one incidence or prevalence threshold rather than another for defining rarity has never been clearly provided, and as a result, chosen thresholds appear arbitrary. The randomized controlled trial (RCT) remains the criterion standard test of the efficacy of new therapies, provides the basis for cost-effectiveness analyses, and is necessary for the endorsement of new therapies in most jurisdictions. Adequate evidence from RCTs, however, may not be available for truly rare conditions. Here, we describe a five-step approach to a more functional definition of rare that takes into explicit account the difficulty of conducting an RCT of sufficient power to provide reimbursement policy decision makers with clear evidence of clinical effectiveness. It anticipates the need for closer collaboration between regulatory authorities, industry, clinical scientists, and patient advocacy groups across the globe than has been customary in the past.

Proposed Protocol

Step 1. What Counts as a Disease?

Because a disease may be defined at several different levels, including clinical, genetic, or pathological, the definition of what counts as a specific, rare disease requires critical reflection and will often evolve as new information on etiology and pathophysiology emerges. For example, breast cancer would not be regarded as a rare disease by almost any criteria. Genetic subclasses of the disease, however, have been identified with dramatically different responses to anticancer treatment [11]. A rare subtype of the cancer for which a subtype-specific treatment was developed would reasonably qualify as a rare disease even though cancer itself is a common condition.

The practice of subclassifying diseases is well known as a means of circumventing barriers to, or restrictions on, marketing of certain drugs by "creating" a "new disease" out of another well-known diagnostic entity, what some have dubbed "excessive diagnostic splitting." In this situation, a definition as rare may be sought by the supplier to facilitate approval and reimbursement for a newly developed drug treatment on the basis of observations of subjects with a specific, rare variant of a common disease. The treatment, however, may be equally applicable to more common variants of the condition that may not be identified in the brief submitted for regulatory or reimbursement approval. The problem of classification is particularly challenging in the case of psychiatric conditions [12], and off-label prescription of drugs approved for treatment of one diagnostic entity is often extended to other variants of the disease. Even Mendelian genetic diseases, which would appear at first inspection to be easy to identify as specific diseases, often exhibit marked clinical heterogeneity. For example, the most common clinical variant of mucopolysaccharidosis, type II (MPS II), Hunter disease, caused by hemizygosity for mutations of the *IDS* gene, is a progressive disorder in which primary involvement of the brain is common and prominent and death, without specific treatment, generally occurs before the age of 15 years. Attenuated forms of the condition, however, occur in which primary brain involvement is minimal [13,14]. MPS II might legitimately be considered to be several diseases, each exceedingly rare by comparison with the whole group. Although genotype-phenotype correlations are helpful in general, the predictive value of a specific mutation may be poor in individual patients and the capacity to use this information meaningfully still remains under development; the potential for it to change medicine from a generalized paradigm to a personalized paradigm should not be underestimated but has not yet been realized.

The emergence of pharmacological chaperones as potentially effective treatments for some genetic diseases underscores the importance of specific genotypic diagnosis. In this case, only some of the mutations associated with a particular disease would be expected to respond to chaperone therapy, namely, those shown by appropriate *in vitro* studies to be associated with the production of an abnormally labile, though catalytically active, mutant protein [15].

In the application of the framework proposed here, the onus would be on providing adequate "proof" of the existence of the rare disease entity on the basis of appropriate condition-specific criteria, including clinical severity, its incidence or prevalence, and that the drug under consideration is specific for that condition.

Step 2. Based on What Is Known about the Natural History of the Disease, What Clinically Relevant Outcomes Would Likely Yield Clear Evidence of Drug Efficacy?

Knowledge of the natural history of a disease is central to the identification of clinically relevant outcomes to be used for evaluation of any therapeutic intervention by means of clinical trials of a new therapy. It is futile, for example, to mount a clinical trial to evaluate the impact of a particular intervention on a manifestation of the disease that affects only a handful of the patients likely to be enrolled, or contributes little to the overall morbidity and mortality of the disease. It is also critically important to enable disease modeling (such as Markov modeling) to estimate the predicted impact of interventions at various stages of a disease, and/or the eventual evaluation of whether the predicted effects were borne out in the real-world setting after introducing the new treatment [16,17].

This step needs to consider the appropriateness of surrogate outcomes versus clinically relevant outcomes in the evaluation of a specific therapeutic intervention. Surrogates are generally easier to measure than clinical outcomes, and the impact of therapy on a surrogate outcome is often demonstrable long before a beneficial clinical outcome can be demonstrated. This has generated growing interest in the identification of surrogates with the potential to demonstrate biological efficacy. In many instances, however, the predictive value of a surrogate outcome is uncertain, and in some cases, surrogates initially thought to be reliable have been shown over the course of time to be unreliable [18]. It is important to distinguish between surrogate markers that are clinical measures of disease progression and those that are biochemical markers. The former can often be more clearly linked to the disease course, whereas the latter relies more on an assessed statistical relationship with clinically relevant outcomes.

Detailed information on the natural history of rare diseases is often lacking. Indeed, the rarity of diseases in this category is precisely what makes confident predictions of meaningful outcomes, based on extensive experience with the disorders, impossible or extremely difficult. Published series of more than a handful of cases are generally nonexistent, or at best rare. There are some noteworthy exceptions: the large-scale industry-sponsored study of the natural history of infantile Pompe disease stands as an exemplary model of such a project. The results were sufficiently robust that the short-term efficacy of enzyme replacement therapy (ERT) was clearly established without recourse to an RCT of the treatment [19].

Studies designed to establish the natural history of a rare disease and the predictive value of any proposed surrogates are seen to be primarily the responsibility of those seeking identification of a particular disease as rare. In most cases, this would

be drug manufacturers who stand to profit from regulatory programs designed to encourage drug development. However, specialist physicians and patient advocacy groups also play a role. Patient advocacy groups are viewed in particular to have a major role to play in this step and are seen as working closely with physicians to understand the true incidence, the clinical spectrum, and the natural history of a rare disease. The information on natural history obtained by surveys of physicians and patient advocacy groups will likely be biased toward more severely affected individuals with the disorder because they are the most identifiable. In fact, screening programs for some rare diseases carried out after the emergence of a new treatment for a rare disease and sponsored by the drug manufacturer have shown that the true prevalence of a disease may be orders of magnitude greater than previously thought as a result of the detection of mildly affected variants, which escape diagnosis by reference to conventional clinical diagnostic criteria. An excellent example is Fabry disease, a rare X-linked, multisystem, lysosomal storage disease. The incidence of the disease was generally considered to be very low, of the order of 1 case per 50,000 male births [20,21]. Newborn screening programs in Italy and Taiwan showed, however, that the identification of males with mild variants of the disease increased the overall incidence to 1 per 3100 and 1 per 1250 newborn males, respectively [22,23]. The clinical relevance of the mildly affected end of the spectrum remains unknown, but the pressures to provide prophylactic treatment are immense, often before the effectiveness of early intervention is clearly established. Thus, the limited clinical evidence that is available may not be applicable to most of the patients now identified with the disease.

Ultimately, the selection of suitable outcomes for any clinical trial of a novel therapy for a rare disease would require consultation with appropriate specialist physicians armed with as much information as is available about the natural history of the disease, including the major systems consistently involved in most of the patients and the evolution of the complications with time. This might require a comprehensive, industry-sponsored survey of a large number of patients similar to that undertaken to elucidate the natural history of infantile Pompe disease [19].

Step 3. What Is the Inherent Variability of the Outcome Measures to be Used to Evaluate Drug Efficacy?

Having identified one or more relevant outcomes, on the basis of a sound understanding of the natural history of a disease and the relationship between any proposed surrogates and clinically important outcomes, the next step is to establish the standard errors for measurements of these outcomes. This is a relatively straightforward process for well-established outcome measures, such as pulmonary function tests or measurements of serum cholesterol levels. It is more difficult for outcomes designed for the assessment of the effect of an intervention on a specific aspect of a rare disease. The measurement of urinary glycolipid excretion in the evaluation of treatments of Fabry disease is an example of a highly specialized and specific surrogate outcome that involves at least three sources of uncertainty: the variability of the measurement itself, the daily biological variability within an individual patient, and the relationship between the surrogate and clinically relevant outcomes. The first two of these sources of uncertainty are relatively easy to resolve by appropriate preliminary studies. The relationship with a clinically relevant outcome is more difficult. In fact, in this specific instance, the treatment of Fabry disease by ERT is associated with highly significant reductions in urinary glycolipid excretion and is generally regarded as clear evidence of a biological effect. The relationship of this biomarker to clinical outcomes, however, has been challenged [17]. How this should affect decision making is still unknown, owing to a paucity of information.

Step 4. How Many Patients Would be Needed to Perform a Clinical Trial of Reasonable Duration Using Relevant Clinical Outcomes with a Power of 80%?

This step is perhaps the easiest of all. It simply involves a power analysis based on the inherent variability of outcomes selected for the evaluation of the efficacy of a particular new therapy, coupled with a decision regarding the anticipated effect of the therapy [24,25]. The results of the analysis indicate the number of patients required for an RCT to establish with acceptable certainty that an intervention works or does not work. Armed with a relatively small amount of information on the proposed outcomes, almost anyone would be able to carry out the required power analysis in a matter of minutes.

Step 5. Is an RCT Using the Clinically Relevant Outcomes Identified Feasible?

The number of patients required to perform an adequately powered RCT can be estimated from the sample size calculated in step 4 together with an estimate of the prevalence of the target disease in a relevant population. Uncertainty about prevalence is inevitable; however, prevalence is currently the only criterion on which the definition of rare is based in most jurisdictions. In the case of rare diseases, the need for multicenter trials is taken for granted. As a result, it may not be unreasonable to insist that RCTs be multinational. For example, this has become the norm for clinical trials of the treatment of many cancers and cardiovascular disease. Such transjurisdictional clinical trials would require considerable negotiation to ensure the uniform application of standards of diagnosis and monitoring.

One approach is to limit the denominator to that population that might be eligible for reimbursement from a central, public drug cost reimbursement program. Another would be to use the combined populations of a subset of all the countries where a drug manufacturer anticipates seeking regulatory approval to sell its product. The true incidence of a rare disease is always difficult to determine: failure to recognize the possibility of a rare disease resulting in delayed or missed diagnosis, combined with incomplete understanding of the clinical spectrum of rare diseases, routinely results in the underestimation of disease incidence. One way to decrease the impact of the failure at the outset to take into account the existence of a potentially large population of patients, which includes mild variants escaping recognition, would be to base the definition of rare on the clinical severity of a disease classified diagnostically according to a generally accepted biochemical or genetic marker rather than on the biochemical or molecular marker alone. For example, by focusing on patients with Gaucher disease or Fabry disease demonstrated in clinical trials to benefit most from ERT, reimbursement of patients has been based on the severity of end-organ damage [26–28]. Accordingly, a large number of asymptomatic or minimally symptomatic patients would not be eligible for reimbursement unless earlier intervention has been demonstrated clearly to lead to a significantly greater long-term benefit than later intervention. This approach has worked well in the case of Gaucher disease because, except in the presence of advanced skeletal complications, the response to ERT is almost always brisk [29]. In Canada, therefore, symptomatic or minimally symptomatic patients are treated differently than symptomatic patients. Analysis of over 6 years of experience with a nationwide study of virtually all individuals in Canada affected with Fabry disease has shown that despite a rigorous application of this approach the outcome of ERT of patients with Fabry disease in this country was

not worse than the outcome of patients treated on the basis of biochemical or genetic diagnosis alone [28].

Estimation of the number of patients available for enrollment in any RCT needs to also take into consideration the proportion that would be considered eligible for enrollment. This is likely to vary according to the ages, geographic distribution, and inclusion and exclusion criteria, as well as the anticipated willingness of patients to participate for whatever reason. This will require more information about the patient population than would normally be readily available. It is the sort of information that is often collected routinely by patient advocacy groups, who have the potential to play an important role in the process at this stage, along with appropriate specialist physicians. At present, however, the involvement of patient advocacy groups has been limited. What is proposed here is a much larger and earlier involvement, including active participation, along with specialist physicians, in the identification and recruitment of subjects suitable for inclusion in clinical trials.

This step requires a realistic determination of the difficulty of recruiting an adequate sample size, and the feasibility of retaining the population for an adequate duration to determine the clinical relevance of the effect of the treatment, on the basis of types of outcomes that are "feasible" to collect. For example, neurocognitive decline is difficult to measure but may be evaluable in the shorter term, whereas death is readily measurable but may require several years or decades to ascertain. Similarly, consideration of feasibility should be based on availability of concentrated patient populations (i.e., where genetic variants may have a geographic concentration) versus dispersed patients (whereby, random mutations are spread worldwide, and not concentrated within a localized population), wherein the former may be more accessible to delivery of clinical care and follow-up for clinical outcomes, whereas the latter are spread across various geographic areas and countries, and across a multitude of health systems and health providers difficult and expensive to connect, such as through a global RCT.

Discussion

The approach suggested here derives from a functional definition of rare based on the practicality of undertaking an appropriately designed RCT (or series of RCTs) with sufficient power to establish with confidence whether a drug or treatment is effective. The framework proposes a multiple-stakeholder approach, and would be best applied "upstream" in the drug development process so that expected evidence requirements can be "a priori" defined. This may improve efficiencies of drug development and will allow for a two-way iterative process to define evidence expectations as the development proceeds. It would also be amenable to enhancing "coverage with evidence development" reimbursement policies, whereby evidence expectations could be defined early in the process, and with collaborative investigation of which patient groups have met "adequate" levels of evidence for conditional reimbursement. For example, this framework could significantly enhance the New Drug Development Paradigms approach adopted by the European Medicines Agency and Singapore Health Sciences Authority, taking a proactive, strategic design of policy with broad stakeholder input, followed by the empiric evaluation of these designs to inform iterative discussion to support adaptive licensing [30,31]. With the proposed protocol, the most straightforward component is the power analysis, especially when it makes use of the known inherent variability of well-established and appropriate clinical outcomes to establish the required sample size. It also, however, involves uncertainties, some of which are inherent, such as the typical natural history and the true prevalence of a disease.

Dealing with the uncertainties should be regarded as a collaborative undertaking involving the principal stakeholders: government regulatory authorities, private or public reimbursement agencies, drug manufacturers, physicians, and patient advocacy groups. The proposed process implies considerable early consultation among the various stakeholders, especially between government regulatory authorities, including those involved with reimbursement from public funds, and manufacturers. Because of the importance of establishing the true prevalence, the clinical spectrum, and natural history of a condition, the negotiations should also include patient advocacy groups and appropriate specialty physicians. Overall coordination of the negotiations is seen as primarily the responsibility of government regulatory authorities, particularly in those situations in which the payer is another government agency.

The success of the proposed process hinges on the willingness of the stakeholders to engage in meaningful negotiations. In this regard, regulatory authorities have a decided advantage, for it is government that ultimately makes the decision regarding when treatments for a rare disease should be granted relaxed expectations for the burden of proof, and the allowances and provisions for this designation. What is proposed here represents the application of a new working framework requiring a rigorous approach to diagnosis and the specificity of a proposed treatment. With respect to new drug development, the benefits gained when a disease is formally accepted to be rare are substantial and are not likely to represent a significant impediment to the development of novel treatments for rare diseases. It is important to emphasize that this approach is intended only to target the definition of rare; it does not, by itself, provide the basis for deciding whether the treatment for a particular condition should be reimbursed. For example, the application of the statistical power criterion, using a generally accepted confidence level of 80%, may work well for deciding whether a condition is rare. If the number of patients with a particularly rare disease is so small that achievement of this level of statistical power is virtually impossible, then some other level of statistical power, or a different study design (such as observational studies), might be accepted as the "best possible evidence" of efficacy when it came to deciding whether to reimburse and under what other conditions. It is worth noting that the decision concerning the definition of "best feasible evidence" required for drugs for rare diseases as applied here is necessary, but not sufficient, for the decision to reimburse. Local considerations of competing priorities for limited resources and local sociopolitical considerations related to providing socially acceptable concessions will inevitably play a role in the ultimate decision. What these conditions might be is beyond the scope of this article and would necessarily involve close consultation with regulatory authorities.

In summary, this framework proposes a functional definition of best feasible evidence expectations for treatments for diseases that goes beyond the definition of incidence or prevalence alone for rare diseases based on the practicality of undertaking an appropriately designed RCT. Such a framework, if applied upstream during drug development and with transparency and collaboration with multiple stakeholders, could improve decision-making processes for regulators and reimbursement agencies and would better inform innovative development and reimbursement processes such as adaptive licensing and coverage with evidence development. This approach could advance the current paradigm, which typically defaults to suggesting that evidence is "impossible" to achieve for rare diseases, when, in fact, there are different underlying realities relating to best feasible level of evidence, and these should be reflected in the development and reimbursement decision-making process.

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