A NEW TOOLKIT FOR STUDY OF THERAPEUTIC INITIATIVES IN RARE DISORDERS: WILL THIS DOG HUNT?

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Abrahamyan et al[1] have provided a valuable summary of innovative methods that may be applied in the design of clinical trials for small populations such as those suffering from rare disorders. In that context they point out the many limitations encountered in relying upon traditional randomized trial designs, both with respect to the challenges in providing power to assess small treatment effects, and the consequent dilemma for payers in determining economic and/or social value from outcomes measured in such studies.

Regulatory authorities have sometimes been pressured to lower the bar when it comes to evidence requirements for market authorization of new therapies directed against rare or undertreated conditions. By "getting out of the way" after a minimal drug development program, a permissive approach by the regulatory agency allows a variety of stakeholders including patients, families, clinicians, researchers, and politicians as well as manufacturers to have major influence on the perceived therapeutic value of the new therapy. Many of the resulting missteps could be avoided through adoption of an innovative approach to trial methods such as that described by Abrahamyan and his colleagues.[1]

The adoption of a reformed clinical trial paradigm in rare disorders will eventually require some new skills and important adjustments on the part of those engaged in the regulatory process. The standard for market authorization will evolve to recognize the validity of data emerging from new trial methods but, at the same time, will need to retain a requirement for high levels of proof of significant outcomes initially, and subsequently of a positive benefit to harm profile. The process of implementation for the new trial methods suggested will require a high degree of collaboration among those interested in regulatory science along with methodologist innovators and with clinicians/patient stakeholders. In particular, there will be a need for an early engagement process that will bring together sponsors, researchers, regulators and HTA/Payers at a very early stage of the drug development process. If all stakeholders have a shared understanding of the methods to be employed, the time course of market approval may be shortened for the benefit of patients and families. Even with the best of intentions on the part of all stakeholders the transition to the use of alternative trial methods will be challenging. The standards for proof of efficacy should not be lowered because of the proposed transition.

Arguments for requirements of larger therapeutic effects, particularly in conditions that are serious and/or life-threatening present a commonsense alternative from many perspectives. A small treatment effect, i.e., a small absolute risk reduction, with a consequent large number needed to treat (NNT), does not provide great likelihood of the individual outcome that is sought by prescribers or patients. There are examples of drugs[2,3] recently approved with NNT's of >50 that translate into odds of an individual patient deriving a benefit of less than 2 in a 100.

Arguably, the regulatory "hurdle" is not the most significant factor limiting access by patients to therapies for rare disorders. Societal values have yet to be uniformly applied to payment for treatments that often prove to be highly expensive. The opportunity cost of shifting

health budgets toward an expensive new drug may have substantial negative effects on others.[4,5] Furthermore, there is no international standard that crosses sociocultural boundaries applicable to such decisions. In the absence of an agreed framework, small treatment effects often translate into low utility scores that are used to estimate QALY's. High price and a low return in QALYs leads to extreme cost-effectiveness ratios, typically beyond the range traditionally funded by public payers often by factors of 10 and as high as 100.

In considering this dilemma we should extrapolate the case of rare disorders to the promise of personalized therapy where, in the case of the ideal personalized medicine, the NNT = 1, or the number needed to harm (NNH) approaches infinity. Costs of treatments in these situations may be justifiably higher than present standards. One may argue that different incentives, beyond price protection through market exclusivity, are necessary to stimulate research and production of therapies for such conditions. In the case of the stimulus provided under the Pediatric Research Equity Act in the United State,[5] incentive is gained through extension of market exclusivity across the entire product market, adults and children, not just in the, at times, very small pediatric market population. Perhaps in the case of novel therapies for rare disorders, rather than permitting a practice of extreme pricing, incentives could be provided through tax incentives across the innovating manufacturer's portfolio.

In summary, current regulatory requirements for market authorization of drugs for rare disorders are insufficiently explicit and may allow for marginal, or flawed clinical trials that fail to serve the needs of other health decision-makers. The Canadian health system would be better served by an approach that encouraged greater expertise in the conduct and interpretation of small trials such as those likely to expand our knowledge of optimal treatment of rare conditions.

In order to support evidence-based decisions in a value-based health economy, new methods in clinical trials need to be coupled with new strategies providing incentives to creative drug research if we are to promote access to cost-effective and affordable solutions for patients with rare disorders. Such reforms will eventually provide for the threshold of cost-effective personalized medicine to be realized

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