PREVENT THE REAL WORLD FROM DERAILING YOUR CLINICAL TRIAL: FOCUS ON PROTOCOL DESIGN

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While clinical trial sponsors are continually seeking ways to improve the speed and efficiency of their trials, they often overlook one of the most basic elements that, if done improperly, can quickly derail even their best laid plans: the protocol. Too often, protocols for patient studies — especially those involving end stage renal disease (ESRD) — fail to account for real-world factors that complicate and interfere with patient and investigator participation. When these factors are discovered, often after enrollment has begun, sponsors are forced to amend the protocol, sometimes repeatedly. Such missteps in protocol design can significantly prolong enrollment time frames and throw the study completely off course.

The ideal clinical trial protocol is one that is robust yet manageable, adhering to good clinical practice as well as standards of care. Problems arise when insufficient attention is paid to its design, including eligibility criteria, pre-screenings and the intricacies of targeted patient recruitment, for example. Studies looking at Phase III protocols by the Tufts Center for the Study of Drug Development have found that the number of endpoints, procedures and eligibility criteria grew significantly in the past 15 years, leading to increased costs and additional burdens.[1]

This growing complexity of clinical trial protocols underscores the importance of simplifying protocol design as a means to promote trial adherence, enrollment and completion. Simplified yet robust protocol design is especially important in renal clinical trials, the success of which depends greatly on thorough consideration of the patient and his or her physical and emotional support system, the investigator's needs and the external competitive landscape.

STARTING WITH THE PATIENT IN MIND

Clinical studies succeed when research needs are balanced with the practicalities of delivering clinical care. This requires careful and informed consideration of patients' circumstances, particularly for individuals with ESRD, an especially challenging patient population with many medical complexities. Unfortunately, sponsors often do not understand these patients' needs and thus fail to accommodate them when designing trial protocols.

For example, certain sponsors or IRBs may require patients to initial every page of an informed consent form, but patients undergoing dialysis typically have one of their arms connected to the dialysis machine. The physical hassle of signing a form in such circumstances is frustrating. Notably, there is no regulation mandating patients' initials on every page of an informed consent document, and yet, the practice continues, presumably because it's considered "best practice."

Dosing schedules are another example that may impact patient participation. Patients with ESRD receiving in-center hemodialysis are typically dialyzed three days a week for several hours at a time. Not only should such logistical considerations be taken into account, but timing the dosing appropriately with

their dialysis standard of care must be considered — which is something only those delivering that care can accommodate.

Patients living with ESRD are medically complex, perhaps more so than any other patient population. Many ESRD patients have comorbidities that impact their care and that must be considered in protocol design. Additionally, it is common for ESRD patients new to dialysis to feel overwhelmed by their new normal. Sponsors often underestimate this when designing studies seeking to enroll such incident patients.

When writing a protocol, it is important that sponsors consider the dialysis providers' defined standard of care and associated algorithms so that they can prevent costly protocol amendments and slowed enrollment. As an example, the care for ESRD patients with anemia is often guided by an algorithm that directs the erythropoiesis-stimulating agent (ESA) dosing schedule and target hemoglobin range. If a study's protocol results in an undesired hemoglobin level, this could result in unscheduled visits and protocol deviations as actions are taken to return Hg to the desired value. Furthermore, Hg levels outside of the desired range could have negative downstream consequences for the dialysis provider.

To write a feasible protocol and avoid the need for future amendments, the sponsor must understand the established standard of care for its targeted patients. Fortunately, when reviewing protocol amendments, the FDA is typically willing to accommodate trial participants in special situations, such as ESRD.

For example, to avoid screen failures using normal lab parameters, sponsors writing a protocol for an anemia study should consider allowing an iron supplementation during screening. Changing the requirement for pre-dialysis physical exams or procedures to allow for more flexibility in the patient's and staff's schedule would also be beneficial.

The technological sophistication of the patient population should be considered when planning patient diary or questionnaire completion. ESRD patients may be challenged by electronic completion of this item due to various reasons such as having impaired vision, not being tech savvy or having limited arm or hand mobility. To the extent that such accommodations can be made during the early stages of protocol design and planning (i.e., before enrollment starts), the greater the chance of minimizing participant inconvenience and enhancing trial enrollment and adherence.

KEEPING THE INVESTIGATOR IN MIND

American consumers have become more proactive about their own health care; however, they continue to look to their physicians for encouragement and advice, particularly concerning clinical trials. In a recent survey of 1,000 U.S. adults, more than 80 percent said they would likely participate in a clinical trial if recommended to do so by their doctor, and a clear majority (86 percent) said their doctor should discuss clinical trials with them as part of standard care. Although fewer than 20 percent of survey participants said their doctor has ever had such a discussion with them, that figure represents an increase over the 9 percent who responded similarly in 2013.[2]

Yet despite physicians' influential role in driving patient recruitment, trial sponsors sometimes fail to consider the schedules and workloads of those doctors willing to serve as investigators, which leads to unrealistic expectations, overly extensive processes and repetitive training. When sponsors take these things into account, they end up with a more realistic and workable protocol as well as a more qualified and engaged investigator. For example, an investigator may need to spread out patient screening and enrollment over time — or possibly limit enrollment — to manage the demand for logistical resources, particularly if the site is short-staffed.

Furthermore, unless protocols are designed realistically to meet patients' and investigators' needs, protocol amendments create a training and change control burden for investigators, requiring them to re-consent patients — which, in turn, becomes an added burden for patients, investigators and site personnel.

CONSIDERING THE LANDSCAPE

Although some renal trial sponsors seek protocol writing assistance from experienced nephrologists, what's often lacking is input from those with recent experience operating in a clinic or system of clinics. For those unaccustomed to working with patients on a regular basis, the standard of care may be a somewhat abstract concept. Only by involving an organization that is integrally knowledgeable about renal disease patients and their daily lives can sponsors ensure an efficient protocol design that meets their own needs as well as those of the patients and investigators.

Consider the external landscape: At any given time, there may be multiple clinical trials that force sponsors to compete for patients and investigators for their study. When this happens, investigators are more receptive to selecting a patient-friendly protocol that accommodates the standard of care while meeting their business needs and goals. Furthermore, when faced with a choice of trials with varying degrees of protocol complexity, investigators will pursue and secure the clinical trial for which they have eligible patients and where the benefits to patients and their practice outweigh the administrative and operational burdens that are imposed.

Additionally, one must not overlook financial considerations. Sites appreciate more frequent compensation schedules because they help to align revenue and costs — a key imperative to running and managing a profitable clinical research site.

PARTING THOUGHTS

Sponsors should engage with organizations that offer clinical care services and insights to the ESRD patient population so they can develop a well-designed clinical trial protocol to meet the needs of kidney disease patients. With expertise in kidney disease patient care, such an organization can ensure the trial runs more efficiently and effectively by helping to develop a protocol that is more patient- and investigator-centric. The organization should also be able to provide insight on competitive trials that may impact the trial's enrollment prospects.

With this expert advice, sponsors can design a protocol that spares them not just considerable aggravation but that also can save time, money and other resources. With knowledgeable insight, a protocol can be designed that will work not just on paper, but in the real world of kidney disease research.

1 Sites wrestle with protocol design complexity, CenterWatch Online, March 1, 2017. Available at: http://www.centerwatch.com/news-online/2017/03/01/post-june-sites-wrestle-protocol-design-complexity/

2 Causey M. Doctors remain key to boosting clinical trial participation, Association of Clinical Research Professionals, 2017 Sep 6. Available at: https://www.acrpnet.org/2017/09/06/doctors-remain-key-boosting-clinical-trial-participation/. Accessed September 15, 2017.

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