WHITE PAPER

IDENTIFYING CRITICAL CHARACTERISTICS IN A RARE DISEASE CRO PARTNER

A QUESTION-FIRST APPROACH TO OPERATIONALIZING RARE DISEASE STUDIES

ATLANTIC RESEARCH GROUP

INTRODUCTION

Rare disease studies are complicated because they include a relatively low number of patients, whose evaluation and treatment can be challenging due to wide variations in sign and symptom presentations. Even locating and retaining enough rare disease patients to power a study is often difficult, as they can be widely and thinly dispersed. Success is determined by a group of partner experts collaborating to ask the right questions that anticipate unique problems and generate appropriate solutions both before trials start and as they are being executed. This paper is a guide to critical questions to ask and best practices to employ when selecting a CRO to operationalize rare disease clinical trials. The answers identify a set of critical CRO characteristics that will mitigate the unique challenges of rare disease studies:

- Experienced
- Flexible
- Engaged
- Transparent
- Patient-Centric
- Value-Driven

IS THE CRO EXPERIENCED IN MANAGING RARE DISEASE CLINICAL TRIALS?

Experience in several therapeutic areas is very valuable but even more important is the capacity to think about each project individually and plan each study for optimization. Over time, an effective rare disease CRO will mature by creating deep relationships with a vast network of rare disease stakeholders, finding ways to get things done with no preexisting roadmap, and adapting to unique study circumstances.

Look for a CRO that creates an atmosphere of curiosity regarding rare disease trials. Forward-thinking CROs gather the leading experts in rare diseases and host regularly scheduled roundtable discussions to discuss emerging trends and issues, fostering a spirit of innovation. Partnerships extend through the rare disease space from thought leaders all the way out to patient advocacy groups. Many patient organizations act as consulting partners, providing insights into study design, data collection, and analysis (1). Advocacy groups become outspoken advocates for desirable treatments in discussions with the FDA. Compelling patient testimonials at an FDA Advisory Committee Meeting on droxidopa played a role in the approval of NORTHERA (2).

A rare disease CRO with experience adapts by thinking disruptively at times. In one recent study, a CRO felt that patient recruitment would work better in reverse and employed a “patient-hunter” model. Instead of the traditional site-then-patients approach, patients were initially identified via specialty pharmacy and other channels, then qualified investigative sites were opened around them. The result was that patients were recruited in nine months versus the planned 24.

"Look for a CRO that creates an atmosphere of curiosity..."

SUMMARY KEY QUESTIONS:

- **DOES THE CRO LEVERAGE AN EVER-EXPANDING NETWORK OF RELATIONSHIPS?**
- **DOES THE CRO DEMONSTRATE THE CAPACITY TO BE EFFECTIVE WITH NO BLUEPRINT?**
- **DOES THE CRO ADAPT TO UNIQUE STUDY CIRCUMSTANCES?**

IS THE CRO FLEXIBLE ENOUGH TO MEET TRIAL REQUIREMENTS?

In an ongoing clinical study of a drug for a rare eye disease, one CRO has demonstrated the traits of being agile and nimble. The condition presents with blinding fibrous membranes growing under childrens' eyelids. In the study, a small number of patients were treated at two large referral centers in the U.S. and Europe. The first interim analysis revealed an issue: measuring membranes manually on squirming children produced inconsistent readings between sites, and even from the same patients at different visits (3).

The potential for wide variability in readings was not anticipated in the protocol, given the lack of an established scale for fibrous membrane growth. The CRO innovatively implemented the use of digital photography at every patient visit. Additionally, a central reader was brought in to evaluate the images, measuring the lesion areas electronically.

The resulting data enabled a robust statistical analysis, supporting the study's original lesion mass reduction endpoint. The data highlighted differences in baseline disease states between the eyes of many patients and separate treatment responses. Analyzing eyes separately effectively doubled the study sample, which was initially defined as individual patients rather than individual eyes. This yielded an unexpectedly detailed and valuable understanding of the relationship between disease severity and treatment response. It was all made possible because of the CRO's capacity to improvise.

"...one CRO has demonstrated the traits of being agile and nimble."

SUMMARY KEY QUESTIONS:

- **DOES THE CRO ADJUST BASED ON UNIQUE RARE DISEASE STUDY CONDITIONS?**
- **DOES THE CRO ADDRESS CHALLENGES VIA ANTICIPATION AND ADAPTATION?**
- **DOES THE CRO COLLABORATE TO FURTHER AND RESHAPE BEST PRACTICES?**

IS THE CRO ENGAGED ENOUGH TO SERVE AS A TRUE PARTNER?

Rare disease projects require constant adjustments; therefore, continual engagement is necessary. CROs must value and recognize the importance of team chemistry and work decisively to foster team cohesion at all levels of the study team. Sponsors should search for a CRO with the knowledge, resources, and energy necessary to manage difficult projects-- and an accompanying collaborative and attentive mindset.

Seek out a strategic partner rather than just an implementer. A CRO that is dedicated and committed to each study can see multiple angles and offer real solutions. In addition, look for a CRO that takes the time to think and engage in open and meaningful discussions. Finally, the CRO must recognize that the sponsor is the key driver of the trial so the intention must be to walk with them to answer the questions they outline.

CRAs taking ownership of a study is a clear demonstration of engagement. The industry's typically high CRA turnover rate and checklist-driven monitoring style can be toxic to the investigators who are passionate about helping patients. Trusting relationships with CRAs should be fostered, facilitated by empowering them to schedule visits, as well as requisition supplies on an as-needed basis. Policies that promote continuous CRA skill-building and back CRA decision-making in the field should be developed and followed. Engagement at all levels of the study is crucial.

"Seek out a strategic partner rather than just an implementer."

SUMMARY KEY QUESTIONS:

- **DOES THE CRO NOTICE DETAILS TO DRIVE SOLUTIONS TO PROJECT CHALLENGES?**
- **DOES THE CRO ENGAGE IN MEANINGFUL COMMUNICATION WITH STAKEHOLDERS?**
- **DOES THE CRO TRUST AND EMPOWER ITS CLINICAL STAFF ?**

IS THE CRO TRANSPARENT ENOUGH FOR VISIBILITY INTO ITS PROCESSES?

True project collaboration is predicated on genuine transparency-- and this means more than simply open communication. It is about talking specifics, exchanging ideas, and providing experienced feedback at every step along the journey. The end result for sponsors is enhanced and measurable value in their clinical trials. Seek a CRO that is cost-conscious, financially responsible, and considerate of budgets, yet understands and clearly communicates how additional activities could add value and reduce time to market. The costs, both financial and operational, from ever-increasing study complexity are high. In 2012, US pharmaceutical developers incurred an estimated $4 billion to $6 billion in direct costs on procedures not related to clinical study primary or secondary endpoints (4). Error rates also rise in proportion to protocol complexity (5), which increases data management costs, delays database lock, and can threaten the integrity of study results.

Visibility begins with flexible and transparent contracts and budgets. Sponsors must completely understand what they are paying, and have clarity in terms of project assumptions and the change-order process and triggers. At the end of site selection, feedback should be furnished on strengths and weaknesses and assistance as needed should be offered. The CRO should be continually aware of the importance of hitting milestones along the way, and maintain transparency through clear, up-to-date communication on timelines, costs, protocols, and enrollment goals.

Beyond updates, a robust medical protocol review must be conducted in order to be as safe as possible for patients, address a clear research question, yield the information needed to meet regulatory requirements, and be usable by investigators in the field. A rare disease focus provides insights to partners regarding disease processes and specific patient populations. It also helps eliminate potential logistical issues (such as scheduling labs and diagnostics) as well as problems that interfere with patient participation (such as difficult-to-open medication packages). Coordinating protocol feasibility in a collaborative fashion between all support functions is important to mitigate the occurrence of alterations with unanticipated implications. In the end, every aspect of the study must be transparent.

"Visibility begins with flexible and transparent contracts and budgets."

SUMMARY KEY QUESTIONS:

- **DOES THE CRO PROVIDE LINES OF SIGHT INTO COST AND TIME PREDICTABILITY?**
- **DOES THE CRO FOSTER FEEDBACK FOR CONSTANT TRIAL IMPROVEMENT?**
- **DOES THE CRO USE COMMUNICATION TO REFINE PROCESSES AND ADDRESS CHALLENGES?**

DOES THE CRO KNOW THE ULTIMATE GOAL IS HELPING THE PATIENT?

The primary goal of the CRO is to improve and prolong the lives of the people affected by rare diseases through the clinical trials they manage. The realization of a patient-centric approach is accomplished by carefully cultivating relationships, fostering meaningful communication, and anticipating and addressing all of the challenges and details of studies. Seek out a CRO that best leverages longstanding partnerships. A CRO with a home health care network partner arranges in-home visits by a study nurse to administer drug-infusions, perform blood draws, or execute other clinical tests. These visits help further patient centricity by easing the challenges of long-distance travel.

There are unique issues when working on rare disease and decentralized clinical programs. The ideal rare disease CRO takes a novel approach and employs the use of innovative study management models to best serve the patients. One example is a “study champion” that acts as a direct liaison between the investigator, home health nurse, central laboratory, and sponsor-- providing amplified organization, engagement, and motivation. Rare disease clinical development often involves children, which introduces regulatory, operational, and ethical issues that can complicate recruitment and retention. Patient safety must be the rare disease CRO’s number-one priority. Protocols require careful collaboration with experts and other regulatory bodies to minimize trial burden and risk.

Patients should be supported throughout the journey all the way to the trial conclusion. Look to formulate easy-to-reference visit schedules so patients understand their commitments. Patient-friendly terminology can help relieve unintentional linguistic barriers too. Find a CRO that takes into account that rare conditions often create disparities in income and employment status, which are compounded by the expense of medical care and lifestyle adaptations. Every patient deserves to be well regardless of the rarity of the disease.

"The ideal rare disease CRO takes a novel approach."

SUMMARY KEY QUESTIONS:

- **DOES THE CRO NURTURE RELATIONSHIPS WITH RARE DISEASE STAKEHOLDERS?**
- **DOES THE CRO INNOVATE WITH UNIQUE STUDY MANAGEMENT MODELS?**
- **DOES THE CRO UNDERSTAND AND ADDRESS HUMAN FACTORS?**

DOES THE CRO VALUE EVERY SINGLE PATIENT?

Every patient counts. While large-scale intricately-designed studies can afford to lose patients, clinical trials for rare patient populations are not buffered for atrophy. Sponsors should look for a rare disease CRO that emphasizes that every patient is vital; in fact, they should place the utmost importance on every data point in every study.

Rare diseases require heightened attention to detail in recruitment. Find a CRO that focuses on specifics, anticipates impediments, and addresses challenges. The movements of patients between offices or lab facilities must be taken into account. The time realistically needed to travel could exceed the intervals for sample collection specified in the protocol, resulting in built-in protocol deviations. If that possibility is seen in advance through a meticulous protocol review, something will be done and every patient will be valued.

Once patients are enrolled, the CRO must continue to stress communication, providing off-hours coverage, rapid turnaround times, and multiple capture channels, including phone, email, and electronic health record portals. The best way to value every study detail is to focus on all of them equally, regardless of apparent scope and seeming significance. The rare disease CRO must find out what kind of centrifuge is used, where lab and other needed ancillary services are located, and when and how they can be accessed by research staff conducting protocol-mandated procedures. Every last detail is crucial.

"...look for a rare disease CRO that believes every patient is vital."

SUMMARY KEY QUESTIONS:

- **DOES THE CRO KNOW EVERY PATIENT IS VITAL IN RARE DISEASE RESEARCH?**
- **DOES THE CRO FOCUS ON EVERY CRUCIAL DETAIL OF A PROJECT?**
- **DOES THE CRO REALIZE EVERY TRIAL IS IMPORTANT REGARDLESS OF SIZE?**

MOVING FORWARD BY POSING THE KEY QUESTIONS

Rare disease clinical trials require innovative thinking and savvy adjustments along the way. There is often no standard trial design or formula for rare disease study success. Rare and orphan disease trials may be rife with challenges, but they are also the most rewarding projects. Working with a CRO with extensive experience in and an understanding of rare disease drug and device development can efficiently alleviate many of the barriers that can stand between patients and much-needed therapies. In the end, the best way to locate a rare disease CRO is to ask questions about their critical characteristics, finding one that is experienced, flexible, engaged, transparent, patient-centric, and value-driven.

"...the best way is to ask questions about their critical characteristics."

References

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(2) FDA. Summary minutes of the Cardiovascular and Renal Drugs Advisory Committee Meeting. January 14, 2014. Retrieved from http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM396029.pdf.

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About Atlantic Research Group, Inc.

ARG is a rare disease-focused contract research organization that provides comprehensive clinical program development services ranging from pre-launch consulting to commercialization. Founded in 2004, ARG has experienced consistent growth across the globe, expanding our reach to include drug and device trial management in diverse and wide-ranging therapeutic areas. ARG has remained true to our original vision: every project is highly significant and visible, delivered through strategic collaboration with partners. ARG is rare for a reason: we successfully operationalize orphan development projects because we believe everyone deserves to be well.

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