



Optimizing Early Phase Oncology Clinical Trials

Oncology products continue to dominate the global therapeutics market. With anticipated continued strength, this therapeutic area will reach approximately \$75 billion in global spending by 2015.¹ Further, anticancer drugs continue to be the leading research therapeutic, with 672 oncology drugs in development.²

This strength depends not only on continued use of existing products but also on the clinical and regulatory success of candidates now under development. The identification and characterization of novel targeted therapies, made possible by science-driven innovation, will grow the oncology pipeline. Such agents, both small molecules and biologics, have potential to extend or improve patients' lives as well as become valuable treatment options — if proven safe and effective in trials. Rigorous evaluations in clinical trials that assess efficacy and safety in appropriate patient populations are critical to the continued development of these highly sensitive targeted therapies. The challenges to such studies, especially in phase I, are particularly great in oncology and cannot be met solely by most small- to mid-size oncology companies' internal staff. When considering protocol development, trial execution and data analyses, such companies must consider many aspects: medical and scientific knowledge; regulatory intelligence, both local and global; site and investigator relationships; as well as trial and data management. Many companies have a range of talent and tools to apply to trials, but partnering with external organizations can bolster expertise and experience to ensure successful trial outcomes in terms of quality data, time and costs.

This paper provides guidance to the small- to mid-size pharmaceutical and biotechnology companies (sponsors) planning early stage oncology clinical trials.

¹ "The Global Use of Medicines: Outlook Through 2015," Report by the IMS Institute for Healthcare Informatics. May 2011.

² "New Frontiers in Focus," Michael D. Christel, R&D Directions. October 2010.

The design and conduct of early stage clinical trials is especially challenging when the therapeutic field is oncology. These challenges begin with the patients themselves, as phase I trials of cytotoxic agents must be performed in cancer patients, usually those with advanced disease. Such patients present complexities for their monitoring, ongoing care and logistics. The trial challenges also include the evolution of agents from conventional cytotoxics to novel molecular targeted therapies, which require development, validation and adoption of new assays and methods of data management and analysis. Additional complexities come from the need to adapt the protocols and conduct of trials within the context of changing regulatory environments, such as new requirements from the U.S. Food and Drug Administration or European Medicines Agency's Committee for Medicinal Products for Human Use.

A sponsor planning an early stage oncology trial can find addressing these challenges daunting. But identifying the right tools and talents, either internally or via an external partner, yields benefits beyond the phase I trial in that it also helps a sponsor prepare the way forward into phase II and beyond.

The first steps of trial development begin in-house. Small- to mid-size biotech or pharmaceutical sponsors, for example, may have very knowledgeable staff regarding oncology, but the staff may have limited availability due to other responsibilities. For example, a sponsor may have few clinical oncology experts or biostatisticians or minimal relationships with investigators and sites that treat appropriate patients. In contrast, larger sponsors may have more staff for site monitoring or regulatory activities but lack deep experience in a particular aspect of oncology necessary to the trial. A best practice is to find a partner, such as a specialty clinical research organization (CRO), that offers a range of services that can be tailored to and mesh seamlessly with a sponsor's specific needs. Each trial aspect, beginning with protocol development through study conduct and data analysis, should be carefully evaluated when screening potential partners. Many of those aspects are reviewed here.

Oncology expertise

Among the most important attributes a sponsor needs is therapeutic expertise. Most sponsors certainly have clinical research knowledge; however, given the complex and evolving nature of cancer science, it is difficult for a sponsor to have all of the essentials for clinical oncology investigations. Partnerships, particularly for trial management services via a CRO, not only are appropriate but necessary to augment a sponsor's capabilities.

Trial protocol design often is the first area for collaboration a sponsor should consider. Nearly 60 percent of protocols used in phase I, II and III clinical trials for new drugs are amended during the trial, according to a 2011 study by the Tufts Center for the Study of Drug Development.³ In phase I studies, 52 percent of amendments happen prior to the first study volunteer

³ "Majority of Clinical Trial Protocols Are Amended, But One-Third of Those Changes Are Avoidable," News Release, Sept. 13, 2011, Tufts Center for the Study of Drug Development.

receiving the first dose, the report noted. Also, when examining all phases of trials, Tufts found that most amendments occur because of new safety information, requests from regulatory agencies, changes in the study strategy or standards of care, or recruiting difficulties. Because amendments cost time and money — Tufts calculates an added two months and averaged about \$454,000 per amendment regardless of trial phase,⁴ sponsors should expect and eliminate errors, defects and flaws as early in the process as possible.

For example, are all of the protocol-defined procedures appropriate for collecting data that will support a new drug application or investigational medicinal product dossier? First-in-man studies for many candidate chemotherapies are designed to identify the maximum tolerated dose and dosing schedule. Yet state-of-the-science technologies have yielded investigational agents that are designed to act with greater precision to inhibit cancer cell growth or promote cancer cell death. For sponsors of these newer targeted molecular agents, such as monoclonal antibodies, signal transduction pathway inhibitors or antisense molecules, trial protocols may require an optimal biological dose endpoint rather than a more traditional maximum tolerated dose endpoint. Consequently, the protocol will need to clearly define how to determine the recommended Phase II dose, and to describe new assays or procedures to measure biologic endpoints as well as to capture traditional patient safety assessments.

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Thoughtful design of an early stage trial protocol can help characterize biomarkers that will facilitate appropriate patient enrollment in follow-on advanced trials, or via adaptive designs, enable adjustments to the study population as the trial progresses. Advanced studies that enroll patients most likely to benefit could finish faster and consume fewer resources, which could yield economies in time to development.

In early stage oncology protocols, sponsors must account for the complex disease processes of patients with advanced cancer. First-in-man trial designs intentionally try to minimize the number of participants, so fewer patients are exposed to safety risks. Moreover, advances in cancer biology increasingly impact trial protocols, even enabling the use of the molecular characteristics of a patient's cancer as part of inclusion criteria. However, sponsors must consider that extensive exclusion criteria may prohibit patients who, with the right clinical trial and clinical management, are appropriate for phase I studies.

Understandably, phase I trial patients usually have comorbid conditions that require numerous medications, and both these illnesses and treatments create side effects that frequently can obscure recognizable effects of the trial's candidate medicine. The trial protocol and data

⁴ "Protocol Amendments: A Costly Solution," Kenneth A. Getz. *Applied Clinical Trials*. May 1, 2011.

management design should strive to make such disease and concomitant medications effects distinct from the tested therapy, particularly in the dynamic phase I trial environment with its frequent dose adjustments. Ideally, the oncology trial team should recognize anticipated disease manifestations, and thus be able to distinguish adverse events due to a concomitant medication from unanticipated adverse events due to a study drug. Such expertise creates trial efficiencies. For example, an inexperienced data manager might mistake a leukemia patient's very low granulocytes count as a drug-related adverse event, prompting an unnecessary data query, when low blood counts are usual and expected in such patients.

Early stage trial protocols also must define how to collect the maximum amount of data as conveniently as possible. Related to this, the protocol must account for the relatively short times available to evaluate patients, as disease progression can limit their participation. And, because the reality of Phase I oncology trials is to enroll patients with advanced disease, protocols must account for high mortality rates as well as the ready detection of relevant data trends, which always require prompt action to ensure patient safety and regulatory compliance.

While budget is a significant consideration for protocol and trial management partnerships, sponsors should consider the potential efficiencies of selecting services provided by deeply experienced, integrated teams dedicated to oncology. A CRO's staff should offer skills and abilities to efficiently manage the intricacies of studying novel treatments in advanced cancer patients based on their therapeutic and phase I oncology trial experience. This knowledge should span key functional groups such as project management, site monitoring, data management, pharmacovigilance, medical monitoring and biostatistics.

One effective staffing model for early phase oncology trials is a combined project manager (PM)/clinical trial manager (CTM) role. A PM traditionally focuses on the management of deliverables on time, on budget and with quality, while the CTM focuses on the day-to-day aspects of managing sites and fielding study conduct questions. However, in smaller-scale phase I oncology trials, these two positions have so many synergistic responsibilities that combining them can yield both operational and cost efficiencies. For example, the PM/CTM can keep his or her finger on the pulse of the study and stay informed of the status of individual patients. A PM/CTM's direct and timely communications can eliminate the cumbersome layers of coordination necessary in later phase trials. Additionally, the combined PM/CTM role also allows for informed and efficient management of patient cohorts, clinical research associates performing site monitoring, logistics of biological samples needed for pharmacokinetic and pharmacodynamic studies, etc.

Enabling Enrollment

Site identification might appear to be straightforward because of the large number of organizations already engaged in oncology clinical trials. However, a site should be selected because it will be both competent and capable of enrolling appropriate patients, has Good Clinical Practice (GCP) facilities and procedures, and employs available and qualified staff.



The National Cancer Institute (NCI) Clinical Trials Cooperative Group Program each year involves more than **3,100 institutions, 14,000 researchers, and 25,000 patients**.⁵ Moreover, NCI has credentialed **66 sites** as cancer centers in part because of their expertise in clinical research.⁶ In the EU, sponsors conduct most phase I cancer studies via expert centers, such as Cancer Research UK, Southern Europe New Drug Organization, Central European Society for Anticancer Drug Research, and the French National Federation of Cancer Centers.⁷

Ongoing, current relationships and experience with institutions, investigators and their staff help tremendously in choosing trial sites. If a sponsor is relatively new to early stage oncology trials, site selection expertise may be a service for which an experienced specialty CRO proves invaluable.

For example, a sponsor should know which sites have sufficient and appropriate patient populations to screen, based on their historic site enrollment patterns, versus those lacking patients or conducting competing trials. And, while two sites may have many similarities, a sponsor or the CRO should know which potential PIs believe enough in the science of the candidate treatment to become truly supportive of the sponsor's trial, versus other trials, and encourage patient enrollment. Knowledge of a site also helps determine which facilities have reliable PIs and staff that understand the

complexities and fluidity of phase I trial protocols, such as patient cohort management, around-the-clock medical monitoring, ability to collect and process extensive biological specimens, and commitment to timely data entry and query resolution. In contrast, a CRO with recent or frequent staff turnover or a site with overly burdened staff can create quality control issues (e.g., substantial delays or errors in data management) that can hinder or even derail a trial.

Operational Excellence

A sponsor can create great trial efficiencies if it is familiar with each site's standard operating procedures, such as a site's institutional contracting procedures, scientific and ethics review boards practices or document requirements and processes. The sponsor also must know and understand how the local trial site complies with federal, local and its own institutional regulations to protect and care for human subjects in research as well as their health information, both in the United States and other countries. The International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use guidelines and GCP principals provide international guidance to standardize the conduct of clinical trials across the United

⁵ "ACCELERATING PROGRESS AGAINST CANCER, ASCO's Blueprint for Transforming Clinical and Translational Cancer Research," Mark G. Kris, MD, Neal J. Meropol, MD, Eric P. Winer, MD, executive editors. November 2011.

⁶ "Our History," and "Cancer Centers," NCI Cancer Centers.

⁷ "Performing Phase I Clinical Trials of Anticancer Agents: Perspectives from within the European Union and Japan," Martin D. Forster, et. al. *Clin Cancer Resea* 16(6) March 15, 2010 pp 1737-44.

States, European Union and Japan, but use has differed among researchers, institutions and countries.⁸ A sponsor must make certain that each site follows good clinical, research and safety practices, from patient education to trial inspections. And, for multi-center trials that involve global sites, cultural awareness and sensitivity should be integrated into all of trial conduct.

A sponsor with extensive early stage oncology trial experience, expertise and staffing can navigate all of these requirements and successfully manage the trial. However, if a sponsor has limited capability in any of these areas, a CRO can augment knowledge, skills and abilities to plan and anticipate the very dynamic, complex circumstances presented by oncology therapies and patients with advanced disease. Contingency planning and risk mitigation are essential.

For example, sponsors frequently underestimate the time involved in enrolling a cohort and advancing from one cohort to the next. A preliminary protocol may call for multiple institutions, even global sites, yet careful evaluation of the inclusion criteria and site selection might permit a smaller geographic footprint to enroll the same patient population.

A foundation for operational excellence includes using vetted, oncology trial-tested procedures and resources that will accelerate the implementation of the initial trial infrastructure. Templates and libraries of standards such as study plans, database structures, edit checks, patient education/staff training materials, electronic case report forms, worksheets and adverse event monitoring materials will reduce drafting, review and finalization cycles while improving quality. Furthermore, considering the similarities across Phase I oncology trials, template-reporting mechanisms that summarize holistic patient results can be created to simplify and expedite dose-escalation decisions and thus minimize trial delays. This is especially beneficial in the Phase I setting for small- to mid-sized sponsors, as there is often pressure for expedited trial initiation to meet corporate funding milestones; thus any solutions for enabling rapid site startup or initial patient data capture can have a substantial impact.

Operational excellence also involves proficient use of eClinical technologies, which facilitate data capture at enrollment and during monitoring as well as ongoing analysis that recognizes emergent adverse events with accurate grading and attribution. Such eClinical technologies include electronic data capture (EDC), which requires an experienced design and build team to properly plan for and incorporate amendments for new tests or assays (e.g., as is frequent with dose escalations); adjudication software that seamlessly works with the databases to allow refreshing in real time based on parameters set by the sponsor; clinical trial management system software that captures and efficiently reports on all site activities from phone calls to emails to monitoring visit information; and safety database software that facilitates pharmacovigilance.

⁸ "Performing Phase I Clinical Trials of Anticancer Agents: Perspectives from within the European Union and Japan," Martin D. Forster, et. al. *Clin Cancer Resea* 16(6) March 15, 2010 pp 1737-44.

Some sponsors may question the investment in EDC for early phase trials that traditionally have functioned with paper data capture. However, the cost of EDC is no longer a deterrent in relation to paper methods, and EDC creates efficiencies and accuracy because it expedites real-time alignment of data with patient profiles, visits and cohort assessments. Moreover, EDC affords immediacy in the review of safety data by investigators and review committees, whether on site or remote. Other benefits include the cost-efficient data cleaning and more visibility and transparency into trial conduct.

Cohort Management

The management of trial cohorts begins at enrollment, when trial staff explain to interested patients who meet the protocol criteria how the candidate therapy and its use might differ from the current standard of medical practice, the potential risks involved and what a decision to participate means in terms of medical care, logistics and expectations. After a patient's initial signed consent, staff must continue to inform patients regarding how changes to the trial protocol, new safety information or new therapies might affect their participation.

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The relative speed of patient accrual depends on the study's dose-escalation protocol and patient availability/site capacities. Accrual adjustments should be anticipated and planned to keep study enrollment on track from the first-patient/first-visit onwards.

Trial managers enroll cohorts based on the traditional protocol goal to determine the highest recommended safe dose for use in advanced trials. That dose ideally has a target toxicity of less than 33 percent, meaning that it is one level below the one in which two of six patients experienced treatment-related toxic side effects. To find this

level, conventional trial protocols follow a patient accrual plan of "3 + 3," in which first three study patients take the same dose. If none of the patients have severe treatment-related side effects, three new patients receive the next higher dose. When a dose-limiting toxicity occurs in one or more patients, then the cohort may be increased to six patients for verification. As more dose-limiting toxicities emerge, the next lower dose levels are tested as a possible maximal tolerated dose until it is found (no more than one of six patients experience a dose-limiting toxicity) or until tolerability of the highest planned dose is verified.

In contrast, trial designs for newer agents may aim to find the optimal biological dose and adapt an accelerated titration design, which may include dose-escalation testing in a patient already exposed to a lower dose. Other adaptive designs such as continuous reassessment are also slowly becoming more prevalent.

Many phase I oncology trials of any design permit continuous administration of drug doses as long as patients do not experience disease progression or an apparent therapeutic response. However, a complicating factor in the cohort management is that slots are not assigned solely on the basis of the availability of the next dose level. Assignments also stem from slot vacancies created by patients who become ineligible or decide not to enroll, or by patient mortality.

Trial managers, by working with site investigators, can efficiently determine which slots must be filled and their priority, which site has patients ready to enroll and how long to hold a slot before offering it to another site. Ideally, as soon as a site identifies a potential patient for enrollment, they contact the trial manager to determine if a cohort slot is open and to then reserve it. If the cohort is already full, the trial manager should project the timing of the opening of the next cohort and reserves the next available slot for the site's patient. Such tracking of study participants and assignment requires near constant communication between the trial manager and on-site managers, and the trial manager's assignment plan must be deemed fair by all of the sites in order to succeed.

Data Monitoring

The study team also needs ongoing access to data and rapid retrieval of intermediate analyses to plan and fill slot assignments. Sponsors are accountable for the quality of these data and analyses, particularly regarding dosing and safety. The trial protocol must include systems to verify the integrity of data and study procedures. Quality data documentation and an oncology-experienced team that embraces integrated data review across multiple functional areas, and thus from different perspectives allows for analyses that can expose viability or liabilities of the candidate therapy. For example, thorough and current data can uncover toxicities that occur in only one site or in a subset of patients, which can be as revealing about the candidate treatment as those that affect all study patients. Quality data documentation also speeds the confirmation in dose evaluation, facilitating further dose escalation or validating optimal dosing.

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While data and analyses in early phase I oncology trials focus on determining safe dosing, sponsors increasingly also seek documentation of patients' quality of life and anecdotal efficacy information. For example, documenting patient-specific information such as duration of stable disease and time to disease progression for a phase I investigational therapy has value to sponsors to consider in the context of established treatments and in determination of specific indications to pursue for further drug development.

Timely Database Lock

The average times to a clean data set, database lock and data analyses are quality checkpoints for trial management. But quality and reliability of data should never be compromised for speed. Planning, expertise and tools can guide the process with great efficiency. For example, early involvement of biostatisticians experienced in oncology can yield case report form designs that from the start capture appropriate data that can quickly and effectively be translated to statistical outputs for trial analysis. Also, early testing of table shells can refine analyses without waiting until study completion. While some sponsors may consider paper data capture, the investment upfront in an EDC system can result in getting to database lock faster, usually at a rate that more than recoups the initial investment, especially when considering the real-time access to safety data EDC tools afford during trial conduct.

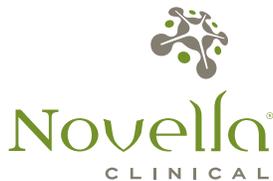
Summary

Most seasoned sponsors have multiple considerations for early phase oncology trials, from patients' health to management of biological samples to slot assignments to data. Selecting a specialty oncology CRO for early stage oncology trials can bring a sponsor counsel that is disease-specific, site-smart and delivers quality data. Partners bring sponsors results that lay the foundation for advanced efficacy trials in the most appropriate oncology patients, particularly when acquired in a time- and cost-effective manner.

About Novella Clinical

Novella Clinical, Inc. is a full service contract research organization specializing in early phase oncology trials. Headquartered in Research Triangle Park, N.C., and Stevenage, UK, Novella provides the experience and insight to bring medicines to market on time and on budget.

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