Meta-Analysis in a Rare Disease Setting: When is the Evidence Enough and What is the Most Appropriate Approach?

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While a rare disease, by definition in the European Union (EU), affects not more than 5 per 10,000 inhabitants, the aggregate burden of many such diseases is vast; in the EU alone, *an estimated 5,000–8,000 rare diseases affect approximately 27 million to 36 million people.*[1] Given this substantial population, decision making about reimbursement of treatments is beset by multiple challenges and has been keenly debated among various stakeholders, including policy makers, third-party payers, physicians, patients, health economists and ethicists. [2,3]

Development and evaluation of an evidence-based value story are often problematic in rare disease settings, particularly given the limitations in clinical trial design. Challenges include patient recruitment, small sample sizes, short durations of follow-up and a lack of head-to-head comparisons, any of which may impede the use of meta-analyses to assess comparative effectiveness. Although recent research indicates that orphan drugs are increasingly being evaluated in randomized controlled trials (RCTs), these studies are much rarer than observational

studies and case series of patients with such conditions. Several recent reviews of health technology assessment (HTA) reports,[4,5] including assessments by the Institute for Quality and Efficiency in Healthcare (IQWiG),[6] found that consistent methodological specifications for generation of evidence to support HTAs have not been developed and implemented.

Recently, Evidera's Meta Research group has undertaken evidence generation projects in rare disease settings and has gained practical

experience on the synthesis of evidence through assessments of observational studies, case series and prospective clinical studies including RCTs, and in the application of various quantitative analytic methods for evaluation of comparative effectiveness as appropriate. In this article, we will discuss the lessons learned from our experiences. We hope to initiate a discussion of the best approach for gathering and evaluating clinical evidence using appropriate statistical methods — our goal being to inform HTA submissions and economic models for reimbursement agencies.

DON'T UNDERESTIMATE THE POWER OF CASE SERIES

The literature on rare diseases often begins with case reports. But over time, papers detailing case series — for instance, all patients seen with a specific rare disease at a given hospital over the last 20 years — have become more common. As clinicians develop an improved understanding of the pathology of the disease and approaches to its treatment, case series may eventually represent a fairly large evidence base. Literature-based research data from case series

are typically considered to be lower-tier evidence[7] with a higher risk of selection bias. However evidence can be particularly valuable in a rare disease setting, especially in areas where higher-tier evidence is limited or unavailable. For example, case series that detail the experiences of every subject with the disease in a given location can be relatively free of selection bias and offer a valuable historical control that can also serve to inform the design of prospective clinical trials.

Naturally, it is important to assess the study quality in relation to the research questions being asked and, in particular, to tease out potential selection bias as one hopes to ensure the generalizability of the data collected. Following a systematic assessment of potential biases, various statistical analyses can be employed to reveal the disease progression patterns based on patient-level data selectively collected from case series. Such analyses could be used to better understand outcomes associated with standard of care management, determine adequate length of follow-up and/or provide information on what size of treatment impact would be necessary with a new drug. All these results can play critical roles when designing a costly prospective trial and potentially increase the

likelihood of a successful trial outcome. For example, when population data is scarce, such analyses can be used to support and validate the results of an existing trial within a broader context.

It may be feasible to pool data across prospective single-arm studies and RCTs

Many rare diseases involve biochemical laboratory assessments; such assessments are often particularly important for inheritable rare diseases. Since the laboratory values do not involve subjective assessments, for which both pre- and post-values are often available, it may be reasonable to directly compare results from two different studies (RCTs or single-arm trials) evaluating different treatments. In such cases, certain arm-level effects (such as pre-post change scores on laboratory tests, either in absolute or percentage terms) may be similar across studies, for some outcomes, where controlling for a varying placebo effect may not be important. Essentially, we may be able to make the assumption that absolute, arm-level effects are "exchangeable," while the traditional meta-analyses make the weaker and usually more reasonable assumption that relative effects, i.e., *differences* between treatments, are exchangeable.

However, there may be no reason to suspect that changes in certain laboratory values should be lower or higher for different studies within the patient population of interest. We wish to emphasize that should this course be taken, it is critical that studies included in analyses are clinically and methodologically homogeneous, as differences in study populations or methods that affect absolute outcomes are not controlled by design.

FOLLOWING A SYSTEMATIC ASSESSMENT OF POTENTIAL BIASES, VARIOUS STATISTICAL ANALYSES CAN BE EMPLOYED TO REVEAL THE DISEASE PROGRESSION PATTERNS BASED ON PATIENT-LEVEL DATA SELECTIVELY COLLECTED FROM CASE SERIES.

Alternative statistical approaches such as MAIC or STC may be appropriate

When treatment comparisons are necessary, the literature is insufficient to allow for an adjusted indirect comparison, and a "naïve" indirect comparison is ill-advised because of population heterogeneity or other issues, alternative methods can be considered. For example, Matching-Adjusted Indirect Comparisons (MAIC)[8] or Simulated Treatment Comparisons (STC),[9] if sufficient data is available (especially individual patient data), allow one to build a more valid indirect comparison between two treatments. These approaches are not a panacea; two studies on two very different and non-overlapping patient populations are unsuitable for these methods, but when there is significant overlap, they may offer opportunities for comparison that would otherwise be lacking.

Concerns about availability and accessibility of orphan drugs, which are valid in many instances, do not imply that the current orphan drug policy framework is deficient but that the means of assessment needs to be improved upon for realistic and affordable payer prices to become the norm.[10,11] From our experience, a strategic and systematic assessment of the literature landscape can address payer and regulatory questions that may be otherwise answered through additional or extended RCTs. Well thought out, systematic data collection and selection has yielded reliable and defendable solutions in the rare disease setting. There needs to be an extension of the current criteria for value assessment to allow meaningful and robust benchmarks around rare disease cost and quality of life within the context and peculiarities surrounding rare disease evidence reporting and the diseases themselves. Policy should continue to evolve in the support of clinically and methodologically sound evidence generation, outside the realm of additional clinical trials.

A complete understanding of the existing available data and how the available information can facilitate clinically appropriate evidence generation is a powerful and cost-saving tool during the clinical development process. This early initiation of an evidence generation plan can serve multiple facets especially within the rare disease setting. Whereby the knowledge and appropriate selection of published clinical research can support evidence generation through indirect treatment comparison via standard meta-analyses or, alternatively, other statistical analysis methods such as those described above. Results of such evidence generation can help avoid extended trials, support existing trials or demonstrate additional clinical trials may not be necessary. Ultimately, intelligent, innovative evidence synthesis has and should continue to assuage some of the payer and regulatory challenges in order to better provide patients in the rare disease setting timely treatment options.

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