An Overview on Rare Disease Research

JCS speaks with Tim Clark and Will Maier at ICON plc to examine the key clinical, regulatory, and commercial challenges associated with the development of therapies for the treatment of rare diseases

Q1: With 350 million people affected worldwide, rare diseases represent a major unmet medical need. There is, however, no cure for the majority of rare diseases and many go undiagnosed. What are the key clinical, regulatory and commercial challenges associated with the development of therapies for the treatment of rare diseases?

Tim: One of the obvious regulatory challenges is recruiting enough patients to generate an outcome that's statistically strong enough to be deemed acceptable. You generally don't get the strongest evidence from a small cohort, which explains the use of historical data in a synthetic cohort.

Will: From both a regulatory and clinical perspective, it can be challenging to know which outcomes to select. A primary defect in a specific disease can yield secondary, downstream effects in different body systems that may also be worth measuring. In addition, we may want to expand outcomes beyond objective measurements to include patient impact.

Tim: It's worth noting that there's sometimes a discrepancy between the endpoint that a regulator wants to measure and the outcome that the patient thinks is most important.

Will: In terms of commercial challenges, in the last fifteen years or so, as the number of rare disease and oncology treatments has exploded, figuring out how to get your drug paid for has become a much bigger problem – especially with gene therapies that correct a primary genetic defect and carry a heavy, one-time price tag.

Q2: Since rare disease research seldom fits the traditional randomised clinical trial mould, collecting and communicating evidence that is compelling to regulators and convincing to payers is challenging. Therefore, how can companies use wearables, apps and electronic health records (EHRs) to generate real-world data (RWD) that fulfills regulatory and payer requirements?

Will: App technology is big in rare disease communities and can be used for everything from communicating disease information to recruiting for clinical trials to facilitating conversations among patients and providers.

In terms of EHRs, they're not being used to full effect in the rare disease community. But as they become more widespread, they have the potential to help us find patients a lot faster and to improve the recruitment process.

As for wearables, we've seen a lot of interest in them for rare neurological conditions. Wearables can provide information about things like sudden movements, respiratory function, weight gain and sleep patterns, making it possible to monitor patients in a much more sophisticated way.

Q3: The FDA has published a guideline on the use of natural history studies in the study of rare disease mentioning the use of historical control groups in place of active or placebo control. How can companies evaluate and plan for the substitution or addition of a historical control in their rare disease clinical trial?

Tim: Both the FDA and EMA have shown a willingness to accept studies with historical controls. There are two primary ways to analyse historical data. One is to use a Bayesian approach. This involves using information in an external database to form your "prior belief" about what the outcome will be. That prior belief is then mixed with the data you generate from your study to form the posterior distribution, or outcome of your trial.

The other method is known as the frequentist approach. This involves setting up two groups – one external and one from your trial – and doing a standard comparison between the two groups using standard methodologies. This is the classical method that most people learn about.

The basic data used is the same for both approaches—the data are just used in different ways.

Will: Deciding whether or not to do a historical control comes down to a couple of things. First, what is the patient population like? Not all rare diseases fit the mould for being able to use historical data as their control. In some instances, it may be better to use a randomised alternative or placebo. You also need to determine the appropriateness of the historical data out there to ensure a valid comparison. What if you're designing a novel outcome? Or what if available medical records don't contain useful data? Often, there are holes in the data or there are temporal incompatibilities. These are a few things that can limit your ability in this area.

Tim: If there is an imbalance in covariates between the external source and your study data, the comparison will be biased. However, there are accepted methodologies for handling this.

Q4: The timely recruitment of eligible participants is a challenge for any rare disease. How does ICON effectively recruit participants through a partnership with patient organisations, patient contact registries, and clinician education to increase disease recognition and decrease time to diagnosis?

Will: We use a variety of strategies to find patients. For starters, we partner with rare disease patient groups such as NORD, EURORDIS and Orphanet. We also employ a digital engagement strategy, which allows us to recruit for clinical trials at specific points in time when patients are searching for information online – such as at the point of diagnosis. In addition, we work with ongoing registries to help identify patients for clinical trials and to locate historical control data.

Designing a clinical trial that can meet enrolment goals and designating an appropriate comparator can make it difficult for rare disease drug developers to gather sufficient data. How can clinicians and statisticians collaborate to not only build a study design that is attractive to patients but also make trials simpler to enroll enough patients?

Tim: Speaking as a statistician, you want to work with your clinical colleagues to understand the best design for the trial and what the recruitment difficulties are. There's no point in the statistician coming up with complex designs or sample sizes if the trial can't feasibly be done.

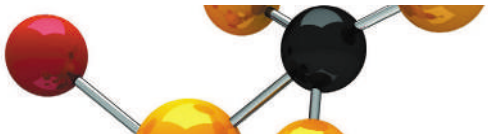
It's a case-by-case assessment based on the clinically relevant outcomes. At the end of the day, you're always limited by the information you can generate. But regulatory authorities seem to be increasingly willing to work with companies to overcome these problems.

Q5: For many rare diseases, well-characterised efficacy endpoints are not available. Therefore, the responsibility resides with sponsors to select or develop trial endpoints based on their knowledge of the disease. Can you give JCS an insight into why the selection of appropriate endpoints is crucial to provide substantial evidence of the efficacy of a drug?

Will: If you don't get the outcomes right, you're going to miss the effect of the drug. Clinicians who treat particularly rare diseases will generally advocate for primary outcomes. If you can correct the primary genetic defect, you'd have a number of outcomes you could potentially measure. But, usually you can't do that and you have to focus on downstream effects for your outcomes. We'll usually design trials using the natural history data from an ongoing registry or a clinician's collection. Many of these trials, interestingly enough, are single-arm studies. In diseases with a high level of unmet need, the FDA has been known to approve a drug even though there was not a statistically significant difference between outcomes from the single-arm study and the historical control.

Q6: In studies where disease heterogeneity is a characteristic challenge, trial protocols must be designed to accommodate the experience of the individual patient. Subsequently, why do you need strong patient engagement to mitigate risks for non-compliance or study dropout in the rare diseases clinical space?

Will: Although many patients with rare diseases are desperate for a treatment, strong engagement is still critical, as patients and their families have been perpetually desperate and get burned out over time. Another problem we often face is that only a few specialists really know how to treat a certain patient population.



If patients don't live near those physicians, you have to figure out how to engage patients in a valid way. That's when you ask patients what's important to them and what they can and cannot do. If we get them to participate in the trial design, sometimes they feel more committed to the study outcome. Adjusting your study design is different in a rare disease trial... because you can't waste a single participant.

Q7: Consistent trial participation is contingent upon the patient's ability to get to and from site appointments. For success in a rare disease trial, the sponsor and other stakeholders must ensure there are no obstacles blocking patient compliance. So why is it imperative that contingencies to assist patients with transportation and accommodation costs be included in a company's trial plan?

Will: We provide them with services to support every aspect of their lifestyle in relation to the trial such as travel, lodging, and periodic home health nurse visits. Somebody makes those arrangements so that patients don't have to. It's important to give patients the resources they need to continue in the study. We want to bring the trial to them.

William C. Maier

William is Chief Scientific Officer, Head of Rare Disease Research, Commercialisation and Outcomes at ICON. William has over 30 years of experience with pharmaceutical companies in Europe, Canada, the United States and Asia. At ICON he works with pharmaceutical companies to provide regulatory, strategic and scientific guidance on medical treatment development and commercialisation. He is a member of the EMEA's European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. He is a frequent speaker at medical conferences and is a member of the Royal Society of Medicine in the UK.

Timothy Clark

Timothy is Vice President, Senior Consultant, Drug Development Services at ICON. Dr. Tim Clark gained his PhD in clinical trial methodology at the Institute for Medical Informatics, Biometry and Epidemiology (IBE), Ludwig-Maximilians-University, Munich. At ICON, he provides strategic drug development advice to customers and internal teams and specialises in clinical study design and protocol optimisation. Prior to joining ICON in 2009, he worked in clinical research and regulatory affairs for large French and American pharmaceutical companies and as an independent consultant advising on a range of drug development issues. He has worked on small molecule and biological (including biosimilars) programmes indicated for cancer as well as CNS, autoimmune, cardiovascular and infectious diseases.