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Cardio-metabolic rare diseases: Strategic insights for country and site distribution.

Contributors

JB Flinders, PhD, Senior Director, Strategy and Planning, CVMER
Lillian Dampman, PhD, Senior Director, Strategy and Planning, CVMER
Peter Alfinito, PhD, Executive Director, Strategy and Planning, CVMER

Clinical plan strategies in traditional indications typically incorporate regulatory considerations, cost, investigator access and an assessment of the competitive and reimbursement landscape, but the strategies for rare disease trials are more complex. To help drug development sponsors run efficient cardio-metabolic rare disease studies, this white paper shares key operational considerations and describes the use of proprietary tools and processes combined with information in the public domain to support both country and site selection.

Understanding the unique differences in rare disease trials

Rare disease trials must focus on a distinct set of variables centering on experienced and dedicated sites that specialize in these research areas; cost and regulatory variables are of less importance. Traditional cost-focused strategies, such as including a minimum of five sites per country and only including regions with multiple strong-enrolling countries are obsolete in rare disease trials, as many rare diseases encompass relatively few experienced sites. In some cases, single centers may function as a referral network across a region, necessitating unique patient retention techniques in a trial. Casting a wide net to provide for the full breadth of patient access is essential, including the consideration of smaller site numbers per country as compared to more traditional indications.

Reviewing country-specific considerations in site selection

In many cases, site identification is driven by country-specific details. Within a global CRO like Fortrea, country leads and internal subject matter experts (SMEs) review protocol details, standard of care by country and endpoints to confirm the protocol maximizes rare disease patient availability. Medical and strategy SMEs also contact their network of key opinion leaders and sites to add depth to the recommendations. Finally, internal quality information and recruitment metrics are interrogated from previous trials of similar design to narrow in on countries for consideration. These countries will often have a set of experienced sites that can harness local prevalence to create robust databases of patients. Sites that can quickly interrogate databases, or use a multi-faceted system of advertising, can increase the chances of successful research outcomes.

CROs devote time and energy to building site partnerships. These common linkages create advantageous relationships by promoting mutual respect and a shared desire for success. When a CRO finds an experienced site partner with strong patient access, the site can benefit from the CRO partner's full-service support, which includes regulatory expertise and patient retention strategies. Together, the site and CRO can combine their skills to deliver timely completion of study objectives.

Maximizing recruitment potential of rare patients with data

Another useful method for site identification involves incorporating laboratory testing values to hone in on rare disease patient locations. We utilize powerful analytical solutions and access timely, real-world diagnostic data, global investigator performance metrics and insights reported by patients that enable us to deliver faster patient enrollment and enhanced patient retention. Given that many rare disease diagnoses require testing to define the appropriate patient population, either the tests or the ICD-10 codes can be reviewed to highlight patient locations.

With ICD diagnosis coding, concentrations of these tests can be mapped and, where available, overlaid with the locations of experienced sites from previous or ongoing trials. Figure 1 below shows an example from a rare thyroid indication trial, where patients with a given ICD-10 code, noted in blue, were overlaid with experienced investigators shown with orange triangles. These data can form an initial site list to narrow in on locations of rare disease providers.

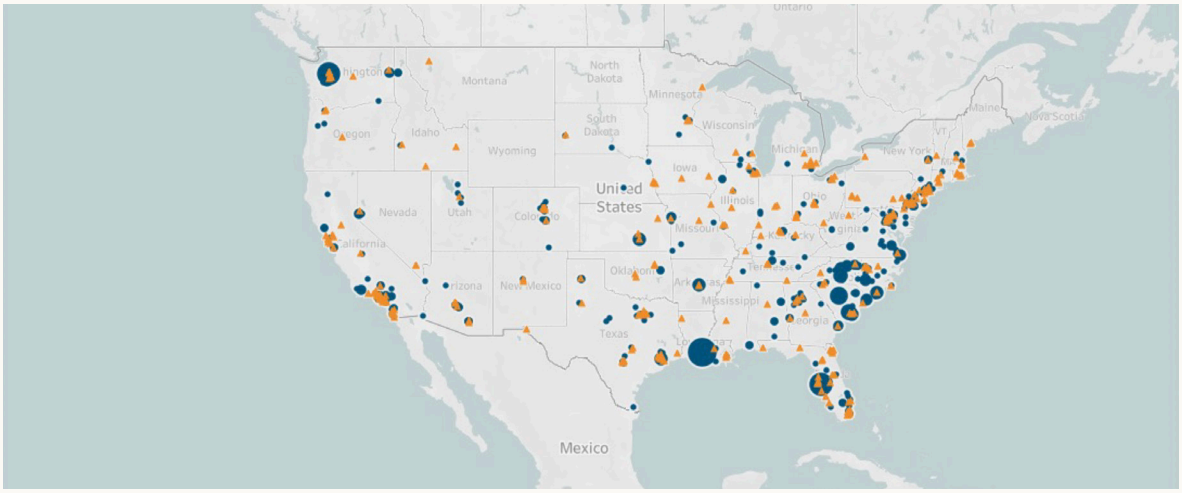

Figure 1: Overlap of experienced research sites with a rare patient population

Even where experienced sites are not available, selecting investigators within clusters of patients can form a referral base to bring additional subjects to a trial (Figure 2). For example, in rare obesity trials, sites that have historical genetic testing databases, or a well-defined testing pathway to newly diagnose potential patients, can be prioritized for selection.

Less experienced sites, or sites without specific testing capacity, may have clusters of similar patients in their databases that could provide additional patient access for a trial. Investigator referral information, or other patient-facing study materials, could be provided to these referral sites to keep potential patients informed and more likely to be included in a trial. Travel reimbursement and other incentives that help patients feel that their time and effort are appreciated can also be incorporated at the site level.

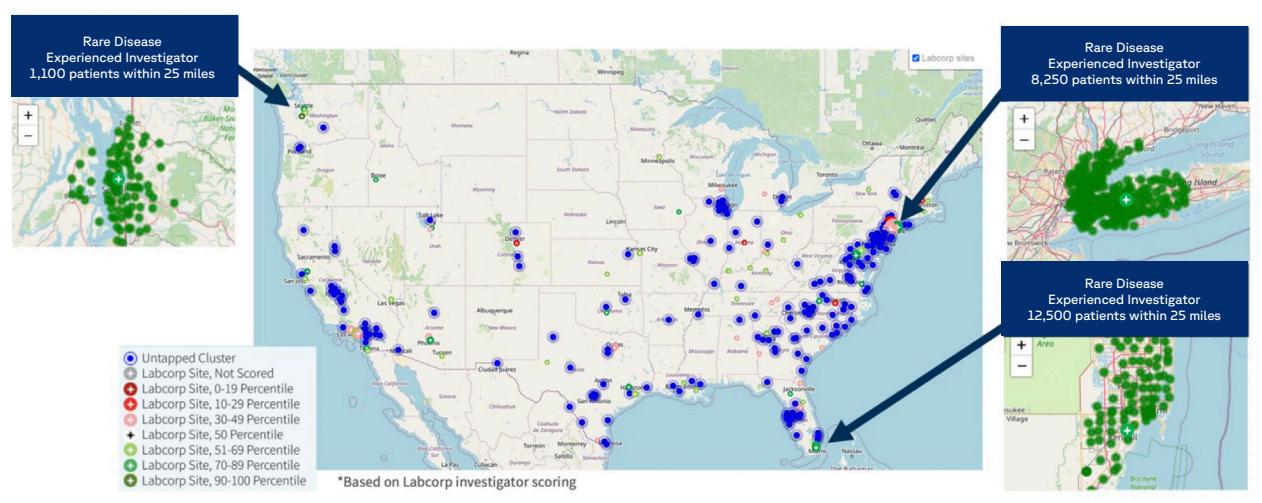

Figure 2: Identifying rare disease populations to facilitate referrals to nearby sites
**Fortrea will maintain exclusive CRO access to the Labcorp data that supports its clinical enabling solutions for a fixed period of time*

Facilitating study conduct with the support of advocacy groups

While companies working in rare disease maintain ongoing site relationships, rare disease patients and their families are also known to local and national advocacy groups. These groups can provide additional site outreach and collaboration. They also serve as collaborative partners, reviewing protocols and study designs, advertising the value of ongoing trials and providing key opinion leader and site access for rare populations. Some sites are hesitant to participate in rare disease trials without the input or approval of the pre-eminent advocacy group in the indication. It is crucial to understand the role these advocacy groups play and incorporate them as needed to ensure the best possible site selection potential.

Promoting patient-centricity with a team approach

The management of rare disease is often a multi-disciplinary approach involving primary care providers, specialists, behavioral health practitioners, ancillary service providers like nutritionists, and even social workers. This team is an integral part of overall care of the rare disease patient, and the access to this variety of practitioners becomes a vital planning piece to site selection for a trial. Similarly, identifying sites with the appropriate equipment, such as DEXA and echocardiography, and applicable licenses for the study drug (if needed) become an integral factor for effective start-up. If sites cannot provide these study considerations, they can serve as a referral site for a more specialized center. Together, these practices can help ensure patients have access to new and innovative treatments through rare disease trials.

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