The Importance of Feasibility Studies for Oncology Clinical Trials

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Executive Summary

The segmenting of the oncology patient population has increased the challenges in designing clinical trials. Once common diseases have now become collections of different conditions defined by molecular subtypes.

As clinical advances have been occurring, there remains economic pressure to bring new compounds to market more efficiently. Failure to complete clinical trials within the planned timeframe can have disastrous financial implications for a clinical development program and may delay the availability of important new therapies to patients.

To avoid delays, clinical trial sponsors are increasingly including feasibility studies in the clinical trial planning process. Clinical trials that include properly performed feasibility studies experience fewer delays and significantly reduce the risk that the trial will close prematurely for poor enrollment.

This paper explores the use of feasibility studies in the planning process of oncology trials. Topics include:

- Defining the goals of your feasibility study
- Trial design and protocol optimization
- Enrollment projection and country selection
- Clinical trial site selection
- Initiating a feasibility study

Introduction

The improved understanding of the biologic basis of cancer has led to the development of a number of new treatments for cancer over the last decade. In addition, the evolving concept of "personalized medicine" is driving efforts to increase the therapeutic index of both newer and older treatments by carefully defining the subsets of patients who are most likely to benefit, thus decreasing patients' exposure to therapy that will likely be ineffective.

This segmenting of the patient population has increased the challenges in designing clinical trials, as once common diseases have now become collections of different conditions defined by molecular subtypes. The identification of unique molecular pathways has also led drug development into diseases that once were rarely studied in large clinical trials due to their low incidence.

As these clinical advances have been occurring, there remains economic pressure to bring new compounds to market more efficiently. Given the current economic environment, failure to complete clinical trials within the planned timeframe can have disastrous financial implications for a clinical development program and may delay the availability of important new therapies to patients. To avoid delays, clinical trial sponsors are increasingly including feasibility studies in the clinical trial planning process. Clinical trials that include properly performed feasibility studies experience fewer delays and significantly reduce the risk that the trial will close prematurely for poor enrollment.[1] This paper will explore the use of feasibility studies in the planning process of oncology trials.

Defining the Goals of Your Feasibility Study

"Although everyone seems able to find the time and money to redo, finding the time and budget to plan properly seems very rare. Planning, however, is a key function, not just an intuitive process that scientific professionals can handle spontaneously."
- Ingrid Klingmann and Anne Vern[2]

Feasibility studies can focus on a range of information, but the key questions most sponsors seek to answer are "Is this the right trial design?" and "What is the best operational plan to ensure that the trial is completed with high quality, on time, and within budget?"

Questions about design are most appropriately asked very early in the planning of a trial, while the operational plan depends on having a finalized (or nearly finalized) design.

Trial Design and Protocol Optimization

When designing clinical trials, sponsors generally rely on their organization's internal knowledge and on interactions with key opinion leaders (KOLs). Although these interactions are valuable and appropriate, several additional factors must be taken into account to ensure that the trial design is optimal:

Compatibility with Prevailing Patterns of Care
Therapy provided within a clinical trial should be consistent with current patterns of care in the geographic areas where the trial will be conducted. This is particularly important in randomized clinical trials in which a new therapy is being tested against "standard" care. Investigators are generally reluctant to enroll their patients into studies that include a therapy that is inconsistent with treatment they provide as routine clinical care.

While it is appropriate to ensure that the treatment planned meets published guidelines (e.g., National Comprehensive Cancer Network, American Society of Clinical Oncology, or European Society of Medical Oncology), gathering data on preferred treatments directly from physician investigators is a more accurate way to assess whether they will accept the treatment planned in a trial. Unfortunately, in many cases, this type of information is not readily available from publicly available sources. A feasibility study can address this with a direct survey of potential investigators or, in some cases, a query of commercial databases that contain current data on practice patterns.

Interest in the Clinical Question

Regardless of the sponsor's (and KOLs') enthusiasm for a particular study, it is prudent to assess the enthusiasm among potential investigators. In some cases, such as when promising Phase 2 data are available for diseases that are generally refractory to treatment, there is obvious interest in the planned clinical trial concept. In many cases, however, it is less clear how much interest a clinical trial will generate among investigators.

One of the best ways to assess interest in clinical trial concepts is to conduct personal interviews, which provide insights not generally available from questionnaires. During the interviews it is possible to determine the impact of prior study results and any potential safety concerns on investigators' enthusiasm for a trial design, and to subjectively gauge their overall interest in the concept. At this early stage, one can also gather information about the role a new treatment may play in clinical practice. This information can be very helpful, especially for earlier stage clinical trials and for companies that don't have extensive market research capabilities.

Appropriateness of Eligibility Criteria

One of the most important reasons for low accrual to clinical trials is the incorporation of strict eligibility criteria. The sequencing of therapies in clinical practice has the potential to impact the number of patients who are eligible for a trial, especially in cases where patients are required to have "failed" a previous therapy. When these therapies are not preferred by the majority of physicians in practice, or are limited in their availability by economic factors, the number of patients available for study will be significantly reduced. In these circumstances, it is prudent to either consider changing the eligibility criteria or to perform the trial in regions where these treatments are available and in common use.

Restrictive criteria such as requirements for measurable disease, organ function and restrictions on prior malignancies can also limit enrollment and should be scrutinized during the feasibility process. Feedback on these issues from practicing investigators often results in changes to (and simplification of) planned eligibility criteria.

Acceptance of Study Procedures

Trials are increasingly incorporating on-treatment biopsies for assessment of biomarkers, other invasive diagnostic procedures, frequent blood draws (especially for pharmacokinetics) and visit schedules that present a travel burden for patients. Investigators and study coordinators can provide useful feedback on their patients' likely willingness to undergo these study procedures. Specific feedback on patient attitudes can potentially alter the plans for clinical trials by making them less burdensome or, in other cases, can also provide reassurance that the planned trial procedures will not likely adversely affect recruitment.

Need for Study Redesign

Occasionally, protocol optimization feasibility studies reveal that the clinical trial envisioned has little chance of meeting its objectives. This information allows the sponsor to reconsider the protocol design and/or the viability of the research goals before investing time, money and patient resources in the trial.

Enrollment Projection and Country Selection

Projecting Enrollment

Sponsors need to accurately project enrollment to properly plan a clinical trial. To this end, surveys are often performed for the purpose of estimating recruitment rates. Unfortunately, the reality is that investigators often overestimate their ability to recruit subjects in order to increase their chance of being selected to participate in the trial. In addition, many sites lack appropriate data sources that would allow them to quantify patient populations that may be available to participate. It is also clear that the tendency to overestimate recruitment is not universal, and that some sites are more accurate in their projections than others. One potential option is tracking the degree of overestimation over time by using an "optimism ratio." This technique has pitfalls, however, since it is often unclear whether the investigator or another staff member at the site is responding to the survey, and the tendency to overestimate may differ depending on who is completing the survey.

Because of the difficulties encountered in projecting recruitment rates from feasibility surveys, it is important to examine other potential data sources when creating recruitment projections. "To the extent that the data are available, PPD has reduced its reliance on surveys for recruitment projection," says Martin Lee, MD, vice president, site and patient recruitment, PPD, Inc. "We feel that recruitment projection is most accurate when performance data are available from large numbers of sites that have participated in prior trials in the same indication and setting. Even this can be variable, though, due to changes over time in standards of care and the competitive trial environment. Trying to estimate the affect of these factors requires a detailed understanding of the therapeutic area as well as the current and planned trial environment."

Published studies of similar clinical trials are also a source of relevant information for estimating recruitment. These reports generally include the number of sites participating in the trial and the overall trial enrollment period. They do not, however, usually provide the number of months that each was open and able to enroll patients, nor do they report factors such as an increase in the number of sites and/or countries participating during the course of the trial – which can lead to an underestimation of the real recruitment rate. Nevertheless, this data can be used to establish a useful lower range estimate for potential recruitment.

Country Selection

In this era of global trials, the decision about which countries to include is also critical. Too few sites/countries can cause enrollment delays; too many can increase costs without a sufficient return on investment. While recruitment rate estimates can differ depending on the country involved, there are other factors that also play a role in country selection. Examples include:

Disease incidence and prevalence

The incidence and prevalence of some cancers varies considerably by geographic area. For instance, there is a high incidence of hepatocellular carcinoma in Asia (largely related to HBV infection), a high rate of melanoma in Australia, and high rates of breast and prostate cancer in industrialized countries. While incidence and prevalence must be considered, it is not necessarily the case that countries with a low incidence of specific cancers cannot be considered for participation; in some cases, referral patterns may drive these patients to centers of expertise where enrollment rates may be comparable to those in geographies with higher incidence and prevalence.

Competitive clinical trial environment

Competing trials limit the availability of the best sites, as most are reluctant to open multiple studies in the same indication and setting. Even if they are willing to open multiple studies, one or more of those studies may enroll poorly. Therefore, the presence of competing trials is an important component of country selection. Oncology studies are somewhat unique in this regard, in that pharmaceutical industry-sponsored trials are not the only studies competing for enrollment. The national and international cooperative groups (e.g., Eastern Cooperative Oncology Group, Southwest Oncology Group, Children's Oncology Group, and European Organisation for Research and Treatment of Cancer) are well developed and enroll large numbers of patients in both community and academic settings. Failing to account for these studies and their timelines can be a critical error in the planning process. Fortunately, clinicaltrials.gov and commercially available databases such as TrialTrove™ provide a comprehensive overview of the competitive environment, sometimes including the identities of participating sites.

Another factor that is often overlooked in the assessment of the competitive trial environment is whether patients' previous participation in clinical trials will affect their eligibility for the proposed trial. For example, a trial of second line therapy with an agent targeting epidermal growth factor receptor (EGFR) in colorectal cancer might reasonably exclude patients with prior exposure to these agents. If a trial is active in a region in which this therapy is being used in the first-line setting, there may be fewer patients available for study.

Regulatory timelines

Because regulatory timelines vary significantly by country, it is critical to consider this factor when planning a clinical trial. Some countries, such as Brazil and China, have exceptionally long regulatory timelines, which makes them less desirable for inclusion in studies with short recruitment timelines. Other key information to evaluate includes the potential for delays related to investigational agent importation and restrictions on the export of biologic samples. Sponsors often benefit from seeking regulatory consultation as an element of their feasibility study, particularly regarding issues such as restrictions on exporting biologic samples, acceptability of placebo controls, inclusion of pediatric populations, gene therapy and the use of genetically modified organisms.

Clinical Trial Site Selection

Although it is important to identify the appropriate countries for a particular clinical trial, the best predictor for a trial's success is the choice of investigative sites. Feasibility studies are often conducted during the planning phase of a trial, but similar concepts are used for site selection. In many organizations the feasibility team can help clinical teams prioritize sites. The best predictors of site performance in clinical trials include:

Data Quality

Quality metrics, such as query rates, and the numbers of deviations and violations on prior trials can be used to assess a site's overall attention to data quality. Sometimes, particularly in large institutions, data quality issues are associated with particular study coordinators and investigators. In these cases, identifying the source of a problem can prevent excluding an otherwise qualified site.

Prior Performance in Clinical Trials (preferably in the same indication and setting)

In most large oncology trials, a significant proportion of sites fail to enroll patients. Recruitment data from prior trials allows early identification and elimination of these sites from consideration, which helps reduce the percentage of underperforming sites. For smaller trials, the ability to choose the highest enrolling sites from prior trials can appreciably accelerate enrollment.

IRB/Ethics and Contracting Timelines

Even if a site has excellent data quality and enrollment potential, long institutional review board (IRB)/ethics timelines or lengthy contracting processes can make the site less desirable for inclusion. It is necessary to consistently maintain these metrics so these issues can be considered in the process of site selection.

Initiating a Feasibility Study

Setting the Goals

Sponsors considering a feasibility study should begin by defining the goals of the study. Is the goal of the assessment to optimize the protocol, receive a recruitment projection and/or focus on site selection? Ideally, feasibility is a multi-step process that begins with protocol optimization and ends with site selection.

Identify the Right Research Organization

Consider an organization's clinical trial experience and global footprint. Does it have a proven track record in the type of study you plan to conduct? Is it large enough to have personnel in the regions in which you are considering conducting your clinical trial? Can it offer reliable insight on regulatory timelines and other country-specific elements (ethical considerations, standard of care for a particular disease, clinical supplies, etc.) that will affect your clinical trial?

In addition to considering the organization's trial experience, it is important to assess its feasibility capabilities. Does the organization have a dedicated feasibility department with experience in designing appropriate studies, including the required medical expertise? Does it have the capability to perform more than a survey? Does it have the capacity to produce comprehensive reports that are easy to understand?

Allow Enough Time

A thorough feasibility study will take six to eight weeks, especially when it includes a survey. If you plan to send the protocol to prospective sites, it is necessary to allow up to two weeks for them to read and sign confidentiality disclosures prior to sending the protocol for their review. In order to shorten this timeline, it is tempting to perform "blinded" feasibility studies in which the design of the trial is discussed without identifying the sponsor or investigational agent. While these studies can provide useful results, it is generally advisable to have the sites complete a confidentiality disclosure so a more full picture of the trial design and investigational agent can be provided. Experience demonstrates that investigators are much more likely to respond favorably to feasibility studies in which the identity of the study agent(s) and the design are completely described.

Analyze the Results

For an accurate analysis, feasibility study conclusions must be supported by data, not opinion. To this end, it is important to examine the data carefully for any signs that questions asked were misunderstood or misinterpreted. In such cases, going back to sites for further information or clarification can avert erroneous conclusions.

Conclusion

Clinical trials in oncology are becoming more complex and costly. Although performing feasibility studies may seem to add up-front time to the drug development process, it nevertheless remains a critical planning step. Sponsors who invest in feasibility studies have learned that the time spent analyzing and optimizing their protocol design, making appropriate decisions on anticipated recruitment rates and country selection, and ultimately selecting the right sites can be the difference between a trial that is conducted within timelines and budget and one that encounters major delays and cost overruns. The best prescription for the successful conduct of clinical trials is to consider these issues early in development, and to work with an experienced feasibility group that is capable of analyzing a planned trial or program, and of advising on the optimal means to answer the relevant questions.

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