

# Setting Your Sites

There are a number of factors that impact the management and monitoring of an oncology clinical trial from the proposal development perspective. Mitigating potential obstacles, with strategies for proactive planning, can help to meet the unique needs of the biotech industry.

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When engaging a contract research organisation (CRO) sponsors expect decreased labour costs based on existing expertise, process and therapeutic experience, as well as the use of templates and standards that have proven successful previously. The CRO must take into account sponsor requirements and deliverables, study specifications and milestones, and the complexity of the project when determining labour requirements for a project. However, oncology clinical trials can present a unique situation in that they combine the most complicated factors when it comes to planning resources. In the biotechnology sector, there are often additional factors to consider in terms of company resources, goals and objectives as one investigational product can often make or break the company. Whether in-sourcing or outsourcing the conduct of the trial, labour costs will ultimately be incurred.

## Assemble an Experienced Team

Successful execution of oncology studies begins with a clear understanding of the type of tumour being evaluated, the study design, the analysis requirements and the inherent challenges involved with conducting these complex studies. An experienced team, while potentially running at higher labour rates, will be able to expedite many of the

planning aspects for the trial. CRO staff who are experienced with oncology projects can use their knowledge in the service of the organisation, creating project templates, providing scientific and medical oversight for the project team, as well as consultation and guidance for the sponsor. The high-level details and strategies that key experienced staff provide ensure repeatedly successful planning and achievement of study goals in the shortest amount of time. This early investment in critical expertise avoids the hidden costs of inefficient efforts and missteps throughout a clinical programme of studies.

Substantial experience – including a thorough understanding and familiarity with the tasks required to successfully complete oncology studies – ensures efficient study implementation. Specialised experience can include tumour response assessment (RECIST, WHO response criteria), validated QoL questionnaires, and experience with biomarkers and imaging. Understanding the safety profile and any potential concerns is fundamental when conducting research. Even with this experience, thorough training in protocol-specific processes and procedures will ensure adherence to regulatory reporting requirements and effective/proactive communication.

## Enrolment Resources are Critical

According to the National Cancer Institute, less than five per cent of cancer patients participate in clinical trials. If participation could just be doubled to 10 per cent, many studies could be completed in less than half the time currently necessary. This is a critical factor when planning resources for oncology clinical trials. By gathering the necessary resources to overcome (or at least mitigate) the obstacles to enrolment, biotech sponsors may find an initial increase in their investment, but significant savings in the long-term.

There are several reasons for low participation in oncology trials. Factors influencing a physician's recommendation of a clinical trial can include whether or not they are aware of appropriate clinical trials or an unwillingness to lose control over



their patient's care. Among the common reasons why potential participants do not enrol in clinical trials is their lack of awareness of the trial, lack of access, or a lack of understanding. The project team will need to include appropriate resources to overcome these factors. This may include:

- Study aid development, such as referral letters, posters, self-screening leaflets, flip charts with study information, and pocket reference tools
- Additional training resources for tasks such as the informed consent process. This provides site staff with the right message to give to the patient as well as how to discuss study participation to aid them when screening and consenting patients. It also closes the communication gap between site staff and potential patients, therefore removing the misconceptions regarding clinical trials
- Planning, coordination and support of additional site activities, such as presentations of the study to institutional/community physicians to raise as much awareness of the study as possible
- Increased time for traditional services such as teleconferences with

investigators and study coordinators to share their successes with other sites in patient enrolment and retention

A resourcing plan must also consider that a certain number of sites in studies involving oncology patients will not enrol patients. Typically, approximately 10 per cent of initially selected sites fall into this category. However, on smaller Phase 1 and 2 studies, enrolment goals are difficult, if not impossible, to achieve when even one site is a sub-par enroller. Investing time in a feasibility assessment test and involvement in patient access activities in advance of study initiation will ensure confidence in the selected sites from the outset. Additionally, the recruitment and initiation of an overage of sites at the start of the trial will mitigate against poor recruiters. While it may appear to reduce costs to identify additional sites that are held in reserve to replace those that do not meet enrolment goals (back-up sites), the potential for delays and the associated costs far outstrip those incurred by including a few extra sites from the start. These are critical considerations when planning for the labour necessary for the identification and qualification of the sites participating in the trial.

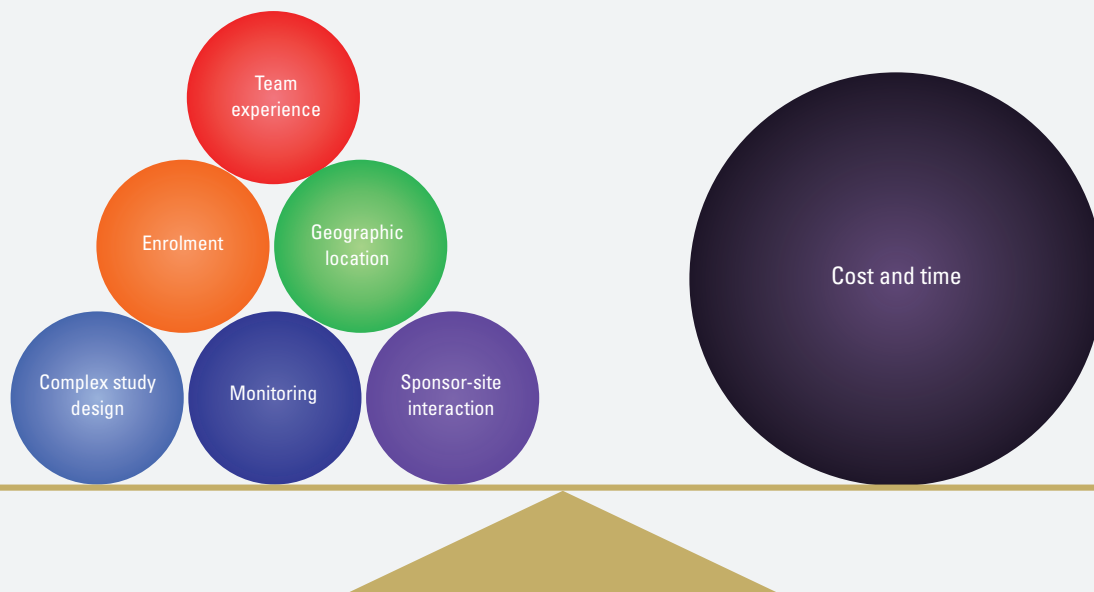
### The Impact of Geographic Location

Where will your trial take place? Obviously, this decision is influenced by your regulatory strategy. However, when there are geographic choices available, they play a key factor in planning resources, and ultimately the cost of the trial.

Different regions will produce different costs for a trial. For example, compared to western Europe, the costs of conducting clinical trials in central and eastern Europe have been competitive due to slightly lower labour and expenses for monitoring and travel. In addition, central and eastern Europe can often support shorter timelines in patient recruitment, more patients, high quality data and less data queries. However, investigator grants are moving closer to those in western Europe.

Like other trials where enrolment can be challenging, oncology trials often necessitate a review of various geographic regions for recruitment purposes. For example, again using central and eastern Europe, patients in this region have not benefited from the most recent advances in medicine

**Figure 1:** Careful consideration of the critical elements in resource planning for oncology trials will allow managers to achieve a balance with resource time and cost



Source: Premier Research

and view clinical trials as a conduit for the latest medical treatments available. Moreover, there are many patients who have not been exposed to treatment, since fewer pharmaceutical products are on the market. This facilitates the recruitment of patients into clinical trials with fairly strict concomitant medication entry criteria.

Patients in this region also tend to see the same doctor every time they visit the hospital, which builds a trusting relationship between the doctor and the patient. This trust has expedited patient recruitment and translated into high patient compliance and low dropout rates even in long-term trials, resulting in more qualitative data.

### Executing Complex Study Designs

The clinical research protocol serves as the origin for all data generated during the study. Oncology protocols in particular involve complex study designs and procedures that require additional labour resources to ensure the safety of the patient. For example, under the standard '3+3' design of Phase 1 oncology trials, cohort slots must be managed very closely, carefully, and equitably across sites. This is especially important if the targeted patient population includes only one tumour type rather than an 'all-comers' design or if there are more than three participating sites. The key to effectively managing cohort slots lies within the site's ability to pre-identify potential patients prior to the opening of each cohort. Patient pre-identification ensures that subject enrolment in the dose escalation stage is limited more by the protocol's cohort advancement rules than by the availability of patients. To aid this process, the project team may consider including additional labour time to hold frequent (at least every other week) meetings with the sites as a group during dose escalation in order to review the status of ongoing patients and to pre-identify specific subjects for open slots.

A Cohort Review Committee will need to be established to review clinical and

laboratory data in order to determine if dose escalation to the next cohort is appropriate or if the trial needs to be stopped. Committee members may include medical advisors from the CRO and the sponsor, as well as principal investigators and other industry consultants. Data will need to be collected and distributed to the committee in advance of cohort review meetings. Adverse event data will need to be presented on an ongoing basis to the committee. Management, monitoring and data management plans also need to be developed to support the committee. The labour required to manage these tasks must be taken into consideration when planning for an oncology trial where study complexity is compounded by a patient population in advanced stages of cancer.

### Clinical Monitoring

A less than robust monitoring plan could put a sponsor at risk for not having the data sufficiently monitored. The savings generated by front-end reduction in monitoring time and resources could be outweighed by compromised data on the back-end, resulting in over-runs in both time and funding in the sponsor's clinical development plan. Therefore, it is critically important to consider the patient population when determining the amount of labour needed to adequately monitor an oncology trial.

A Phase 1 trial in healthy subjects may only require on average three to five minutes review time per case report form (CRF) page. However, advanced cancer patients will have large and complicated case histories and medical records which require a significant amount of time (typically 12 to 14 monitoring minutes per CRF page) to adequately conduct 100 per cent source document verification of CRF data.

Furthermore, oncology trials often involve longer recruitment and treatment durations than a Phase 1 trial in healthy subjects. A typical monitoring plan that includes onsite visits every six to eight weeks could be too rigid and financially prohibitive for an oncology trial. A flexible monitoring

strategy developed with protocol-specific requirements in mind can save the sponsor money. A flexible monitoring strategy may consist of treating monitoring visits as a 'pool' so that higher recruiting sites receive more visits than lower recruiting sites. For example, if a study involves randomisation, one strategy is to perform the first monitoring visit at each site shortly after randomisation of the first patient to ensure that all study site personnel are familiar with the requirements of the protocol and feel confident in performing the study procedures. A follow-up visit could then occur approximately eight weeks later to ensure that all study procedures are being conducted as directed in the protocol. The remaining pool of monitoring visits could then be used on a site-by-site basis depending on recruitment numbers. For non-recruiting sites, the project team may conduct motivational visits. Motivational visits can be shorter than conventional monitoring visits, but these visits serve to remind the site of enrolment requirements.

Using a flexible monitoring approach for an oncology trial emphasises the need for regular and consistent monitor-site communication. On average, a monitor may spend 15 to 30 minutes per week answering site questions and providing additional support and training on study procedures. It is critical to budget for continued communication between the monitor and the study site to ensure proper reporting of all serious adverse events (SAEs), supply needs are fulfilled, new site staff is appropriately trained on study procedures and data queries are resolved in a timely manner.

### Sponsor-Site Interactions

Due to the nature and complexity of cancer treatments, the sponsor may consider including in the resourcing plan opportunities for sponsor-site interaction. This can be accomplished by forming an independent monitoring team assembled from within the sponsor company or by accompanying the study monitor during on-site visits (through co-monitoring or supervisory visits). This approach

works well in early phase studies involving complex drugs/therapies. The sponsor's presence at a site can be used to motivate sites by providing its staff with an opportunity to ask detailed questions of those with an expertise in the administration of the drug/therapy, and thereby improve their understanding of treatment requirements. The ideal time for sponsor visits at the site would be following the investigators' meeting where the staff typically receive their initial instruction on the treatment method.

Sponsor-site interactions can be facilitated by the project team. Labour would be necessary to provide administrative support – such as arranging travel and accommodation – for meetings between the sponsor and the sites, which may involve accompanying the sponsor team at on-site supervisory visits and facilitating communications.

### A Highly Variable Work Effort

When developing a resourcing plan, it is important to consider the highly variable work effort required for an oncology trial. The number of hours each team member spends on the project may vary depending on the particular stage of the trial.

For example, start-up durations for oncology trials necessitate a considerable amount of work effort given the type of sites – including major medical centres, hospitals and academic institutions – used to recruit the patient population. Key to the timely start up of any study is obtaining both regulatory and Ethics Committee (EC) or Institutional Review Board (IRB) approval for European and North American investigative sites. European trials pose a challenge of meeting local, regional and national regulatory requirements in each country, while in North America many of these sites will require the use of a local IRB which can typically take three to six months before approving a study. A resourcing plan may include additional project team members

during the start up stage to streamline this process by identifying each site's competent authority, EC/IRB approval requirements and milestone dates during the site selection process.

While a greater amount of labour is needed to initiate an oncology study, the work effort may be lessened during a long treatment or follow-up phase when subject visits to the site may occur less frequently. Trials in patients with rare cancers may have lengthy enrolment periods where only one patient is enrolled every several months. The resource plan should consider:

- Will the entire monitoring team be needed throughout the duration of the monitoring period? For example, due to more frequent visits, a team may be fully utilised during enrolment and treatment, however, how will you plan for staffing during a one or multi-year follow-up period?
- What is the optimum combination of site visits and phone contacts during a lengthy period of slow activity?
- Can a training plan and/or training materials be developed to ensure fully trained monitors

that can be called upon only when needed?

- Does the training plan take into account staff changes over a lengthy trial duration?

These fluctuations in the required work effort should be considered carefully during the planning stages to ensure that the appropriate levels of team allocations are available during critical or peak times of the study, in addition to fully trained staff throughout the duration of the trial.

### Planning is the Key

Oncology clinical trials can be complex and expensive. However, the effort expended in planning the resources needed to manage and monitor site recruitment, enrolment and data collection affects both the successful completion of the trial and the cost incurred. Keeping in mind the programme of studies planned for the investigational product, the length and complexity of the trial and informational and motivational needs of the site staff, patients and monitoring team, will support the most cost-effective plan, not just for a single study, but also for the entire programme of studies.

## About the authors



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