

WHITE PAPER PRESENTED BY PREMIER RESEARCH

# The Science and Art of Conducting Clinical Trial Feasibility

Designing and executing assessments of country, site, investigator and recruitment feasibility in rare disease and pediatric studies

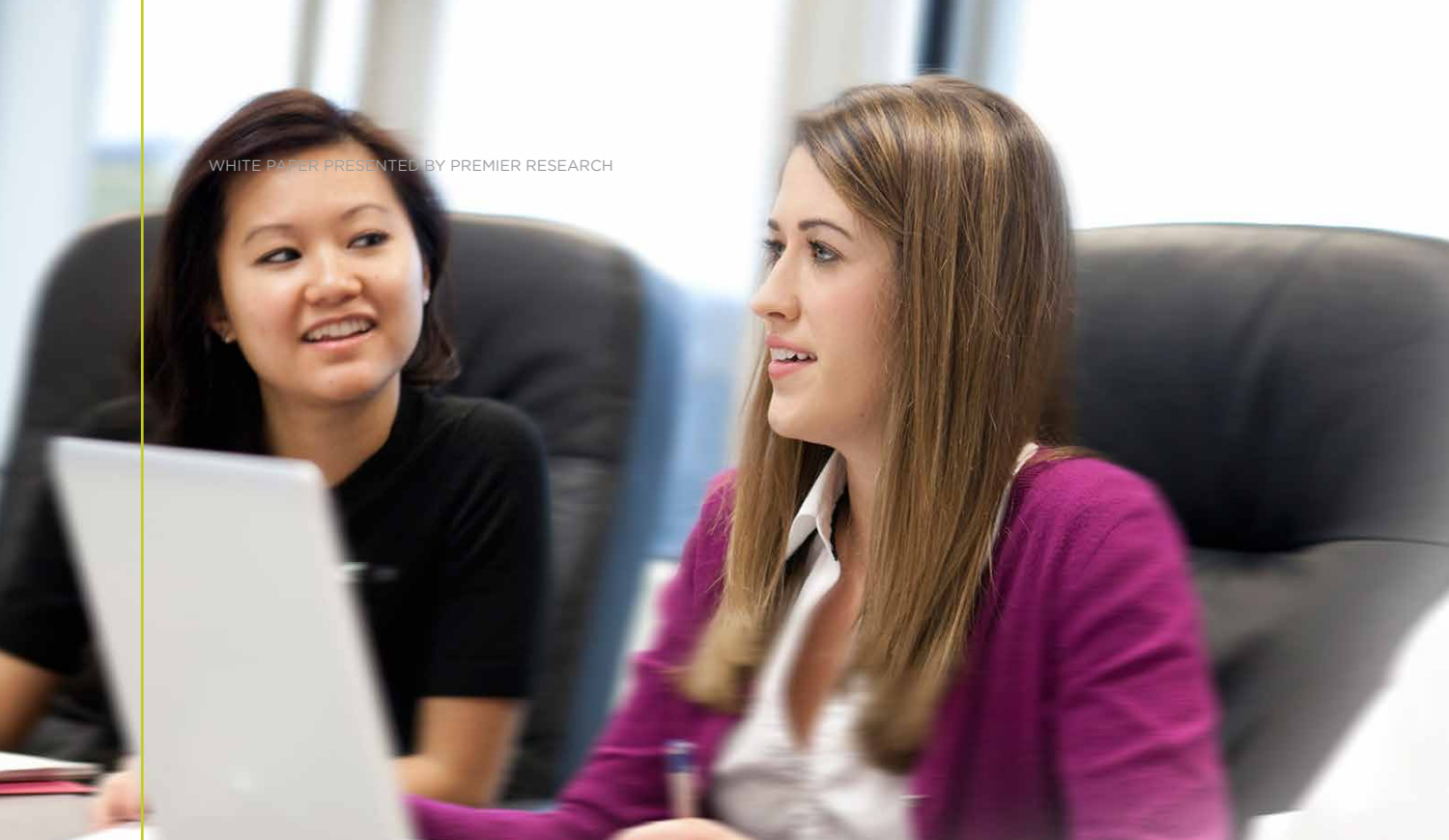


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## ABSTRACT

Rare disease and pediatric studies present significant challenges, including country selection, site selection, and patient recruitment. A thoughtfully-designed, well-executed feasibility study can help sponsors obtain a realistic assessment of the best path forward for developing and conducting successful global clinical trials.

PEDIATRICS  
RARE DISEASE



## Introduction

Performing a thorough assessment of clinical trial feasibility is an important early step in initiating global clinical trials, particularly in rare disease or pediatric studies where country selection, site selection and patient recruitment each represent a significant challenge to successful clinical trial conduct.

A 2015 survey of 50 clinical development decision-makers in the U.S. and Europe revealed that identifying and setting up investigative sites were among the most difficult factors of conducting rare disease clinical trials.<sup>1</sup> According to recent studies:

- + Only six percent of all clinical trials are completed on time<sup>2</sup>
- + Eighty percent of all clinical trials fail to meet enrollment timelines<sup>3</sup>
- + Nearly 60 percent of all clinical trials that are terminated are terminated due to enrollment difficulties<sup>4</sup>

## The Science and Art of Conducting Clinical Trial Feasibility

Clinical trial feasibility helps in identifying potential obstacles to clinical trial conduct, enabling sponsors and study planning teams to proactively work with different countries, sites and investigators to develop processes and practices that mitigate risk and support study completion.

Investing in a robust feasibility process enables sponsors of rare disease or pediatric studies to obtain a realistic assessment of the capability of executing a planned clinical trial and the best path forward for developing a clinical research program. Feasibility assessments are critical tools, but they can be time-consuming and costly if they lack appropriate focus and direction.

A well-designed and executed feasibility study is the linchpin of a successful clinical research program. This white paper delves into three critical aspects of clinical trial feasibility with respect to rare disease or pediatric studies – country feasibility, site selection, and projection of patient recruitment – and offers

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focused insights and strategies that sponsors can leverage to successfully manage global studies on time and in accordance with applicable regulatory and quality guidelines.

### Country selection

Approximately 25 percent of investigational new drug (IND) applications to the U.S. Food and Drug Administration (FDA) include critical data from outside the U.S.<sup>3</sup> In fact, a snapshot of [ClinicalTrials.gov](http://ClinicalTrials.gov) in May 2016 showed that 54 percent of all recruiting studies were recruiting only in non-U.S. locations.<sup>6</sup> There are potential advantages in conducting clinical trials in countries outside of the U.S. and Western Europe, including higher enrollment potential and lower costs. However, there are also variables such as differences in patient populations, local regulatory and ethical guidelines, standard of care, and the number and experience of available sites and investigators, which make completing global studies on time and on target a complex challenge.

#### Utility of country feasibility assessments

A comprehensive review of the planned clinical trial protocol is a prerequisite to any study of clinical trial feasibility. Once a thorough understanding of the protocol has been obtained, there are a multitude of factors to be considered when assessing the potential of conducting a rare disease or pediatric clinical trial in a specific country and making decisions about country selection. Accurate country feasibility assessments can be used to inform strategies for geographical placement, protocol design, and operational execution of a study. They are also useful for:<sup>5</sup>

- + Determining whether there is a sufficient number of patients with the disease of interest who might qualify for the study
- + Confirming that the study design will be acceptable to sites, investigators and study participants
- + Identifying potential regulatory and ethical challenges

- + Establishing general timelines for study approval and site start-up
- + Assessing the overall commitment of potential partners – country offices, sites, and investigators – towards study completion

A high-level strategy for selecting countries in which to open a clinical trial includes three fundamental tactics:

1. Determining where patients with the disease of interest are located around the world
2. Identifying countries where the concentration of potential study participants overlaps with practical access to those patient populations
3. Selecting countries that have a proven track record of recruiting patients and providing dependable, high-quality data

Partnering with a contract research organization (CRO) that has practice experience with the medical, cultural and regulatory perspectives within the countries of interest can help to ensure that country feasibility assessments are accurate, comprehensive and relevant to a planned clinical trial.

#### Epidemiology and eligible population

Study planning teams often use epidemiology as a preliminary, program-level step in the feasibility assessment and country selection process. These teams should be aware that incidence rates of the indication(s) under investigation do not provide sufficient visibility into a country's enrollment potential, unless they are considered in the context of more specific epidemiological data. Careful review of the prevalence of patients with the protocol-based definition of study disease may help narrow down the list of countries under consideration. In conjunction with an understanding of whether patients



Existing treatment patterns and guidelines for the disease of interest vary from country to country, and the specialist and site type may differ, as well. Taken together, these factors can have a significant impact on site selection, the clinical trial experience levels of the suitable investigators, and the potential for patient recruitment.

present with genetic variability from country to country, or even region to region, access to international electronic health record (EHR) information may help in identifying the potential for conducting a clinical trial in specific countries and better targeting patients. However, it is worth noting that this factor alone cannot define country selection strategy due to the need to consider the likelihood of the eligible population to participate in the study, as discussed in more detail below.

#### Standard of care and patient pathways

When planning a clinical trial, it is critical for sponsors and study planning teams to be aware of the current global, regional and country-specific standards of care with regard to the indication(s) under investigation. Existing treatment patterns and guidelines for the disease of interest vary from country to country, and the specialist and site type may differ, as well. Taken together, these factors can have a significant impact on site selection, the clinical trial experience levels of the suitable investigators, and the potential for patient recruitment. As a result, a comprehensive, holistic clinical trial feasibility assessment should include a thorough understanding of the standard of care and associated patient pathways in each country under consideration.

There are examples of pediatric patients who will be seen by adult specialists in some rare, pediatric disorders due to the low incidence of patients and high degree of specialty required of the investigator. Alternatively, patients may be referred to a central site within a country where a key specialist is located. Therefore, it is essential to fully understand the treatment pathways to ensure that a proactive and tailored approach can be developed for patient recruitment. A one-size-fits-all approach applied to these types of patient populations would likely result in an inefficient and unsuccessful strategy.

The factors listed below can help study planning teams to determine whether the treatments, assessments and interventions outlined in the study protocol are compatible with currently available patterns of care:

- + Are protocol-required prior therapies available and routinely used in the countries being considered?
- + Are there reimbursement issues related to protocol-required prior/concomitant treatments or assessments, or can the lack of reimbursement within particular countries drive recruitment?
- + Are alternative drugs and treatments (comparators) licensed and widely available in the countries under consideration, or used off label?
- + How is the healthcare system set up?
- + How do patients with the disease of interest typically access the system?
- + Are study-specific procedures in line with existing medical practices?

#### Competing trials

Competing trials are a key concern for rare indications, where there is not a large patient pool. Country selection should therefore take into account the number of competing trials targeting the same pool of potential study participants. The presence of other trials competing for recruitment of the same, or even a similar, patient population can affect both country and overall study performance, so early identification of this risk is critical. Information on competing trials is readily available at [ClinicalTrials.gov](http://ClinicalTrials.gov), but study planning teams should keep in mind that some active trials and site details might not be listed. Additionally, studies running within the same clinical site that

may involve the same site staff can have an impact on the resources available to dedicate to the study. Consequently, it is important to consider this factor throughout the feasibility and site qualification process.

### Start-up timelines

Assessment of study start-up timelines is a key piece of information in the planning and projection of patient recruitment as it reflects the regulatory and ethical component of clinical trial feasibility. Study planning teams are tasked with understanding the specific regulatory and ethical requirements of each country under consideration, including protocol translation, import/export guidelines for the investigative drug or biological materials, and other special operational issues. In addition, some countries have specific legislation that applies to pediatric studies. For example, in Russia, a clinical study cannot be conducted in children under the age of 18 years unless a study involving the investigational product has been completed in adults (aged > 18 years). This type of country-specific information is essential for determining the time needed for regulatory approvals, ethical clearance, and study or site activation.

### Patient support groups/networks

The availability of country-specific patient support groups or networks in the disease of interest can help drive disease awareness, advocacy, and even patient recruitment, particularly in rare disease or pediatric studies where the target patient pool is inherently limited. Identifying and connecting with these groups and networks to engage their support may be useful on a study-by-study basis.

In today's social media-driven environment, some sponsors have turned to proactive web listening to gain insights into how patients or investigators might view their trials. This listening not only guides feasibility estimates, but also helps sponsors to better position their trials with patients and investigators when reaching out to them.

### Participation motivation factors

Protocol considerations, as well as individual patient, parent/caregiver or child perspectives, may influence the likelihood that consent will be given to participate in a clinical trial. Protocol-related factors such as the need for hospitalization, frequent visits, repeated blood sampling, or invasive procedures may decrease patient motivation, decrease willingness for the parent/caregiver to enter their child into the study or even preclude ethical clearance. On the other hand, drug reimbursement and access a better standard of care may increase the desirability of clinical trial participation.

Questions that should be addressed during the course of a feasibility study include:

- + Are there cultural norms that need to be factored in?
- + Are there country- or region-specific issues that will either motivate or deter patients from enrolling in the trial?

Patient perspectives are often overlooked in feasibility studies due to short timelines or a unilateral focus on the protocol. Insight into these participation motivation factors enables study planning teams to optimize the study design for the target patient population and identify effective recruitment strategies on a country-by-country basis.

### Site and investigator selection

Site selection is a key component of every clinical trial enrollment strategy, which should be conducted in parallel with assessment of country feasibility for global studies. Selecting the right sites can have a widespread, positive impact on the efficiency of resource allocation and the likelihood of study completion.<sup>7</sup> However, in the absence of an organized global network of clinical trial centers, and with the growing number of countries that have emerged as major destinations for clinical trials, site selection can be a daunting task. This is especially true for rare



disease or pediatric trials, which are typically labor intensive and require a higher degree of service or resource allocation for patient recruitment and retention.

### Evaluating sites

The process of site selection is essentially an assessment of a site's competency to conduct the planned clinical trial in terms of medical knowledge, resources, and operational experience. Site demographics that should be considered include:

- + Clinical setting (e.g., academic, hospital, or out-patient)
- + Availability of target patient population
- + Availability and experience of study coordinators, pharmacists, and nurses
- + Protocol-related knowledge
 

Previous experience in the indication(s) under investigation is a significant benefit, but may be difficult to find for rare disease and pediatric studies. However, transferable experience such as previous participation in other trials, experience with special procedures such as blood sampling in pediatric populations, and experience with the consent and assent process is of key importance.
- + Interest in the planned clinical study
- + Accessibility to specific equipment, tests, or facilities outlined in the study protocol. This factor includes assessing equipment that is specialized for pediatric patients, such as blood pressure cuffs.
- + Infrastructure (e.g., drug storage, biological sample processing, site security)

### + Recruitment potential and retention capability

Subject enrollment is a particularly complex challenge when conducting clinical trials in rare diseases or pediatric populations. The factors that influence enrollment vary depending on region, country, site, and even individual patients. As a result, assessing the recruitment potential of individual sites in terms of anticipated subjects per month and over the course of the entire trial is important not only for site selection, but also for tracking site performance during study conduct. Additionally, factors such as resource availability can have a large impact on recruitment and retention. For example, in pediatric studies, parents of potential study participants may have a lot of questions. The availability of site staff to dedicate the time needed to fully answer these questions and provide appropriate, accurate information may make a difference in recruitment and retention.

With the increasing use of clinical trial technologies, such as interactive voice response (IVR) systems, electronic case report forms (e-CRFs), and tools for randomization, site feasibility and site selection should also take into account a site's prior experience with relevant technology tools in the study protocol. Lack of previous experience does not necessarily demand site exclusion, but may require study planning teams to take the need for site training into account when considering site activation timelines and to plan this activity proactively to ensure patient recruitment is not delayed.

Study planning teams may also want to evaluate whether sites have undergone sponsor/independent site audits in the past. In recent years, site inspections have been carried out by the FDA, European Medicines Agency (EMA), and regulatory agencies in emerging countries such as India. If site audits have been performed, it is advisable to inquire about any concerns raised and determine whether appropriate resource allocation and adequate training during study start-up are sufficient to address those concerns.<sup>5</sup>

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### Evaluating investigators

Many of the demographic factors involved in site selection are applicable to investigators, as well. When selecting investigators, it is also important to assess each potential investigator's readiness in terms of:<sup>5</sup>

- + Awareness of, and ability to deliver the standard of care
- + The number of potentially eligible patients treated or seen
- + Acceptance of the study design
- + Familiarity with the tools and technology defined by the protocol

### Helpful site and investigator selection resources

Previous experience with a site or investigator may be the best gauge for selecting appropriate candidates for executing a clinical trial. In the absence of empirical data, feasibility questionnaires are important for screening both sites and investigators for inclusion in a rare disease or pediatric clinical study program. There are a variety of readily available sources of public information and intelligence, including the National Comprehensive Cancer Network (NCCN), the Surveillance Research Program of the Division of Cancer Control and Population Sciences, and CenterWatch, which can be leveraged to direct the site selection process toward or away from key areas and sites. Patient networks and specialist networks, such as the National Institute for Health Research – Clinical Research Network (NIHR CRN) or the European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA) are also useful resources for pediatric research.

### Developing a projection using an effective and accurate recruitment projection model

Patient recruitment is a process that must be managed proactively and efficiently from the planning phase of a clinical trial until the last patient has been enrolled. Statistics show that a high percentage of clinical trial delays across all therapeutic areas are a function of poor enrollment. These delays are expensive, costing an estimated \$1 million per day.<sup>8</sup>

Assessments of clinical trial feasibility and recruitment potential enable sponsors and study planning teams to develop recruitment projection models that estimate recruitment rates and the overall enrollment period required to complete study recruitment. These models range from simple projections of overall recruitment rate, number of sites and enrollment period to complex models, such as the recruitment projection model (RPM) developed by Premier Research that allows full projection on a site-by-site basis. This flexible model can be fully tailored to the study protocol, incorporating the ability to include the following factors in projecting recruitment:

- + Disease factors including seasonal variation, e.g., for an allergy or influenza study
- + Protocol-specific factors, such as the sequential cohort recruitment that is often included within pediatric trials, and the ability to project interim periods within the recruitment should Data and Safety Monitoring Board (DSMB) meetings be planned after a set number of patients are recruited.
- + Presence of an existing patient database, which might lead to bulk recruitment in the initial period following site activation
- + Holiday seasons, when recruitment is typically low



- + Ramp-up of recruitment within the site following initiation projection on a country level (average recruitment spread across sites, with a ramp-up of site activation) followed by refinement projection on a site-by-site basis.

In rare disease or pediatric studies, where low recruitment is expected, it can be extremely difficult to effectively project recruitment. For example, a pediatric rare disease study might only enroll one to three patients per year per site, and these patients might come into any site and at any time of the year. Therefore, projecting these studies and planning at a study level carries additional complexities. In order to more accurately project, it is suggested that a date range is given for the First Patient In (FPI) date, and that care is taken with analysis of recruitment rates at less than one patient per site, per month (p/s/m). For example, while theoretically correct, it cannot always be assumed that 10 sites each recruiting at a rate of 0.1 p/s/m (i.e., each site assumed to recruit one patient per 10 months) would yield in total one patient per month into the study.

The low recruitment rates that are typically seen with studies in rare and some pediatric diseases mean that it is essential to have proactive plans regarding patient recruitment from a thorough understanding of each site and patient retention to minimize drop-out rates in on-going studies, in addition to detailed contingency strategies prior to study start.

## Conclusion

Clinical trial feasibility is critical for helping sponsors conduct global clinical trials that meet their objectives in terms of timelines, patient recruitment targets, and cost. Given the sheer breadth and volume of information needed to complete a comprehensive clinical trial feasibility assessment, coordination among the clinical operations, medical affairs and commercial units is valuable. Collaboration with a contract research organization with regional experience and feasibility expertise may also help ensure that all factors are accounted for and weighed appropriately. Taking this focused, disciplined, and data-driven approach to feasibility contributes to the development of a successful trial operational strategy that combines the right countries, right sites, and right patients.

Given the sheer breadth and volume of information needed to complete a comprehensive clinical trial feasibility assessment, coordination among the clinical operations, medical affairs, and commercial units is valuable.

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