

# HIGH YIELD CONSIDERATIONS FOR CLINICAL DEVELOPMENT IN RARE & GENETIC DISEASES OF THE KIDNEY



**Ajay Srivastava, MD, FASN**  
*Vice President,  
Medical Department*

Dr. Ajay Srivastava is a board-certified nephrologist with an extensive background in both clinical and academic medicine. Specializing in adult nephrology, he brings over 14 years of experience in both the common and rare conditions of the kidney, renal replacement therapies, ICU nephrology including IV fluid resuscitation and management, and comorbid conditions such as cardiorenal syndrome and hypertension.

## INTRODUCTION

Rare diseases not only represent a tremendous opportunity in drug development to make a difference in the lives of those who suffer from illnesses that have no effective therapy but are remarkably quite numerous with several thousand identified in just the United States and impact many more across the globe. However, the specific qualifications for a disease to be classified as rare vary across the world. For example, a disease must have a prevalence of less than one in 2,000 individuals in the European Union to be considered a rare disease, whereas in the United States, the designation applies to a disease where less than 200,000 total individuals are affected. For inherited kidney disorders, the diagnosis and management are complex – especially as diseases of the kidney often result in multisystem complications.

Patients impacted by these diseases typically spend years consulting several health care providers before ultimately receiving an accurate diagnosis of a serious disease that's often chronic, progressive, and may have a high potential for fatality early in life.

Although advances in renal replacement therapies such as dialysis or kidney transplantation have included greater access and have paved the way for prolonged survival, patients often continue to struggle with poor quality of life. For example, children born with severe congenital nephropathy have a high likelihood of altered cognitive, physical, and psychosocial development and a need for complex care. Therapeutic advances in rare kidney diseases have historically had notable challenges, including populations with highly heterogeneous and variable clinical phenotypes and limited knowledge of the natural history of the disease, which impact outcome and endpoint measures. Other challenges include a lack of biomarkers to monitor disease progression, oftentimes with dated diagnostic classifications that don't necessarily reflect the underlying pathophysiologic mechanisms. Treatments for rare and genetic diseases of the kidney represent a notable unmet medical need, especially in the pediatric population, with a requirement to continually advance strategies to overcome these unique challenges.

Overall, the development of treatments for rare diseases and orphan indications represent special and rewarding opportunities to make innovative contributions to medicine that have a meaningful impact for patients that suffer from these diseases. In this article, I explore eight key considerations for strategies to optimize clinical development in rare and genetic diseases of the kidney.

## GENERAL

Outlining the clinical development program early is fundamental – this is especially critical due to the complex paradigms associated with development for rare and genetic kidney diseases. This includes having a solid scientific foundation, which requires a good understanding of the mechanism of action of the IP as well as the characterization of the disease with a defined natural history, the latter of which is relatively uncommon. Therefore, an emphasis on data monitoring or starting a natural history study early is essential.

Population-based considerations are also key, which require an informed understanding of available therapies, the potential for curative or mitigating aspects of the disease, and navigating the course of the disease in terms of its chronic or progressive nature. Understanding whether there are expectations toward remission and relapses is another important dimension that adds to the inherent complexity of disease management and its psychosocial impact on the patient. Furthermore, potential patients may be at various stages of a disease which needs additional consideration since this will impact the natural course of progression of the disease.

**Key general considerations include:**

- Clinical development program
  - Outline early
  - Requires solid scientific foundation
    - Mechanism of action of IP
    - Characterization of disease
    - Disease natural history defined
- Population-based considerations
  - Current available therapies
  - Curative vs. mitigative
  - Chronic, progressive, remitting, relapsing
  - Stage of disease may be variable

## FEASIBILITY & SITE IDENTIFICATION

Patients with rare diseases often represent challenging populations to recruit and require important considerations. Pre-identification and properly selected sites are essential. Usually, patients with rare diseases are seen at academic institutions, specialized centers, and pediatric hospitals. Pediatric research networks are fundamental, especially if they already offer genetic testing for disease confirmation.

Additional strategies for selecting appropriate investigational sites include identifying sites with a thorough understanding of the epidemiology and inherent patterns for the disease, have familiarity with the standard of care, and are institutionally consistent, especially regarding background care and medications. It is also important to have diagnostic and therapeutic resources available. In this regard, understanding the start-up processes for these sites, including the development of study-specific recruitment plans and materials, and ensuring fundamental study site training is vital.

**Key feasibility and site identification considerations include:**

- Pre-identification
  - Academic institutions, specialized centers, pediatric hospitals
  - Genetic testing
- Thorough understanding of epidemiology/ demographics & disease inheritance patterns
- Familiarity with current standard of care
- Availability of diagnostic & therapeutic resources (country and regional)
- Start-up processes
- Study-specific recruitment plans
- Site training

## PATIENT RECRUITMENT & RETENTION

Site databases are usually the primary source of potential subject pre-identification, including information on genetic testing and biopsies. Leveraging site databases to pre-identify potential subjects will allow for efficient enrollment optimization. Partnering with an institution's pathology department is key because often – especially for biopsy-proven diseases – all avenues lead to the pathologist. As such, this partnership is fundamental in helping to identify potential cases, thereby maximizing the pool of potential study participants.

Following site selection, the development of a recruitment plan allows the teams to evaluate any challenges to individual participation. Collaboration with patient advocacy groups, which have an abundance of information, can significantly enhance study awareness and understanding – which can lead to an increased site and patient interest. It is important to understand individual patient concerns and to be prepared to assess and address them, such as the psychological considerations in the setting of those that suffer from the disease. Additional key considerations related specifically to IP include ensuring proper site and subject IP storage, and also the impact of IP administration (e.g., route and timing), which can influence compliance.

The provision of travel and lodging, home health nursing, and properly describing the key procedures to the patient in a way that he or she will understand, as well as the sequencing, timing, and frequency of evaluations are all important considerations from the patient perspective.



## Key patient recruitment and retention considerations include:

- Site database as main source
- Pre-identification/pre-screening
- Site-specific recruitment plans
- Patient advocacy groups
- Assess/address individualized issues
  - Psychological considerations, family, social dynamic, scheduling, transportation, IP delivery, compliance, storage
- Travel/lodging
- Home health nursing
- Establishing study procedure sequencing
- Minimize patient discomfort
- Timing/frequency of evaluations
  - School, work, family schedules
- Regulatory timelines



## ETHICAL

Studies in rare diseases often encompass pediatric patients, who represent a vulnerable population with dynamic changes. It is imperative that the study team anticipate the complex operational, regulatory, and ethical considerations for pediatric populations, including those raised by both the investigator and the patients' parents.

Studies should be conducted on those who directly benefit from participation in the study. Typically, the study IP is evaluated in older, more fully mature cohorts before evaluation in younger patient cohorts occur. Unless the risk is minimal or the study will yield information that contributes substantially to the benefit of other children with the disorder, it may be difficult to ethically justify studies in young patients when there is no opportunity for the patient to directly benefit. Therefore, these studies require designs that would optimize meaningful outcome data while also minimizing patient discomfort and risk, while also providing notable justification for anything that increases safety risk, including sedation, radiation exposure or invasive procedures.

In general, the minimization of procedures also need to be attempted. Blood volumes for lab sampling must be anticipated, documented, and monitored to ensure compliance with WHO guidelines. Fully informed consent must be obtained from the legal guardian, and patients should assent to participation as determined by ethics committees or local legal requirements. Communication abilities based on age and development will impact both the content of assent documents, as well as the process of conducting the informed consent. The utilization of pictures, videos, and child-friendly demonstrations to help explain procedures to younger children may assist in the successful completion of this process.

The ability to use rescue therapies during the trial, as well as the integration of an open-label extension, will help with the justification of a placebo-controlled design with regard to regulatory approval and will also likely help with patient recruitment and retention.

### Key ethical considerations include:

- Vulnerable population with dynamic changes
- Population enrichment with age consideration
- Optimize outcome data while minimizing patient risk
- Notable justification required for increased safety risk
  - Sedation, radiation, invasive procedures
- Minimization of procedures
- Compliance with WHO guidelines regarding blood volumes related to labwork
- Informed consent/assent
- Communication differences
- Rescue therapies & open-label extension

## REGULATORY

Orphan drugs are held to at least the same evidence-based standards as non-orphan drugs in the approval process. Two common reasons for a clinical hold from the FDA perspective are patient exposure to unreasonable and significant risk, and insufficient information to assess that risk. Common safety considerations include sufficient characterization of the drug or the biologic and having sufficient pre-clinical or non-clinical data such as animal toxicology which is important.

The successful translation of regulatory and ethical standards to study conduct requires a comprehensive understanding of the unique concerns raised by ethics committees, investigators, parents, and the patients themselves.

Timelines for ethics committee reviews may be prolonged if the rigor of their review is unanticipated. For example, ethics committees may want to involve pediatric experts if the committee does not have a member that is one. They also may request to involve investigators who are experienced in working with children, especially if the study is not run at a site specializing in pediatrics.

Ethics committees will inspect patient documents such as the ICF and other patient items, and they may require the involvement of a specific pediatric committee in the process. In order to decrease the potential for protracted negotiations or deficiencies, knowledge of the previous experiences with each site and discussing the review process with expectations with the Investigator before submission is key.

### Key regulatory considerations include:

- Orphan drugs held to same evidence-based standard as all others
- Common reasons for clinical hold [FDA]
  - Subject exposure to unreasonable and significant risk
  - Insufficient information in IND to assess subject risk
- Common safety considerations
  - Characterization of drug/biologic (CMC\*)
  - Sufficient pre or non-clinical data (e.g., animal toxicology)
- Local IRB/special ECs vs. central IRBs
- Ethics committee reviews
  - Pediatric expertise
  - Document review including ICFs
  - Previous site experience

## SAFETY MONITORING

Safety monitoring is one of the most fundamentally critical aspects of clinical trials, especially with regard to vulnerable populations. As such, safety aspects in rare disease clinical studies must consider several parameters regarding this unique patient population. This includes lab monitoring for critical and conditional alerts that are nuanced for both the age group being studied, as well as the underlying kidney disease so as to capture potential issues early before they become critical. The study and population-specific lab alert flagging can be used as additional layers of subject protection by providing study-specific safety guidelines to investigators with provisions for additional diagnostic evaluation, such as background medication and diet review, IP interruption or withdrawal, and/or the use of rescue medications.

Considering the unique physiology of the patient population, including an understanding of the common comorbidities and the interaction of these conditions in the context of the IPs mechanism of action, as well as the different age groups that are often more susceptible to particular toxicities due to age-related changes and physiology is key. Lab and vital sign ranges may need to account for the age, gender, and height and weight adjusted norms, as necessary.

Ensuring that sites have adequate study equipment for assessments such as appropriately sized blood pressure cuffs and scales that are correctly calibrated also requires proper review. All of these considerations allow for

\*CMC = Chemistry, Manufacturing, and Controls



---

the anticipation of potential adverse effects, which in turn ensure rapid detection of safety signals and would need to account for study-specific parameters. Those parameters should address the needs of all cohorts and be interpreted appropriately in the setting of normal physiology.

Automated calculations of percentiles and z-scores for parameters such as weight, height, velocity, and BMI parameters, using EDC programming are very helpful for ensuring the accuracy of data and avoiding unnecessary queries. Also, the use of visual analytics programs can help with signal detection with trending, especially when reviewing complex data which are typical of lab-heavy studies.

**Key safety monitoring considerations include:**

- Unique patient population considerations
  - Lab monitoring/alerts kidney disease population
  - Physiology, age cohort
  - Age-adjusted considerations/percentiles and references in protocols
  - Appropriate cuff sizes and calibrated scales
  - Study specific
- Rapid AE/signal detection
- Automated calculations
- Visual analytics
- Study specific safety algorithms

## PATIENT PERSPECTIVE

The concept of reviewing the patient perspective in terms of clinical trial design is very important, especially in the rare disease space. One consideration is the burden of trial participation, especially as it relates to addressing individualized concerns, such as the psychological considerations in the setting of those that suffer from the disease. This includes family and social dynamics, transportation assistance requirements, and the impact of IP administration, which can further impact compliance. As such, the provision of travel, lodging as well as home health nursing services are important.

It is imperative that the subject and guardian understand very clearly the study procedure sequencing, including the timing and frequency of evaluations, especially those involving invasive procedures and the number of blood draws. Early involvement of patient representative groups and organizations can be key by helping to evaluate these parameters in the setting of clinical trial development.

Interestingly, expectations for outcomes can be age-dependent. For example, parents of young children may have higher expectations for finding a cure than those of older patients who may be looking at more of an impact on symptomatology, which can affect overall study participation. Similarly, cultural differences can also affect participation, especially as it pertains to the collective view on clinical trials or pharmaceutical companies in general.

Considering the patient perspective on certain trial design aspects is important. For example, patient age can be a limiting factor for study recruitment if PK analyses with multiple blood draws are a requirement for all patients, rather than obtaining samples from a representative proportion. The use of placebo in certain instances may hinder recruitment unless an open-label component is available, or potentially utilizing an open-label sequential design where subjects can act as their own control. Also, comparisons to registries are an option which require confirmation that the appropriate amount of data is available for propensity score matching.

Lastly, while ensuring appropriate clinical trial duration to achieve an appropriate outcome is crucial, it is not uncommon to find trial subjects requesting a longer duration, which is an added advantage of an open label component.

**Key patient perspective considerations include:**

- Consider burden of trial participation
- Early involvement of patient representatives, groups, organizations
- Age and culture considerations
- Trial design aspects
  - Eligibility criteria
  - Placebo group vs. registries
  - Procedures [invasive]
  - Outcome measures



---

## COLLABORATION

Overall, the overarching message is the importance of collaboration, which fundamentally is a key component of clinical trials, especially in the rare genetic kidney disease space.

The collaborative piece must ensure that patient safety needs are considered at the very start of the entire process. Close operational and medical collaboration is fundamental to the development of proactive and contingent planning with streamlined communication to address issues early and ensure trial success. Enough cannot be said about the continued development and application of innovative and flexible solutions, which includes digital and tech opportunities, as well as the aforementioned visual analytics, which can help reduce patient and site burden while optimizing safety. Ultimately, patient and site support are fundamental as is the oversight to ensure quality data and endpoint protection.

### Key collaboration considerations include:

- Therapeutic and scientific leadership throughout the program
- Patient safety
- Proactive planning
  - Contingency planning
- Regulatory guidance and support
- Streamlined communication
- Practical, innovative, flexible solutions
  - Digital innovations/enhancements
  - Apps
- Patient and site support
- Trial oversight
  - Endpoint protection and data quality
  - Analysis

## FULL-SERVICE CLINICAL DEVELOPMENT

Medpace is a scientifically-driven, global, full-service clinical contract research organization (CRO) providing Phase I-IV clinical development services to the biotechnology, pharmaceutical and medical device industries. Medpace's mission is to accelerate the global development of safe and effective medical therapeutics through its high-science and disciplined operating approach that leverages local regulatory and deep therapeutic expertise across all major areas including oncology, cardiology, metabolic disease, endocrinology, central nervous system and anti-viral and anti-infective.

