Predicting and Achieving Clinical Study Enrollment Goals: Leave No Rock Unturned

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White Paper
10/14/2014

The ability to accurately predict and achieve subject enrollment goals is one of the most difficult clinical study tasks. It has been reported that only 7% of clinical studies in the U.S. are able to meet pre-specified enrollment goals.[1] This result may have profound effects on individual careers and companies, especially the survival of new companies where delays achieving study enrollment and achieving regulatory clearance for entry into the marketplace may result in significant funding consequences or other significant and sometimes catastrophic issues. Publicly-traded companies may also see a material impact on the Wall Street valuation of the company when enrollment goals are not met.

There are a large number of interrelated variables that contribute to enrollment, spanning every area of the clinical study process. The product, disease, patient, and procedures all influence enrollment as do the study design, selected sites, budget, study timing, human interactions and others. The inability to predict or achieve enrollment goals is seldom due to only one factor. It is more often due to a combination of factors which separately, and in combination, reduce the value proposition for the patient or investigator, and the desire to participate. The following discussion will point out a few example areas that impact enrollment, but a specific plan to gather information unique to your product and study will help make enrollment predictions more accurate and also provide guidance on areas where training and tools may be incorporated in study operations to minimize enrollment loses.

Early Evaluation

Early in the clinical study planning process, an estimation of study enrollment is required to secure funding and formulate high level plans. Unfortunately for some products and studies, this estimate must be provided without much guiding information. Many of these early estimations are calculated based on general disease statistics, published timelines from other studies, and the opinions of a few physician advisors who provide their input without any commitment to deliver. As such, these early estimates are typically not very accurate. So it is important to begin analyzing the many considerations for enrollment as early as possible in order to adjust the initial estimation throughout the early clinical study development process. With early recognition of enrollment hurdles that can be managed, adjustments and mitigating processes can often be built into many areas of the study from the beginning. Since every product and study is unique, the areas of focus and challenges to predicting and delivering enrollment are often quite different from one another.

Consider the Risk/Benefit Analysis

By the time a product is ready to be clinically tested, an initial risk/benefit analysis will have been developed. Using this information as a guide, one can begin to assess and predict the acceptability of the product and procedure to both patients and investigators. Evaluation must be unbiased and provide an honest and critical look at both the product and procedure. Do the product and procedure relate well to the current standard of care? Do they provide much anticipated enhancements or solve significant problems? Is the product appealing to

both investigators and patients, or does it have characteristics or behaviors that introduce significant doubt to either party? Sometimes issues perceived as small can substantially slow down enrollment. For example, a first generation implantable device that is larger than expected when compared to similar products is not uncommon. However the lack of competitive size may result in declined enrollment from both the patient perspective and the investigator perspective for different reasons. It may be entirely a cosmetic concern for the patient, but for the investigator, it may be a reluctance to promote return to a large device and the known drawbacks of size.

Evaluate the Study Design

The clinical study design also influences both site recruitment and enrollment. Does the study answer a compelling question or provide an unanswered solution or does it repeat already known work? Are the study procedures burdensome to the patient or site? Does the frequency of follow-up visits compare well to standard of care or will they be perceived as burdensome? Are patients randomized into different treatment groups and if so, will they cross over and receive the investigational product at some point? Do the inclusion and exclusion criteria limit the available patients? Whenever possible, issues related to enrollment should be considered in the clinical study design and recognized when predicting enrollment.

Once a draft study protocol is available, sites can be approached to discuss participation. The site selection process is a key area where information can be gathered regarding potential enrollment. It provides the forum to gain more understanding about product acceptance, expected patient populations, and many additional details. So a well-crafted site questionnaire can be invaluable for gathering useful information to predict enrollment as well as to choose appropriate sites. You can learn more about the hospital, the practice, the investigators, the research structure and staff, and their performance in other studies. It is important to note that the answers to questionnaires may not always be accurate so one should be cautious when interpreting the results. Sites may inflate their patient numbers to be seen favorably by the sponsor or have simply provided ballpark numbers without doing the research. Numbers may reflect an entire group and not reflect only those available to the investigators. But despite inaccuracies, these questionnaires form a foundation to establish the site's target enrollment and provide the opportunity for further discussion with the sites, where the answers they provided can be placed in context and important additional information can be gleaned with regard to their true interest and capabilities. You may discover that the sites you thought would be ideal for the study may not be, simply because the characteristics of the site are not suitable for this particular study. For example, if your study has frequent follow-up visits after discharge, you may need to choose sites based on the percentage of their patients that are local, eliminating some famous institutions that have adequate populations but draw these patients from around the world. You may also discover that the sought after sites are performing similar studies that will reduce their ability to participate in yours.

Be Aware of What the Device Treats

The disease or condition being treated can also influence enrollment either positively or negatively. If there are few or no alternatives, patients may be lined up to participate. If there are other treatment methods the interest may not be strong. The disease or condition also affects the flow of patients in the health care system. An understanding of the relationship of the patient with the investigator and all the ways patients may be engaged for potential study participation can be critical for enrollment and guide the marketing of the study. The chances for enrollment are often different when the investigator is known and trusted by the patient as compared to a new relationship with a specialist. Patients often consult with their trusted physicians prior to agreeing to participate so it is important that these referring physicians also know about the study and ideally support it.

One may also find instances where the product is in high demand and there are many excited patients trying to participate in your study. Are your sites going

to have the staff required to screen all the willing candidates? Do you need a screening service to support the sites and sort out the inquiries? Even this favorable situation requires significant planning to meet enrollment goals.

In summary, predicting and achieving enrollment is quite challenging and is influenced by every aspect of the clinical study structure and operation, some of which can be modified and some that cannot. Careful planning to reveal the difficulties that will be faced in your particular study will not only lead to more accurate prediction of study enrollment, but will identify key areas where you can influence enrollment in your study design and operation and help move closer to achieving your goal.

RCRI has experienced professionals capable of providing strategic planning and support for study enrollment efforts as well as other study or product needs. We welcome the opportunity to be a collaborative partner and achieve great results together. Contact David France at 952-746-8080 or dfrance@rcri-inc.com

References:

1. *2008 State of the Clinical Trials Industry: A Sourcebook of Charts and Statistics, CenterWatch, 2008.*

About the Author

David France, RCRI Clinical Principal Advisor, has 28 years of successful Clinical Research and Education leadership in the Medical Device field for start-ups as well as large established companies. He has expertise in a wide variety of clinical and regulatory settings and geographies including site and investigator relations, strategic planning (including Class III active implantable devices), protocol development, enrollment strategies, report authorship, FDA advisory panel membership, and publication strategy development and support.

David has built and managed numerous clinical study teams both in-house and in the field, and has utilized his training experience to strengthen clinical operations and to provide highly technical product education to physician customers, sales teams, and field engineers. At RCRI he provides leadership as an overall project advisor and manager, serving as a strategic consultant and providing regulatory and clinical guidance both internally and externally.