# Rare trials you can trust:

# Biostatistics

There is a desperate need for new ways to diagnose, treat, and improve the quality of life for people with rare conditions and their families. Although around the globe an estimated 300 million people are known to have a rare disease[1], for each specific condition there may be only a few hundred affected families. The rare disease community deserve to be able to make informed choices about their treatment options just like everyone else. To do this, they need diagnostic tests and medicines that have been studied in clinical trials with the same rigor as mainstream treatments.

There are many challenges with running clinical trials that tackle rare diseases. As the recent news about Covid-19 vaccine trials show, clinical studies normally have hundreds, if not thousands, of volunteers taking part to gather the information needed and test the therapy. This is simply not possible for rare diseases and unfortunately 25-30% of trials of rare conditions, many of which affect children, fail.[2,3]

Although difficult, it is possible to run high quality trials involving such small numbers of people scattered around the globe. It is simply that, for a challenging problem, you need an expert team who will work seamlessly together to design and deliver something that fits. Each area of specialty is important, but what is even more important is their understanding of the rare disease landscape and their ability to see the context beyond their own specialism. In such a unique environment, it's their skill at working together and with partners to solve critical problems that makes such a huge difference in people's lives.

Although not discussed by the news, social media, or even in the doctor's office, there is a group of people who quietly form part of this expert team. These people sit behind trials and provide a pivotal foundation. The term 'biostatistics' may not be at the top of news articles, but biostatistics is at the core of every single piece of research. It is the critical element that is needed so that we know how much we can trust the results.

Biostatisticians working in the field of rare disease are, themselves, uniquely qualified for the challenges the area brings – people with years of experience who are driven to use their skills every day to help others.

This white paper aims to shed light on the difference that biostatisticians specializing in rare conditions bring to this united trials-team.

## The role of biostatistics

You'd be forgiven for thinking that biostatistics is just about deciding which statistical test to use at the end of a trial and/or deciding how many volunteers are needed before the 'answer is known'. These things are, of course, important - but it's not even the tip of the iceberg. For a trial to have the power to make a difference, it must deliver results that can be trusted. This is because authorities need to be able to rely on the information when making their decisions about whether to approve and/or reimburse prescriptions of new treatments. Get it wrong, and all the efforts and sacrifices of those involved will not have the impact that was hoped. Once you have developed the potential rare disease treatment, there are three key areas that need to be understood so that an innovative trial can be delivered and good quality results achieved (Figure 1).

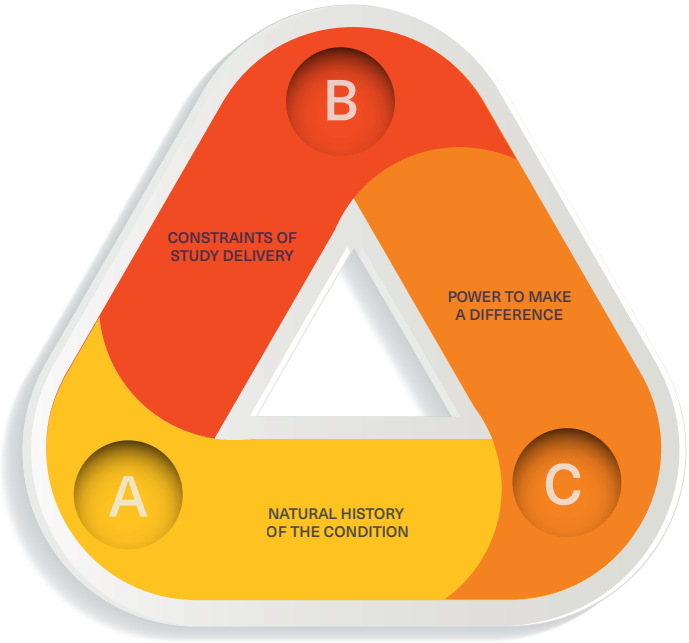


Figure 1. The 3 key areas for designing a successful trial to test the benefit-risk of a drug in rare disease

High quality information needs to be gathered for each of these areas to deliver a successful rare disease trial. Collaborative biostatisticians, who have the specialist techniques essential for underpinning each of these areas, can ensure that trustworthy data are gathered throughout to support authorization of a new medicine.

 

## Natural history of the condition

A

Everyone is a little bit different: in the way their health condition manifests, impacts on their life, or in their experience of the local healthcare system. For mainstream trials involving large numbers of patients, all of these differences are easily controlled by only allowing similar people into the trial. A particular disease aspect is picked (e.g. time-duration before cancer progresses) and there are enough 'similar' people who volunteer that the trial can be delivered within a reasonable time.

Logically, this is just not possible in rare disease. People are distributed around the globe, they may have received all sorts of medications before being diagnosed, and then afterwards there may be no accepted standard treatment for their condition. Everything can vary between people, from the genetics underpinning the condition, to the stage of their disease, and the burdens that are imposed on daily life.

This variety between people is referred to as a 'heterogeneous' population and it is problematic for running fast trials for the following 2 reasons:

| Understanding what you're seeing | Knowing what to measure |
|---|---|
| If we don't understand what normally happens for people with the rare condition, then how can we spot whether a medicine is working or not?<br><br>• If we see a benefit, would it have happened anyway without the medicine?<br>• If condition makes people's test results (e.g. blood tests) vary wildly, then amongst all this change, how will we spot a difference due to the medicine? | People who live with rare conditions can have very different experiences and what is important to them may vary. Changes may also take many years to show.<br><br>How do we decide which one or two things to measure?<br><br>And how to we spot meaningful changes a medicine makes if it's going to take years to get to the first 'hint'?<br><br>As Tandon & Kakkis (2021) described it earlier this year "Depending on the study design, different observers may have different views of the same disease, like seven different blind doctors studying an elephant."[4] |

These problems are all solvable. The first approach involves 'real-world data' or the natural history of the disease. This is the gathering information and test results from people about what is happening with their condition and the impact it is having as they go about their daily lives. Information like this, either from people with that specific condition or 'extrapolated' from trials of a similar treatment or same treatment in other diseases, gives researchers insight into how much things change naturally.

With this knowledge they have far more chance at selecting a measure (called an 'endpoint') that matters to the people making treatment decisions (e.g. patients and caregivers, physicians, authorities etc). The endpoint also needs to be practical and stable enough so that medicine-induced changes can be seen.

 

Registries are a good example of a way to collect real-world data. An example of this is the Fabry Registry where researchers can follow treated and untreated patients diagnosed with the genetic condition, Fabry Disease[5]. With this information a picture begins to develop of the long-term safety and benefits of therapy people are prescribed. It enhances knowledge about how the disease develops and can be used to improve the way that healthcare systems provide support and disease management. There are other natural history studies designed to collect insights, particularly around specific biological mechanisms or clinical markers. An example of this occurred in people with the slowly progressing condition 'retinitis pigmentosa' (RP) that can lead to loss of sight. There have been very few successful trials for this condition in the past because 'normal' disease progression was poorly understood and vision loss occurs over such a long period that trials where vision was an outcome were simply impractical.

Ocular imaging data were gathered and analyzed to gain a deep understanding the natural course of disease. Measured structure changes were correlated with the functional changes that may take longer to realize, such as vision loss.

Statistical analyses have since confirmed that these structural measures can potentially serve as viable 'surrogate' endpoints for clinical trials that, critically, can be measured faster. Trials can now be run in a shorter time frame using this validated biomarker for disease.[6,7]

A similar problem has also been solved in another condition that leads to vision loss called idiopathic macular telangiectasia type 2 or Mactel. Here Emmes biostatisticians and research partners integrated information from a natural history study to successfully get a new structural endpoint approved by the FDA. This paves the way for researchers to develop new treatments, using a measure where patients don't have to wait until their condition has deteriorated so much before knowing whether the treatment is effective.[8]

## Constraints of study delivery

B

As discussed in our previous white paper 'Key Considerations when Conducting Rare Disease Pediatric Trials', there are many constraints when designing and delivering research for people with rare conditions. Taking on these challenges requires integrated thinking from both rare disease study operations specialists and biostatisticians so that the trial ends up as practical and helpful as possible, whilst still testing the medicine soundly. Some frequent challenges are described below.

Small population and study design optimization: There are statistical methods that work well in small sample sizes. When combined with an innovative study design, a trial that initially seems impossible can become a success.[9] The improved understanding of the condition using real-world data, gives researchers the opportunity to predict who is likely to gain the most benefit from treatment.

Trial enrichment is the technique that uses this knowledge to ensure that more of these people are included. This benefits people who are included because they have defined characteristics that have a greater chance of success. Those not involved are not taking part in something with low chance of benefit for them, and researchers can run a faster study with more reliable results because patient variability is reduced. It's an approach endorsed by the FDA and is within the routine skills of rare disease biostatisticians who work closely with the clinicians and patients to understand the implications of each decision.[10,11,12]

 

Another popular choice for study innovation is to create an adaptive clinical trial. Although this requires deep understanding of the statistical power (i.e. the ability to reliably detect when something is/is not happening), through the use of built-in opportunities for modifications, these studies bring several advantages:[13,14,15]

- They shorten trial duration without compromising how much people can trust the result
- Treatments that don't work can be identified quickly and people can stop taking things that are unlikely to help
- They are more efficient – study resources are not used supporting research into treatments that don't work

There are also several ways to build in the adaptations and biostatisticians can weigh the merits of each and advise the best way forward. These approaches use interim (part-way through the trial) analysis of the emerging data to get an early look at what is happening. This is then combined with formal ways to make a decision, such as 'futility assessment' (i.e. if we gather more information do we think it will show benefit or not?); adaptive randomization (emerging information is used to estimate treatment effect and ensure that more people end up on the 'better' arm of study); or identification of sub-populations (i.e. people with particular disease-characteristics that respond especially well, or badly, to treatment).

**Simulations of the trial to optimize trial performance:** Trial simulations act almost as a 'try before you buy' way of testing out the chosen design and analysis methodology. This is especially important for rare disease studies where the research teams are being highly innovative to navigate challenges on many fronts.

Simulations are 'computer experiments' based on what is already known about the condition being studied, the biological characteristics of the people who have the condition, the study design, and the methodology for gathering, testing, and interpreting the data. It gives teams a glimpse of how well their approaches are likely to work and how well things such as bias are controlled (outside influences that can end up disguising the real effect).[16]

**External controls:** If a potential treatment comes along, most patients with a rare condition would prefer to try the treatment rather than be in the study and not receive anything. Using an external control means that everyone taking part in the study gets the potential treatment and the comparison to untreated people is done through selecting a similar group from the data gathered in real-world studies (described above).

This benefits the rare disease community and at the same time means that trials can run faster with greater chance of success. Biostatisticians are the ones who check all assumptions when using this approach and ensure that things such as data collection methods, population characteristics, measurement definitions, sensitivity, and relevance are all figured out so that the results of the trial remain trustworthy.[17-21]

 

## Power to make a difference

C

Research questions must specifically address the aspects of disease that matter – be it in terms of quality of life, treatment of a disease, or symptom control. How the study is monitored, measured, and its ultimate level of success all relates back to whether this original question was the right one, and phrased in the best way to measure the predicted effect of the treatment. It is therefore essential for each of our experts to have experience and understanding of delivering research in the rare disease community environment, so that the question can be shaped by their knowledge of the condition, study design and testing possibilities.

Biostatisticians bring clarity to the phrasing of the research question as well as defining the link between this question, the design, and ensuring that results can provide the specific answers required.

The statistical test used gives a measure of how much you can 'trust' the result – in other words, that if the result is different from what would normally have happened without treatment, how confident we are that this difference didn't just occur by chance? Each of the statistical tests to measure this 'confidence' have strengths and weaknesses ... especially in the challenging study environment of rare disease described previously. It's therefore important for biostatisticians to understand this context and be able to select the best approach after all aspects have been considered. This may include:

- Bayesian adaptations, where the analysis changes as understanding grows.
- Exact /non-parametric tests, avoiding some of the standard assumptions of traditional stats.
- Responder analysis, where several 'composite' endpoints are used to define a 'responder' to treatment and analysis is based on this responder status.
- Not ineffectiveness, which is particularly helpful for small populations.[22] This approach splits the analysis into 2 stages, each involving only a few people. As long as there's no evidence of a medicine having 'no effect' in the first group (i.e. it either seems to work, or it looks likely but there isn't enough information to be sure), then it's tested in a second small group. Stage 2 tests the hypothesis that the probability of inconclusiveness is less than a pre-specified value – if this can be concluded then the treatment is effective.

Whichever method is selected, the entire approach should always be clearly defined in a statistical analysis plan and documented in a way that ensures the definitions of endpoints, use of natural history data, and analysis methodology can be repeated with the same outcome by someone else – i.e. that it's reproducible and reliable.

This documentation is especially important when using the innovative approaches often required in rare disease so that the full analyses can be independently confirmed by the authorities during their assessment and, ultimately, decision whether or not to approve the drug.

All the methods above have a place in ensuring that a trial can be successfully delivered, and trustworthy information gathered, even in challenging conditions. It is key that the approach used fits the research question and deliver results that are also meaningful for those involved. It's therefore essential within the rare disease space that the statistical aspects of a trials are integrated with expertise from other areas from the start of the process.

 

It's also important that biostatisticians be a part of the process from the start to provide high-quality advanced data visualizations to give deep understanding across all parameters – not just the main endpoint. Several areas can benefit from having the information pulled together and shown in a way that it can be accurately and quickly interpreted, such as genetic screening, safety characteristics, or quality of life. Experts reviewing their data can spot trends and subtle linkages far quicker and easier with data visualizations and, instead of spending their time reading endless tables, their expertise can be focused on interpreting and gathering knowledge. This integrated approach is essential to ensure that balanced and accurate decisions can be made by those debating whether to approve a medicine and make it available on prescription.

## Conclusion

Biostatisticians are some of the unsung heroes and heroines of the clinical trial world. When trials become challenging, their understanding of the different innovative methods can make a huge difference in shining a light on poorly understood rare conditions and their treatments. However, it's the seamless integration of such biostatistical knowledge into a team of rare disease study experts across all 3 key areas of understanding that transforms these advanced approaches into study success. The collective knowledge and experience mean that teams can start their research journey together the right way, ensuring that trials are designed to address the most meaningful questions, with feasible delivery approaches, to gather data we can trust.

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