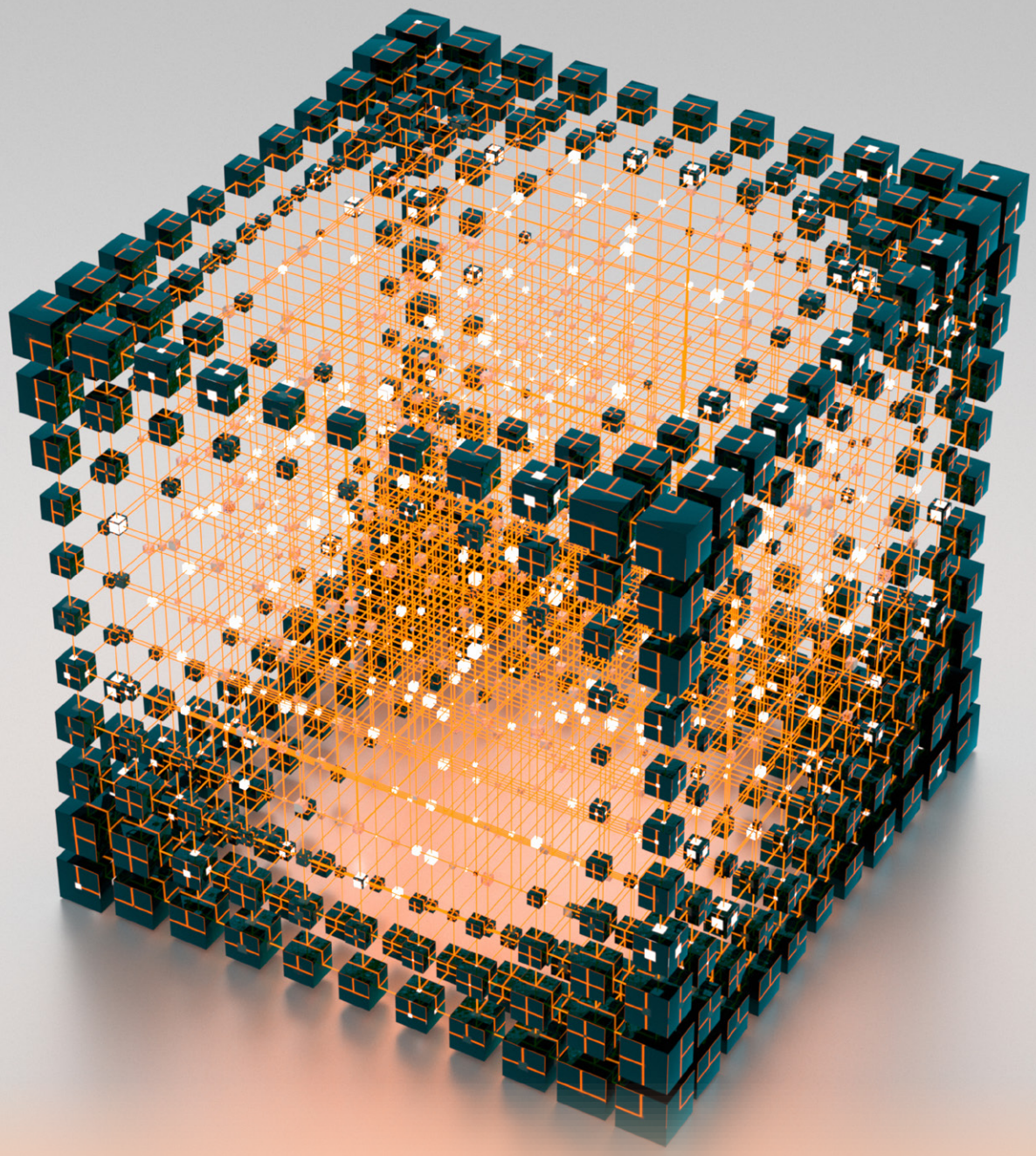
exploristics
INNOVATIVE ANALYTICS SOLUTIONS



Whitepaper

Why thinking big for small populations is transforming rare disease drug development.

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Individuals with rare and orphan diseases face substantial unmet clinical need and so there is a demand for continued improvements in the way we approach drug development in this setting.

Estimated that **300 million people** worldwide are living with a rare disease.
approx. the population of the United States

95% still don't have a treatment option.

Approximately **7,000** known rare diseases, with more added each year.

It is estimated that **80% of rare diseases are genetic** in origin and approximately **75% impact children** [1].

On average, patients **wait nearly 5 years** for an accurate rare disease diagnosis and see 7 physicians during that time [2].

Annual **costs per patient are more than 5 times higher** than non-orphan drugs [3].

Source:
https://rarediseases.org/understanding-rare-disease/rare-disease-facts-and-statistics/

Despite the challenges involved in developing rare disease therapeutics, there are now significant opportunities for increasing the efficiency in delivering safe and effective treatments. Here, we consider the challenges and outline the innovative approaches that can be used to overcome them.

What is a rare or orphan disease?

Rare Disease Definition

The Orphan Drug Act defines a rare disease as a disease or condition that affects less than 200,000 people in the United States. The European Union defines a disease as rare when it affects less than 1 in 2,000 people.

Other countries may have their own official definitions of a rare disease. Many rare diseases may only affect a few hundred or a few thousand patients worldwide.

What are the challenges for rare disease drug development?

There are numerous challenges for drug development and approval of drugs, biologics and devices for treatment of rare diseases. These include:

Low prevalence

Low prevalence and availability of patients to obtain sufficient evidence on the effectiveness and safety of a treatment under investigation is one of the greatest challenges faced by developers. This makes conducting a clinical trial difficult and the inherent smaller size trials need efficient designs to ensure the study gains the most information from the available data.

The low prevalence of rare conditions can also make it **difficult to raise funding to develop a new treatment** as only a small number of people will benefit from it on approval. This can create a barrier to development as it can be hard to generate sufficient return on R&D investment and can result in high drug prices for providers. Regulators like the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have sought to tackle these financial barriers with orphan drug designation programs to incentivise development of rare disease therapeutics (Figure 1) [4,5].

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Figure 1. Development incentives obtained with orphan drug designation.

Difficulties with diagnosis

Many rare diseases suffer from **limited knowledge of the disease pathology** and **phenotypic heterogeneity** in the patient populations. They can be biologically and clinically complex to understand, with a single condition often having multiple subtypes resulting in different clinical manifestations, disease progressions and patient experiences. Hence, rare disease populations are frequently heterogeneous which can create issues with diagnosis and personalised treatment approaches for patients. Running clinical trials in this setting is more complex due to such difficulties and so study designs need to consider and account for these logistical limitations.

Ethical considerations

Rare diseases often impact **paediatric patient populations** and can be **serious or life-threatening**. This adds complications regarding safety risks and in many cases, it may be unethical to use placebo-controlled trials. Increasing the chance of being randomised to the active arm vs. placebo can help here, but such allocation ratios result in lower power than the optimal 1:1. Therefore, extrapolation of data from adult to paediatric populations, use of historical controls and modelling and simulation should be considered when planning clinical development.

Regulatory issues

There is often a lack of well-defined or established and validated endpoints, outcome measures and biomarkers within rare diseases which can lead to **regulatory hurdles**. The FDA and EMA have developed guidelines to support clinical trial design for small populations [6, 7], but substantial safety and efficacy evidence from well-controlled trials is still required. There are no markedly different assessment standards routinely used for orphan drugs versus non-orphan drugs, however, regulators are often flexible and supportive of new clinical trial designs if they are well planned and justified.

What are the opportunities for innovation within rare diseases?

Despite the numerous challenges involved in developing new rare disease therapeutics there are also growing opportunities for innovation. Randomised controlled clinical trials are still considered the gold standard, however, traditional adequately powered studies may not be feasible. Therefore, when developing treatments for a rare disease it is important to consider alternative design options and novel approaches. Numerous designs have been utilised to account for the complexities in rare diseases and it is an area which is continuing to evolve.

Choice of appropriate endpoints

Rare disease drug development often lies in an unprecedented space, therefore, the prospect for use of novel endpoints is high. It's important to ensure that designs are fully examined with regards to the optimal primary endpoint, supportive endpoints, surrogate

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endpoints, patient identification and segmentation. Relationships between these endpoints and risk factors should be captured and explored at the design stage to understand the impact on the likely success of a trial. This is not always easy to do within the rare disease setting, due to restrictions on historical data availability and information. **Simulations** of hypothetical clinical trials assuming different uncertain aspects of the data or scenarios can be extremely informative to augment partial information from historical data. It can support evidence to rule in or out potential endpoints and designs of interest. This involves up front framing and planning to identify the valuable features to model.

Application of adaptive designs

Assumptions are required to inform power calculations for a clinical study. With rare diseases, these will often be obtained from a small dataset(s) and much uncertainty will surround the validity of these assumptions. Power calculations and simulations are only as good as the assumptions that underly them, so it makes sense in a rare disease setting to reduce the dependency on those initial assumptions by checking the trial data at an interim analysis in a pre-defined manner. This can:

- **prevent needless recruitment** into a trial destined to fail (e.g., when initial assumptions were too optimistic)
- **reduce the sample size** if it is clear at an interim analysis there is overwhelming evidence of efficacy (e.g., where initial assumptions were too pessimistic)
- **boost power via sample size re-estimation** in trials estimated to be promising but not successful (e.g., where assumptions were slightly too optimistic)

Adaptive designs (Figure 2) such as seamless and group-sequential designs provide efficient ways to study rare disease indications. **Seamless designs** combine data from exploratory (learning) and confirmatory parts of a study, meaning effective re-use of data from patients. There needs to be adjustments in the analysis to incorporate possible bias related to the risk of false positives, and this needs to be investigated and addressed at the design stage. **Group-sequential designs** allow for studies to stop early for efficacy (or futility) by incorporating interim analyses, thus providing a potential saving in sample sizes.

In addition, more complex **Bayesian approaches** can be used to optimise the adaptive design decision rules with regards to when and how to adapt. **Adaptive randomizations** can also help maximise the total number of patients' success in a trial and address logistical barriers related to recruitment. While there has been some progress in the use of adaptive designs potential remains for further advances in methodology. Early engagement with statisticians ensures that the risks, benefits and implications of such methods can be identified and effectively communicated to inform decision making.

Efficient use of patients

Since patient numbers are likely to be limited, exploring trial designs which allow patients' data to be used more

Figure 2. Different adaptive designs for consideration in rare disease studies.

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than once is beneficial. Different approaches include n-of-1 trials, crossover trial designs or randomised withdrawal designs. One example is the 'blind start' approach where all patients receive a minimum duration of active treatment but are randomly assigned to begin this treatment at different predefined timepoints. This allows for a smaller sample size whilst maintaining statistical power compared to a traditional parallel group study. It also maintains the benefits of a placebo-controlled study but ensures all patients receive the investigational treatment, therefore alleviating issues with recruitment where patients are on only placebo.

Efficient use of data should not be limited by designing one trial for one product within one organisation when there are small populations. Platform designs (Figure 3) can be useful in rare disease research as they bring multiple subgroups and studies within a single design framework or master protocol to support the most effective use of eligible participants. In this way, several interventions can be assessed in parallel against a common control group while new interventions can be added, and the control group updated during the study.

Platform strategies such as Multi-Arm Multi-Stage (MAMS) trials could provide savings both in the operational costs of trial setup and site management, and in the total amount of individuals recruited to the comparator arm. However, with this approach Type I error rates must be closely considered given the same group is used amongst multiple comparisons and statisticians can guide discussion on the need and impact of controlling these error rates.

Use of historical control data

External historical control data which describes the natural history of a rare condition can help to support the development of a treatment where a randomized, placebo-controlled trial may not be possible. However, the relevance of this data needs to be considered prior to use in a clinical trial, for example if there have been changes to diagnostic capabilities, standard of care endpoints of clinical relevance or surrogate endpoint status within regulatory bodies.

External or synthetic control arms offer a useful strategy for incorporating historical data into the design and analysis of clinical trials in a robust way [8]. There have been many methodological advances in the use of synthetic controls arms including weighting, Bayesian methods and microsimulations to ensure unbiased analyses and conclusions by including the external control. These approaches require upfront specification and investigation at the design stage and discussions with regulators to agree on the methods.

With a small patient population available, such as within a rare disease, recruitment can be an insurmountable challenge, heightened in cases where patients do not wish to take a "50:50" chance on receiving placebo. A 2:1 or 3:1

Platform Trial

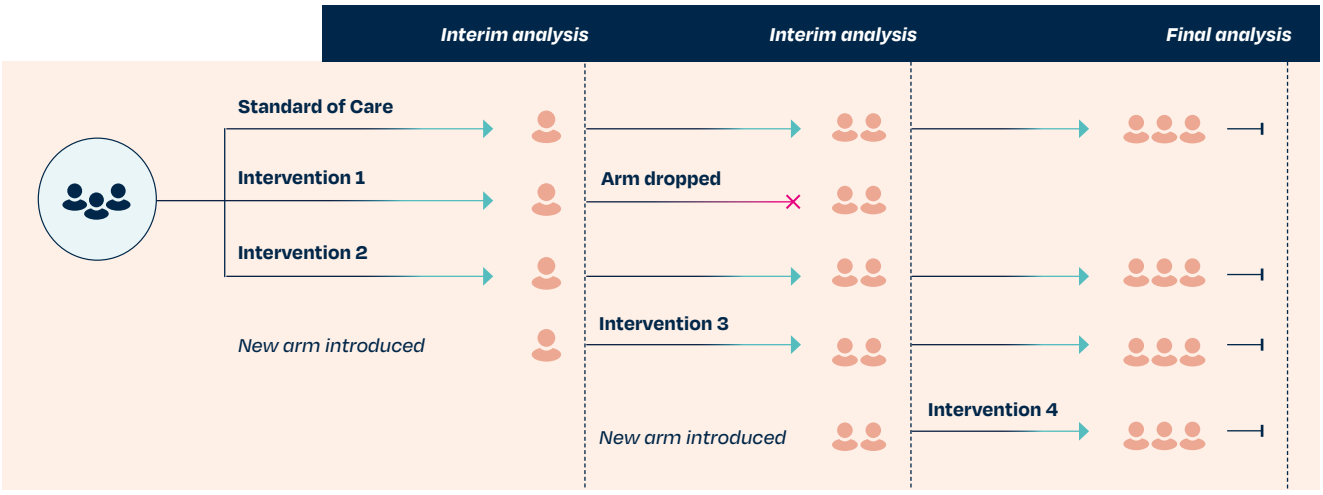

Figure 3. Platform trials assess several treatments and indications within a single master protocol.

allocation ratio may be more appealing from the patient perspective and so hybrid approaches using external control data to augment the concurrent control arm are a fitting choice in this scenario. Bayesian borrowing with a Meta Analytic Prior (MAP) on the control arm can achieve a similar power to a balanced allocation ratio while reducing the size of the concurrent control arm. However, this approach and any that involve the use of historical data, will have a dependency on how similar the observed study data is to the historic data.

Utilisation of modelling and simulation for disease progression

Modelling and simulation of the **disease progression** within rare disease populations has broad utility and can evaluate, inform, and optimize the design of clinical trials. Quantitative modelling of disease progression increases the understanding of how an investigational treatment can improve outcomes for patients and how biomarkers relate to outcomes. For example, relevant patient populations and risk factors related to disease progression can be identified, and study design elements such as inclusion/exclusion criteria, and follow-up duration can be defined.

Like using historical data to form all or part of a comparator arm within a clinical trial, using the data to formulate assumptions for the trial design is dependent on the data available. Good assumptions will be based on an adequate supply of robust, reliable, and relevant data. Issues can arise when progression definitions are not clear or have changed within a disease area leading to difficulty relating past data to future assumptions. Or similarly when characterisation of disease stage is not consistent over time, it can be difficult to compare past and current patient populations. Key Opinion Leader (KOL) or disease area expert input is crucial in ensuring data are comparable.

Engagement with patients as expert collaborators

Ensuring patient engagement throughout the development process is key to success. Patients are often the people who best understand the diseases, especially in conditions where there is little knowledge. This is particularly important when designing clinical trials as there are logistical constraints which need to be understood and are often unique for each disease. There are numerous networks, consortiums and patient advocacy groups, such as the Rare Disease Clinical Research Network, which get involved actively with rare disease research, enhancing the drug development process.

Why is prospective study design vital in rare disease research?

Close consideration of study design approaches at an early stage can help improve the outcomes of clinical trials investigating treatments for any indication. However, given the multiple constraints commonly associated with rare disease studies it is particularly beneficial to examine innovative and flexible study options upfront. When designing such trials, alternative design options should be identified, explored, and quantified to highlight the benefits and risks associated with different choices in a prospective manner. Many designs could be possible, but understanding their applicability with respect to efficiency, risk of bias and practical implications is vital to conducting a successful study. Engaging early with multiple stakeholders, including statisticians, facilitates such key decision-making and drives down development timelines, risks and costs.

At Exploristics, we approach the design of clinical trials by focusing on the 3 R's: the **right data,** in the **right patients**, in the **right way**. This is always important, but within rare diseases, the importance is magnified. Patients with rare diseases are in desperate need of innovation and there are more than 700 medicines currently in development for rare diseases and conditions [9]. With a prospective approach to designing clinical trials for rare disease interventions, we can also help deliver the 4th R: that more of the **right treatments** can successfully get to the patients.

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References

1. Regulatory strategies for rare diseases under current global regulatory statutes: a discussion with stakeholders | Orphanet Journal of Rare Diseases | Full Text (biomedcentral.com)

2. https://genomemedicine.biomedcentral.com/articles/10.1186/s13073-022-01026-w#:~:text=The%20diagnostic%20delay%20for%20rare,decade%20%5B8%2C%209%5D

3. https://www.statista.com/statistics/373353/average-cost-for-orphan-drugs-per-patient-per-year/

4. https://www.fda.gov/industry/medical-products-rare-diseases-and-conditions/designating-orphan-product-drugs-and-biological-products

5. https://www.ema.europa.eu/en/human-regulatory/overview/orphan-designation-overview

6. https://www.fda.gov/media/120091/download

7. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-trials-small-populations_en.pdf

8. https://exploristics.com/wp-content/uploads/2023/02/Exploristics-Whitepaper-Synthetic-Control-Arms.pdf

9. https://phrma.org/en/resource-center/Topics/Medicines-in-Development/Medicines-in-Development-for-Rare-Diseases-2021-Drug-List

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About Exploristics

Exploristics is a global provider of state-of-the-art software and biostatistics services to the life sciences sector. We offer key support to organisations involved in the clinical development of new healthcare breakthroughs with our strategic consultancy expertise and flagship simulation software, **KerusCloud**.

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