



# Enhancing recruitment and retention in rare disease trials

In a world with close to 7,000 rare diseases, an estimated 350 million patients and very limited available treatment options, developing medicines to address these diseases can be both exciting and satisfying.

In recent years, the number of orphan designations has increased markedly and reports predict that the global orphan drugs market is expected to grow from USD 201.5 Billion in 2023 to USD 454.8 Billion by 2028<sup>1</sup>. Ongoing support from government agencies, a favorable regulatory environment, comparatively lower development costs, tax benefits and marketing exclusivity all serve to fuel investment and growth in rare disease drug development. However, designing and conducting the clinical studies necessary to deliver treatment registration for rare diseases is not straightforward. It brings distinctive challenges in terms of disease understanding, in a therapy area where information on disease progression is often limited.

There is frequently little previous experience in the field that might inform study design and limited understanding of the requirements regulators may have to review and approve such treatments. Common challenges include identifying and setting up the right sites, recruitment in a restricted and scattered patient population and patient retention, as well as the usual logistical considerations. Clearly, when compared with standard clinical trials, conducting clinical studies in the rare disease space requires an additional skill set and an innovative thought process.

Patient recruitment is essential to the success of any clinical trial, yet nearly 80% of clinical trials fail to meet their enrollment timelines and up to 50% of research sites enroll one or no patients<sup>2</sup>. Similarly, retaining patients in the trials from start to finish is essential to ensuring data reliability and integrity. And yet, more than 85% of clinical trials fail to retain a sufficient number of patients. The average dropout rate across all clinical trials is in the region of 30%<sup>3</sup>. In the world of rare diseases, small patient numbers and having only few key opinion leaders who properly understand the target disease and thus can serve as investigators further complicate the standard challenge of patient recruitment and retention.

Low patient numbers and too few key opinion leaders who properly understand the target disease make patient recruitment and retention challenging. Furthermore, over half of rare disease patients are children, which adds an extra level of complexity to recruitment and retention. Addressing these challenges alone, impacts significantly on the time it takes to get life altering and life saving therapies to the patients who need them the most.

We believe that the first step in ensuring that patients are recruited and retained in rare disease trials is to identify and recruit the most appropriate sites and Investigators. In rare disease trials, Sponsors may not be in a position to define the countries and sites. Rather, they must be open to using those countries and sites where sufficient eligible patients are available for their study. Your trial may require you to use sites based in several different countries spread across the globe, with sites contributing no more than one to two patients. When working with so many different countries and sites, factors such as standard of care, cultural nuances, regulatory context and import/export requirements must be considered carefully.

Planners must utilize all available resources to develop a delivery strategy that will address the various challenges. Resources such as orpha.net, the National Organization for Rare Disorders, the European Organization for Rare Diseases, country specific rare disease organizations and disease specific societies can provide valuable insight into the site identification and selection process. Site selection can be well supported by a CRO partner that understands the complex nature of rare disease trials and has the flexibility and agility to provide tailored solutions.

Once sites have been selected, all possible means of identifying and recruiting patients should be considered in terms of a study's likelihood of success. Every single patient is vital in rare disease trials. Standard approaches such as identifying patients from a database and registries as well as encouraging referrals must be complemented by approaches that may seem out of place in the traditional clinical setting.

These may include data analysis and data mining to locate potential patients, involvement of patient advocacy groups and the use of social media, study specific web sites etc. However unlikely it may seem, no alternative approach should be discarded without due consideration when you are planning to work in the field of rare diseases.

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We can assume that most patients suffering with a rare disease (and their caregivers) have undergone tremendous psychological, physical and financial distress as a consequence of their disease and will have experienced a reduced quality of life.

They most likely face limited life expectancy. It is important therefore to understand the experience and expectations of these patients and their caregivers so that you can engage with them and gain their support in the design of a study protocol that is sensitive to the needs of the patients and their comfort. Many regulatory agencies encourage Sponsors to consider patient involvement in their proposed study design and have enhanced the role of the patient in the process of drug development. It is also essential not to overlook the value that arrangement of travel (for patients and caregivers) and home support for study procedures and/or drug administration can have.

## Study Protocol and Visit Schedule

Study protocols for orphan diseases must be designed meticulously so that they incorporate all the legal and ethical considerations, only involve a reasonable number of invasive procedures, anticipate safety risks and justify blood volumes for pharmacokinetic sampling etc. Such an approach helps to minimize the risk and discomfort for patients while at the same time permitting investigators to collect invaluable data in a practical manner. Study visit schedules and assessments can be intense and demanding on the patient in many rare disease conditions. They can also use up a significant amount of a caregiver's time. Providing for flexibility in the study visit schedule (without affecting the outcome measures) for example around school holiday time for children, etc. can promote better patient retention.

It is important to understand that many rare diseases can also involve a high degree of co morbidities and such patients will often require consultation from multiple medical specialists. Coordination of the broader patient care should be considered while defining study procedures.

## Data Mining and Data Analysis

Organizations that specialize in analyzing health data can combine clinical knowledge with big data technology and techniques that transform petabytes of data into meaningful constructs. In healthcare, 'big data' is being used to map epidemics, predict cures, improve quality of life and avoid preventable deaths.

Our ability to collect volumes of health data present an opportunity for us to gain new insights, learning as much about a patient as possible, as early in their life as possible hopefully, identifying early warning signs of serious illness. By applying proven analytical methods and advanced machine learning algorithms it is possible to reveal complex data patterns and uncover unique and compelling insights that can be useful in the design of future clinical trials for rare diseases. Using real world evidence for specific inclusion/exclusion criteria allows us to determine patient counts, examining competing trials helps us to understand the impact on our trial recruitment and site location while reviewing the most successful key opinion leaders gives us the opportunity to align to locations with high patient populations.

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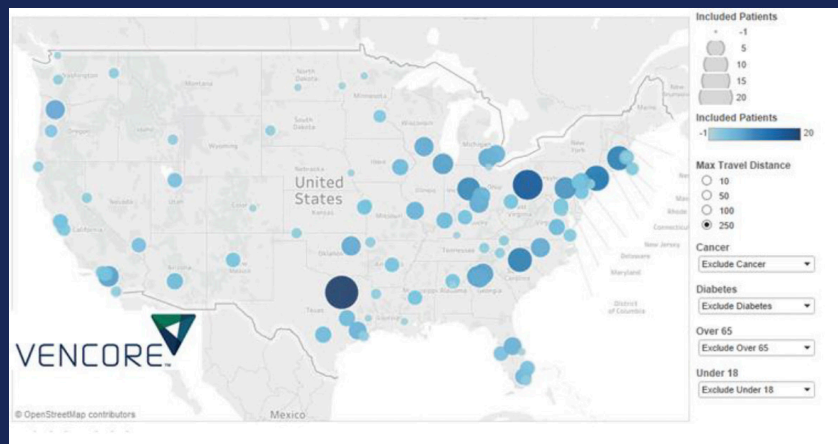
## Importance of Patient Advocacy Groups

Many rare diseases have advocacy groups, often comprised of 'informed' and 'interested' patients as well as supportive relatives.

However, establishing such groups in the extremely rare and ultra rare diseases can be challenging and occasionally there may not be a group specifically for the particular indication in question. There may, however, be an umbrella group that covers several similar conditions. For example, the Mitochondrial NeuroGastroIntestinal Encephalomyopathy group does not have its own advocacy organization but there are several active advocacy groups who support patients with mitochondrial diseases.

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### Site Selection & Protocol Design



Data kindly provided by Vencore<sup>4</sup>

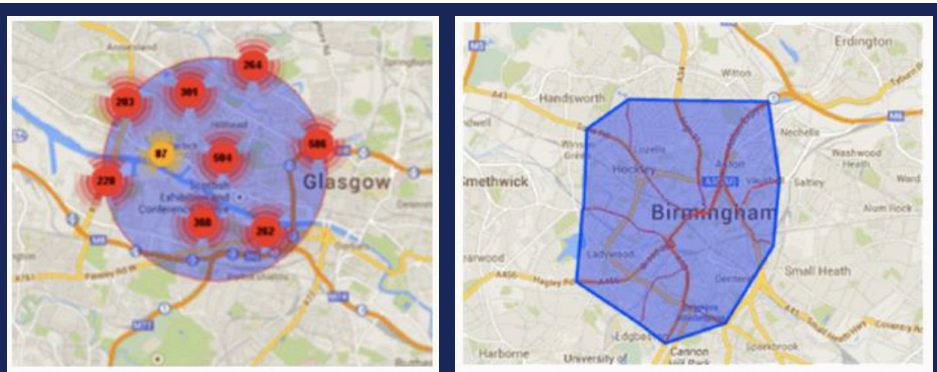
#### Figure: Clinical trial site selection

Cutting edge algorithms provide data driven insights to expedite the time to trial and drive efficiency in patient recruitment.

It is important to build good working relationships with advocacy groups both on an international and national level. Patient groups can provide valuable information throughout the clinical development program, in particular advising on any potential logistical challenges for participants and how the protocol will 'flow' at the sites. In fact, for any rare disease study, one should connect with various patient support organizations and obtain important feedback on study design and the location of potential patients. These groups not only help to engage patients, but are of valuable support to identify and recruit investigators. Sometimes there are forums within advocacy groups that describe the main challenges and concerns that these patients face.

Only by understanding the disease from the patient's perspective is it possible to design a clinical trial that addresses their challenges and predicts risks, ensures optimal patient recruitment and retention.

Advocacy groups not only help to engage patients, but are of valuable support to identify and engage investigators



Data kindly provided by Clinical Cube<sup>5</sup>

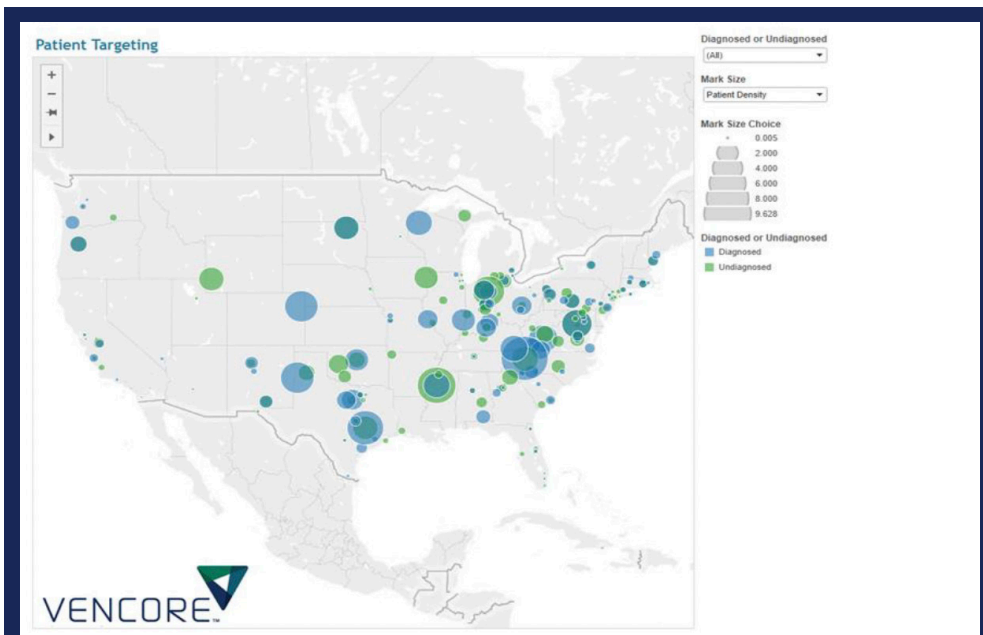
**Figure: Geographic Mapping of Potential Patients**

Potential patient cohorts that are tailored to the study protocol can be identified using efficient tools. Easy to use geo mapping and geo fencing allows specific locations to be investigated and detailed analysis of potential trial recruits to be completed within hours.

Activities known to help to connect with patients through advocacy groups include:

- Taking part in forums where valuable patient information is exchanged. Often people who suspect that they may be suffering with the condition but, are waiting for a diagnosis, take part in these forums looking for diagnostic advice
- Promoting your study on advocacy group websites describing its goals and how it is likely to better the understanding of the disease and the value of their contribution
- Gaining an understanding of the challenges that these patients are facing and how they could impact on the clinical trial
- Exploring real world data on standard of care and alternative medications/diets etc., that have been explored by the patients and how these medications/treatments fit around the study protocol
- Attending conferences, meetings and rallies organized by the pharmaceutical industry, academics and patient advocacy groups where you can take the opportunity to talk directly to patients and their families





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#### Figure: Estimated Disease Prevalence

Establishing an underlying diagnosis can be long and frustrating for both patients and providers. In the world of rare diseases, the average time to diagnosis is 7 years, experiencing various episodes of misdirection along the way.

Shortening the time to diagnosis is crucial to connect patients to appropriate therapies. With the advent of electronic medical records, we have a unique opportunity to collect, aggregate and analyze the journeys of known patients to inform early diagnosis and intervention of undiagnosed patients. These techniques can be used to enhance recruitment in rare disease trials.

Sophisticated pattern extraction and machine learning analysis techniques can uncover patient clusters who have gone undiagnosed but whose medical journey matches those of known patients.

## Websites and Social Media

Many patients and caregivers have a good understanding of their disease and its management. Information often comes from the internet and is communicated across the groups. The internet has created opportunities to share experiences and knowledge and connect patients and caregivers to the latest research and clinical trials.

Study information dissemination is achieved via initiatives such as developing study specific websites, running online campaigns, advertising on patient group websites, Google advertising, promotional videos and/or the adoption of a 'channel' on YouTube etc.

All these initiatives enhance the number of inquiries about clinical trials from potential participants. Websites provide the information a patient needs to know when they are considering participating in a trial. Search engine optimized sites help them to appear at the top of any particular search strategy. Password protected areas can provide patients and investigators (and their teams) with more specific information and communication.

Interactive online modules let patients register their interest in participating in trials, keep them updated of any changes to key aspects of the study and provide news about the disease. Patient engagement related matters can be managed automatically by websites alone. For example, automated delivery of reminder cards via email/SMS, monthly news updates, medication and appointments as well as providing the Investigator with the opportunity to follow up with the patient. Sites can serve as a resource center providing general study descriptions and responses to frequently asked questions.

Social media is a widely accessed tool used by patients to obtain disease related information. For rare disease patients, social media serves as a one stop platform that not only connects them to the world and to fellow patients affected with a similar disease but also with social support. A recent interview conducted with rare disease patients showed that they rely on interaction through social media groups like Yahoo groups, Facebook, Twitter to provide suggestions and support<sup>6</sup>.

As patients and relatives are well connected through social media, recruitment and retention for clinical trials has become more efficient. It aids study delivery when patients are better connected with their doctors, follow ups become easier and patients can be contacted easily in case of change of address details etc. It is believed that the full contribution that social media can bring to the operational challenges of clinical study delivery have yet to be discovered.

## Travel for Patients and Caregivers

As there are limited treatment options currently available for the majority of rare diseases, patient continuation in a clinical trial is less often governed by a lack of motivation, but more often by logistical challenges such as travel to the study centers. Many of the patients and their caregivers end up traveling long distances to specialty centers for the management of their disease.

A high frequency of such visits, coupled with any specific disability associated with the condition, continuously required medical assessment and treatment and their dependence on family members lead to distress and frustration. This is often a deciding factor when it comes to patient participation or their continuation in an ongoing clinical study.

Providing logistical support to patients and caregivers has a positive impact on patient retention and improves patient adherence with the protocol, preventing missing data.

There are different ways of managing the patient travel and expense reimbursement process. A traditional approach is to seek help from investigator site staff for the reimbursement of patient travel and other associated expenses. However, care must be taken to ensure that this doesn't place a burden on already busy staff, thus interfering with efficient study delivery. An alternative approach is to utilize services of specialized companies experienced in providing travel and expense management. This can really help patients as well as site staff as it reduces administrative tasks and allows them to focus on clinical work.

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The site staff only need to provide information on patients at the outset, after which the company can organize travel and lodging arrangements i.e. train tickets, hotel accommodation etc. as well as manage the receipts/ payments. It is essential that service providers understand the importance of maintaining patient confidentiality and have the necessary local compliance systems and procedures in place to provide such services.

## Home Support

Patients with a rare disease are often not able to travel to study centers due to their debilitating disease condition. As a result, such patients require care and support in their home environment. Sending nurses to patients' homes is not uncommon in rare disease trials and this practice has been utilized increasingly to provide adequate support to patients and enhance their involvement in clinical trials. Home support can include activities such as blood draws and pharmacokinetic sampling, completion of quality of life and patient facing questionnaires, physical assessments and drug infusions etc.

Another important factor when it comes to patient recruitment and retention is communication and relationship management between investigator staff and patients/caregivers. In rare disease trials, investigator and site staff are expected to build close relationships with the patient/caregiver, taking every opportunity to build a rapport in order to promote two way communication. The site staff should coordinate each study visit with the patient in order to ensure compliance.

Little reminders and kindness can go a long way (reminder cards, birthday cards, general cards, etc.) in keeping channels of communication open. Patient families can be updated on the progress of the clinical trial.

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