

Easing the Burden

A guide to best practices in conducting rare disease trials

As members of the clinical trials industry, it's paramount we understand the life of someone managing a rare disease. As the industry advances, it is increasingly focused on developing cures and treatments for conditions which impact smaller subsets of populations. This means sponsors, sites and trial stakeholders must be flexible for our patients' sake. It also means we must be willing to overcome any hurdle, accommodate any need, and remove any restriction that may affect a rare disease patient.

While no method of reducing the burden on patients and sites in rare disease trials is ever perfect, some have proven to work better than others:

Before starting, step into their shoes

It's important for sponsors to speak with patients, their doctors, and their caregivers before planning a study. Understanding how a patient's quality of life is affected by their condition will help sponsors in creating the trial. Are they able to commute easily? Do they have accessibility requirements? Will it be challenging for them to spend hours at a site? Sponsors should use the information they learn to shape everything from the enrolment criteria, to logistical visit design, to the consent questionnaire.

Remove any barriers to enrolling patients

With so few patients available, recruitment and retention are arguably the most important challenges for sponsors to conquer. To ensure success, sponsors must be willing to make the necessary accommodations for each patient to meet their enrolment numbers.

While sponsors may be tempted to craft specific inclusion/exclusion criteria using the information learned from patients, doctors and diagnoses, they should refrain from doing so. Instead, sponsors should be as flexible as possible to accommodate as many patients as needed. In certain instances, it may even be best to waive the inclusion/exclusion criteria when it was in the best interest of the patient. While it's up to each sponsor to decide how flexible they can be, here are some potential guidelines:



Do...

- Be flexible with inclusion/exclusion criteria
- Design or select a primary outcome measure defined in context of whole phenotype
- Select outcome measures that work in concert to maximise value of all data obtained
- Consider a study design to take account of small numbers.

Don't...

- Make inclusion/exclusion criteria so strict that recruitment suffers
- Assume study designs and statistical methods from non-rare disease indications will translate to the rare disease arena
- Assume a change in one aspect of a phenotype will be relevant to patients, regulators, or payers.

By keeping the trial as open and welcoming as possible, sponsors will maximise sites' ability to recruit and enrol patients who may truly benefit from the trial.

In addition, to improve retention rates once patients are enrolled, sponsors should make every effort to minimise the burdens to patients and study teams by using less stringent study protocol wherever possible. This includes using more open enrolment criteria and assessments – or waiving them when necessary – and creating wide visit windows and flexible locations where possible to accommodate diverse needs of specific patient populations.

Getting patients interested and enrolled in the study is critical, and it's just as important to keep them active and engaged throughout the study to avoid drop-outs. Starting with a well-designed protocol that is considerate and convenient for patients will go a long way to improving traditional retention rates.



Physical accommodations

With some rare diseases, patients may encounter difficulties in traveling to site locations. In these instances, sponsors must consider making the necessary arrangements to prevent increasing the burden on patients. Some of the solutions could include:

- Utilising home nursing services that can come to the patient's home to collect blood, administer the study drug, or perform other study-related services as needed
- Offering reasonable travel or relocation accommodation. This can include covering the cost of flights, hotels, pre-paid debit cards, meal and parking reimbursement
- Opening study site locations that are closer to patients' homes.

Also consider extending the period of the study trial if patients benefitted from the main study. Using a single extended study reduces the burden for sites by letting them focus on enrolment, instead of performing activation activities for a second study.

Explain the clinical trial process and provide continued patient support

Sponsors never want a patient to drop out of a study because s/he doesn't understand what it involves. It is best to engage with each patient, their caregiver, and their doctor(s) whenever possible. Use this time to discuss the clinical trial process, answer any questions they may have, and leave behind tools such as video, materials and websites that patients can refer to later.

In addition, try to train study teams on the study protocol using onsite or remote training, role-playing and video. Sites that better understand the trial and its design can better educate patients, reinforce trial benefits and answer patients' questions.

Lastly, consider connecting patients to support groups and communities. Sites often report that patients' quality of life increases when surrounded by peers who understand their condition and their day-to-day life.



Increase understanding and knowledge of the disease

It's very important sponsors make every effort to raise physician awareness of the disease, its impact and any relevant clinical trials. In the case of rare diseases, sponsors should be open to sharing relevant information from previous trials with the industry at large whenever possible. The clinical research community and its patients both benefit when sponsors share experiences and best practices.

It might also be a good idea to offer physicians access to labs to provide an easy path towards diagnosis and enrolment. In certain instances, physicians who suspect a patient may have a rare disease may also suspect that family members could carry the same disease. In either instance, it's important for the prescriber to be able to confirm their suspected diagnosis.

Finally, sponsors should consider conducting natural history studies instead of a traditional clinical trial whenever possible. Natural history studies are studies which follow a group of people over time who have a specific condition or disease. They are extremely important in understanding how rare diseases work, developing best practices for patient care and identifying research priorities.

Make sites' lives easier

Sponsors should remember sites must complete all startup paperwork and activities, regardless of the number of patients they enrol. They must also remember sites may have limited experience in conducting rare disease trials. Thus, sponsors must make every effort to train sites and eliminate burden whenever possible.

Remember – investigators and study coordinators are responsible for answering patients' questions. Thus, sponsors should be prepared to explain the details of the study, from explaining why a placebo is required to adequately describing how patient safety is handled throughout the course of the study.

Running a rare disease clinical trial is not an easy task, but it is a critical one for millions of patients worldwide. Due to their nature, these trials require sponsors, sites, CROs and vendors to operate and collaborate at peak performance throughout the duration of the trial, while making every feasible concession that could allow patients to participate and stay in the trial. While that sounds difficult, it's certainly achievable. More importantly, it's worth it, as each extra step they take is one less for their patients.

