WHITE PAPER

Optimizing Evidence Generation in Rare Disease Studies with Patient-Centric Strategies

Addressing study challenges with real-world solutions

UBC

The Unmet Need for Rare Diseases

Most rare diseases are serious, complex, and life-long and can be permanently disabling and/or life-threatening. For persons with rare disease(s), the diagnosis journey takes an average of 4-5 years and includes multiple medical consultations[1] (Figure 1).

Historically, research and development of therapeutics for rare diseases was considered financially prohibitive based on the small market size; however, progress has been made with support coming from various incentives including additional patent exclusivity, research subsidies, tax credits, and research grants. In 2021, the FDA proposed guidance on Individualized Antisense Oligonucleotide Drug Products for severely life-threatening genetic diseases[2] and, in 2022, launched the Accelerating Rare diseases Cures Program (ARC)[3]. Through these and other efforts, about 800 therapies were in development for rare diseases in 2021.

Still, 95% of rare diseases do not have disease-specific therapy[4]. This is due, at least in part, to small patient populations and ethical considerations that often make placebo-controlled studies difficult or impossible. However, the challenge of low patient numbers can be overcome. This white paper will address two broad strategies that can be implemented when planning begins early in product development: 1) methods for optimizing patient identification, recruitment, and retention and 2) incorporation of Real-World Data (RWD)/Real-World Evidence (RWE) into evidence generation strategies.

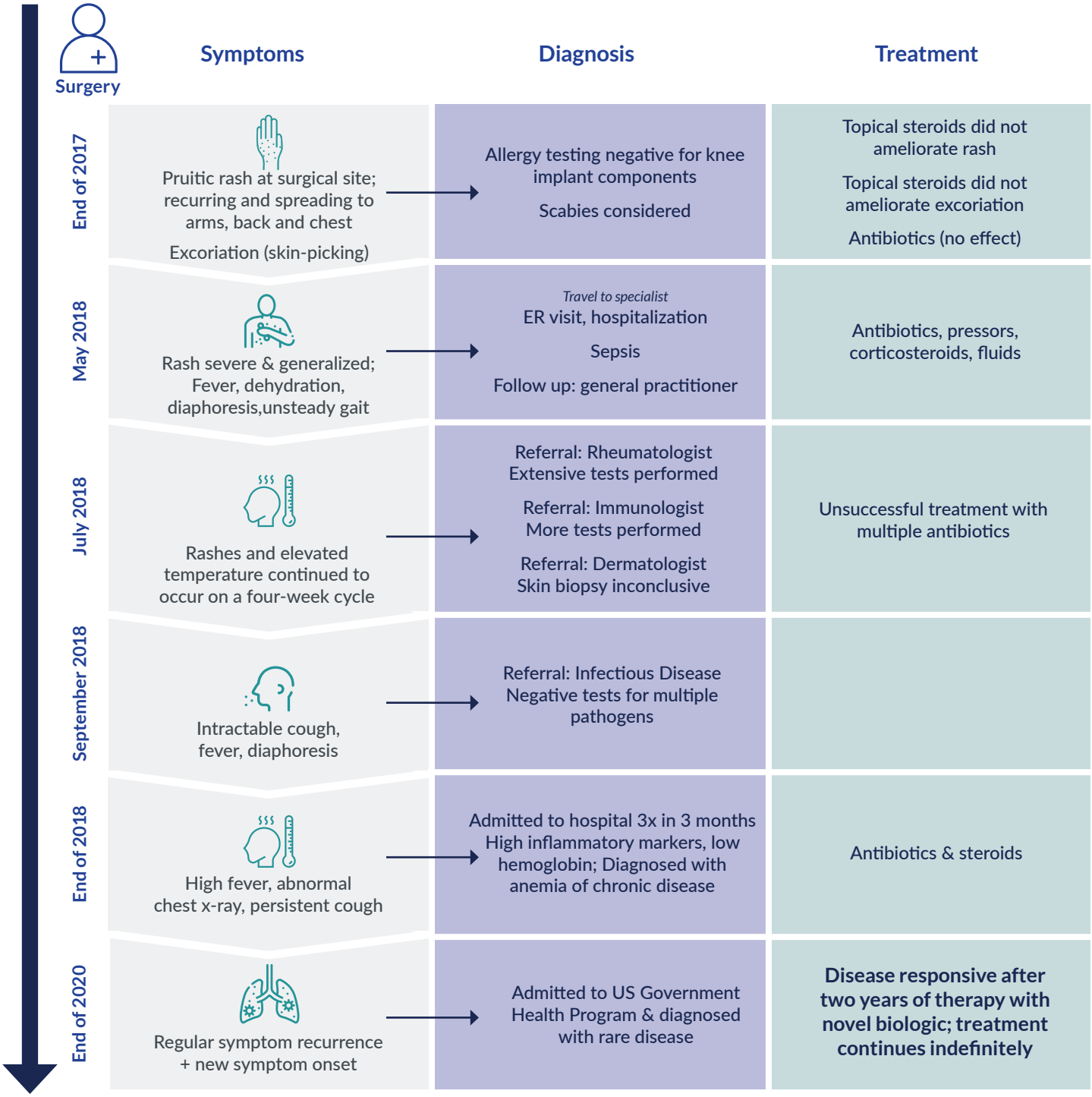
INCIDENCE & PREVALENCE

In the United States, a rare disease is defined as one that occurs in less than 200,000 people[5-6]. Approximately 84.5% of rare diseases evaluated have a point prevalence of less than 1 in 1 million[7-8]. With an overall rare disease prevalence of <650 people per million[9], 25-30 million people in the US, or about 10% of the population, have a rare disease[4]. Nearly 80% of the population disease burden is currently contributed to by 4.2% of rare diseases[10]. The US NIH-Genetic and Rare Disease Center (GARD) indicates there are now ~10,000 diseases qualifying for rare disease status[11], an increase from the 7,000 referred to in the Rare Diseases Act[12]. With enhanced testing capabilities, about 250 rare diseases are being added per year[8].

About 80% of rare diseases are genetically based, and about half of all rare diseases manifest in the pediatric population[13]. Some rare diseases occur at a far lower incidence and are referred to as ultra-rare diseases. Some of these ultra-rare diseases may have less than 100 known cases in the US or globally and are often genetically inherited[14].

FIGURE 1: The Symptomatic, Diagnostic, and Treatment Journey of a Patient with Yao Disease

Diagnosis is often a process of elimination from other diseases that present similarly. Specific diagnostic tests may not be available or may require that testing is performed in a special research laboratory. Various treatments may be tried. Many patients receive the best available supportive care (e.g., oxygen, physical therapy, alimentation), providing symptomatic relief, but not modifying the underlying disease. Off-label treatments may be considered, but third-party payors may not reimburse the treatment. Often the high cost of an intervention is not considered in the context of mitigating other costs which may recur on an ongoing basis without therapy.



Leveraging Real-World Data to Optimize Patient Identification, Recruitment and Retention

Clinical studies offer an opportunity for patients to receive treatments to slow disease progression and improve quality of life. However, there are too few patients in the US or globally to conduct the typical large, randomized controlled trials that are considered the gold standard for drug approval. The number of patients required for a study would need to approach 100% of the patient population in many diseases. Furthermore, many genetically based diseases have variants, so patients with a disease of interest may not meet criteria for inclusion in a study. One solution for identifying eligible patients is to leverage RWD (including claims databases) to identify healthcare providers. Patient and provider outreach solutions that are geo-targeted can then be developed. In many cases, however, a physician may be treating only one or two patients with a rare disease. Unlike most traditional clinical trials, patient recruitment for a rare disease study may begin by first identifying patients and, through them, their treating physicians.

For some rare diseases, patient cohorts or registries have been established, and patients can be identified through registries in which they are enrolled. Often, however, these registries are small and not connected to one another. The registry may be owned by a national agency, an advocacy group or an academic center or consortia. The ideal situation would be to integrate disparate registries into a universal registry, which can be linked to other sources of patient medical information for a deeper, longitudinal view of the registries and integration with other sources of RWD (e.g., electronic medical records, claims) is often needed to gather enough information about outcomes that occur infrequently. Patient data can be de-identified and aggregated, and duplicates can be identified and removed, particularly as patients with a rare disease often see multiple providers.

But even then, not all patients are enrolled in registries. Another solution is to develop close ties with patient advocacy groups, and to collaborate with physicians, specialists and specialized research consortia to raise awareness about clinical studies and provide opportunities to identify and engage patients and investigators. Considering the importance of identifying as many patients with the rare disease as possible, engaging patients early and often (e.g., through advocacy organizations) in the drug

development process is vital. Sponsors should start with a deep understanding of the disease, patient journey, and the caregiver or care-partner impact and concerns. With this understanding, the needs of the patient can be addressed in a protocol design that captures the patient's or caregiver's perspective, disease progression, symptom variability and patient mobility.

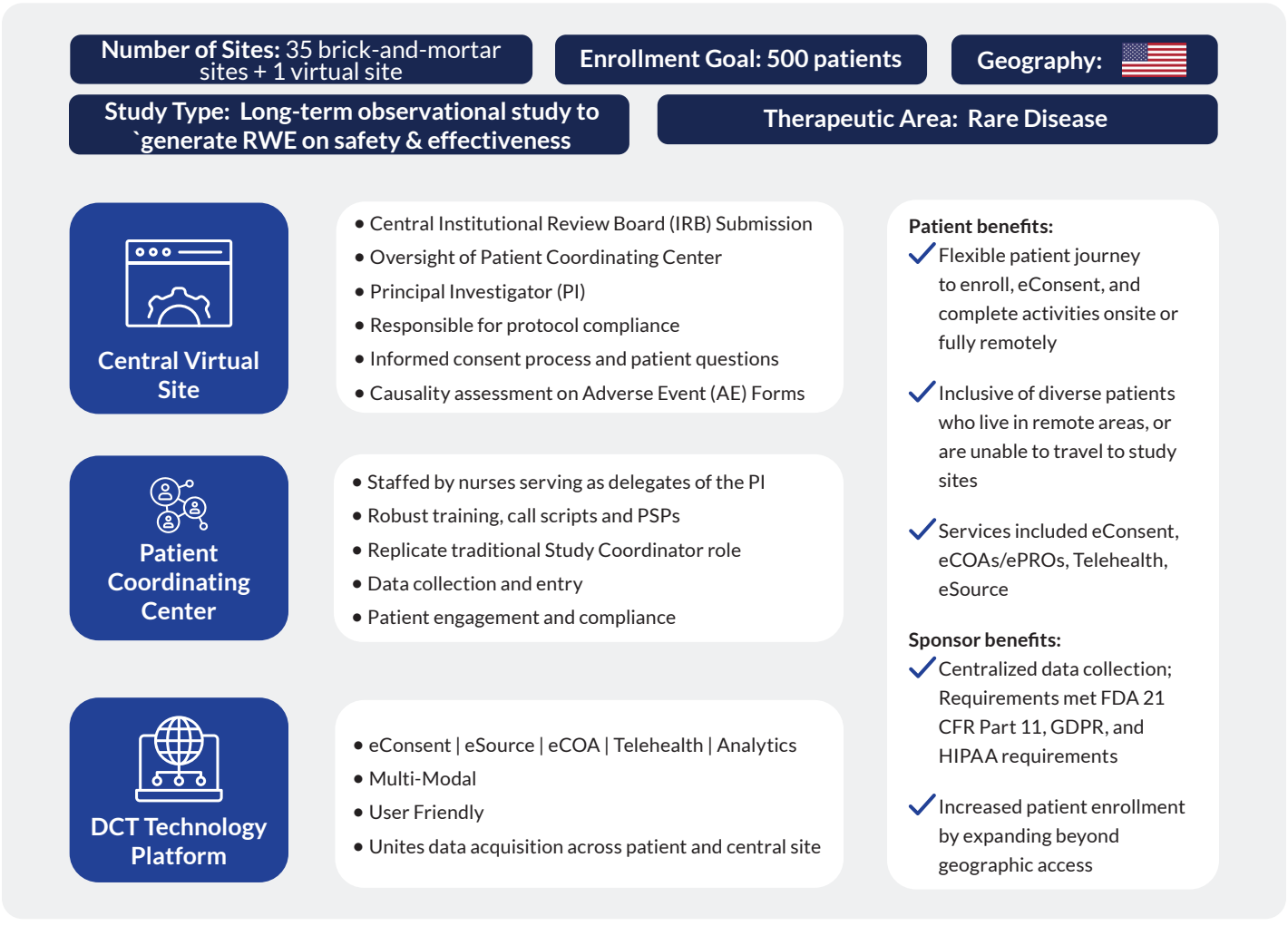
Incorporating decentralized study elements (including web- or app-based forms, remote monitoring, in-home nursing, and telehealth options) into the design allows patients to participate in studies remotely for some or all study activities (Figure 2). This approach also dramatically expands the addressable patient population; moving beyond the limitations imposed by geographic proximity of a fixed number of traditional brick and mortar sites; and provides the opportunity to enroll a larger and more diverse patient population[14].

When patients with a rare disease are identified and are eligible to participate in a study, they often enroll because there are no or limited usual care options. Therefore, care must be taken to ensure risks versus potential benefits are clear and acceptable from an ethical perspective. By addressing any challenges within the population under study, as well as the concerns of patients and their care givers, protocol adaptations can be made to make participation less burdensome and optimal for patient recruitment and successful study participation.

Once patients with a given rare disease are identified and recruited, retention becomes paramount. To maximize patient retention, it is important to:

- **Set expectations upfront during the informed consent (ICF) discussion.** Tools like ICF flip charts or animated videos that use patient-friendly language can clearly explain the purpose of the study, risks of participating, importance of the patient's participation and address common concerns.
- **Address logistical barriers by providing transportation or accommodations.** Participating in a clinical trial is a major commitment for patients and their families and should be made

Figure 2. Case Study Incorporating Decentralized Study Elements into a Real-World Observational Study[16]



as easy as possible. With limited treatment options currently available for the majority of rare diseases, patient continuation in a clinical study may become less dependent on patient motivation and more dependent on logistical challenges. Patients with a rare disease often need to travel long distances to participate in study visits and by alleviating the logistical and financial burden related to these nonmedical considerations, there is increased likelihood for patient enrollment and retention.

- **When possible, allow for care and support in the patient's home environment.** Patients with a rare disease face challenges that are linked to the nature of their condition. As discussed above, decentralized approaches allow for care and support in the patient's home environment.

RWE is Emerging as a Strategic Tool in Rare Disease Evidence Generation

RWD and data-driven insights can improve understanding of disease prevalence at a global level. RWD has also been used historically to inform clinical study design, as well as in post-marketing surveillance and in drug safety monitoring to detect adverse events (AEs).

More recently, there is growing enthusiasm for the role that RWD and RWE are playing to support regulatory decision-making in the rare disease space, including for purposes of demonstrating safety and efficacy. This occurs most as RWD-generated external controls in single arm trials[17], but only when the natural history of the disease is well-understood[18]. With low patient numbers, and ethical considerations making placebo-controlled studies unacceptable, such externally controlled trials may be considered suitable in rare diseases. Sponsors are, however, encouraged to engage the agency early. The recently released draft FDA guidance on externally controlled trials largely discourages the use of external controls *post-hoc*, and encourages prespecified study designs, data sources, and data analytics approaches[18].

Several recent publications show how RWE is being leveraged to support evidence requirements for regulatory activities[17,19-21]. From an external stakeholder perspective, RWE is currently being utilized to address the needs of regulators, payers, providers, and patients[22]. Since the FDA published their real-world evidence (RWE) framework in 2018[23], the agency has approved at least 14 applications incorporating RWE to support efficacy, with all approvals going to products for orphan diseases[24]. As the industry and regulators continue to evolve the role that RWD/RWE can play, it is becoming evident that RWD/RWE can contribute in a meaningful way when data are fit-for-purpose and studies are well-designed *a priori*.

In a recent press release, CDER's ARC program reported that one of their aims this year is to "support platforms that facilitate rigorous use of data for natural history studies and other RWD[3]." Natural history studies can elucidate demographic, genetic, environmental, and other variables that correlate with the disease's development and outcomes[25]. With so few patients, there is little-to-no published natural history information describing disease progression in many rare diseases, resulting in a lack of understanding of standards of current care, treatment guidelines, and endpoints/outcomes on which to base an assessment of therapeutic effect and adverse events. Such gaps can impact the ability to define study measures to show outcomes of an intervention or identify appropriate clinical outcome assessments. Given the time and cost to conduct a natural history study, these studies must be carefully designed to be fit-for purpose.

Planning Your Real-World Evidence Strategy

There exists a great need to bring medicines to rare disease patient populations. Significant hurdles have made it challenging to enroll patients in studies and to better understand disease natural histories that can greatly inform care. Modern patient-centric technologies and RWD-driven approaches can help the industry overcome those challenges.

It is vital to develop customized solutions that support optimal patient identification, recruitment, and retention. Collaborating with patient advocacy groups across the rare disease community and leveraging data-driven solutions are critical tactics in successful patient recruitment and retention for rare disease clinical trials. Furthermore, planning studies that strategically incorporate RWD can help address evidence gaps that will inform patient care.

When planned early in the product development life cycle, strategies for optimizing patient recruitment and retention and incorporating RWD/RWE as part of overall evidence generation can more quickly help bring needed therapeutics to patients living with a rare disease.

About UBC

United BioSource LLC (UBC) is the leading provider of evidence development solutions with an expertise in uniting evidence and access. UBC helps biopharma mitigate risk, address product hurdles, and demonstrate safety, efficacy, and value under real-world conditions. Bringing over 30 years of experience, UBC is uniquely positioned to develop end-to-end integrated evidence generation strategies, identify fit-for-purpose data sources, operationalize planned studies and ensure regulatory-grade, publishable outputs.

To learn more about how UBC can help develop your RWE strategy for rare disease, reach out to us at contact@ubc.com.

About the Authors

JUDY LYTLE, PHD, MBEE, PMP

Executive Director

Real-World Evidence Study Solutions

Evidence generation strategies, powered by rigorous science, designed to demonstrate value

BRUCE SMITH, PHARMD

Executive Director, Clinical Research

Unique understanding of the real-world landscape in rare diseases, implementation of expanded access programs and clinical studies, and application of real-world evidence to meeting post-marketing requirements

SHAZIA AHMAD

Senior Director, Head of Patient and Physician Services

Patient-centric programs in rare disease, designed to engage and inform patients and caregivers alongside advocacy organizations.

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