Cost-Neutral Clinical Research Enterprise

This article is the fifth in a continuing series of articles focusing on the exemplary attributes of successful research in clinical practice. ASCO described a core group of standards and exemplary attributes of clinical trial sites in the initial article of the series in May 2008.¹ This article addresses the challenge of creating a research program that at minimum will be self-supporting. Two attributes of a cost-neutral clinical research enterprise are diversification of trial mix and high accrual activity.

Background

Mature, established, exemplary clinical trial sites have a broad, diversified portfolio of clinical trials offered, which in the words of the ASCO statement, “provide the broadest array of options for patients treated and to maximally use their clinical research infrastructure and resources.”² This is accomplished by offering a variety of trials that cover a range of diseases that appeal to a wide patient population served by the site. Diversity applies to the phase of trials offered and the mix of modalities, including surgery, radiotherapy, and chemotherapy treatment options. A site’s trial portfolio can also be expanded by offering prevention, quality-of-life, symptom control, and correlative trials for patients. Sites could also consider offering risk assessment or prevention trials to patients’ family members. Although having a diverse trials menu is important, a site should also take care to open trials that it is likely to accrue patients to, because all trials involve start-up costs for activities, such as institutional review board (IRB) approval.

Another attribute of an exemplary clinical research site is to accrue as many patients as possible. The ASCO statement suggests each site should establish its own goal for accrual on the basis of its patient volume, patient mix, and the availability of clinical trials. The statement recommends 10% patient accrual as an overall goal. Another goal is to focus accrual activity on under-represented populations. These goals, and progress toward achieving them, should be assessed regularly. Development of both an appropriate infrastructure and realistic budget are crucial to accomplishing these goals.³

Determining the Proper Infrastructure

It is important for clinical trial sites to determine the proper infrastructure for a clinical research program, including staffing, division of responsibilities, use of computer-based and other technologies, responsibilities for meeting regulatory and record-keeping requirements, and other activities.

Gary I. Cohen, MD, Director, Cancer Center at Greater Baltimore Medical Center, Baltimore, Maryland, gave a presentation in September 2008 at the ASCO Clinical Trials Workshop on Defining Personnel Resources. He noted that different personnel have different training and hourly wages, so staffing ultimately affects the budget. Office staff (eg,

administrative assistants) can do the photocopying and other tasks involved in preparing documents for IRBs at far less cost than if the work were done by a research nurse. Likewise, having a medical assistant enter laboratory test results into the database will be more cost effective than using a clinical research associate (CRA) as a data manager. “The critical element for clinical trials,” he says, “is to have full time personnel devoted to trial activities.” If not, the trial activities may end up last on their list, eg, if the administrative assistant is also required to answer the office phone, or the medical assistant is needed to take vital signs for all the practice’s patients.

Alan Lyss, MD, Missouri Baptist Cancer Center, St Louis, Missouri, agrees. “One point that is really critical and a lot of people miss is that they need a dedicated CRA or research nurse conducting research activities, rather than having that responsibility shared among staff who also have clinical responsibilities. The CRAs or research nurses could work part time, but should not split their time between research and clinical duties. I can’t overemphasize this,” he says. He suggests that programs that cannot afford a research nurse should start at the very least with a dedicated CRA who has responsibility for regulatory documentation. Another role for the CRA is to monitor scheduled patients to ensure they return for required tests, monitor the data collection, and see that documents are handled appropriately. It is also important to have staff who are knowledgeable about each study, including expected and possible adverse effects. These staff members will be needed to inform patients about the studies and need to be able to answer any patient questions. If patients have a problem during the trial, these dedicated personnel should be available for patients to contact, should be able to double check doses, and should be knowledgeable about any allowable interventions. In addition, there need to be dedicated staff responsible for ensuring all laboratory and other tests are performed, specimens are sent to the correct places, and x-rays and scans are reviewed.

Lyss says that a goal should be to find and develop tools and technology that will remove as many impediments as possible to conducting clinical trials. He observes that electronic health records (EHRs) for patients are generally designed for clinical rather than research use, but could make it easier to find eligible patients to enroll on trials. Some EHR vendors have research modules; some products may need to be tailored for research use. (For additional information on EHRs, visit www.asco.org/ehr.)

Budgeting

Practices must know how to develop a budget for their clinical trial activities, including dealing with costs of start-up and participation. “My main point when giving my talk is

ASCO Statement on Minimum Standards and Exemplary Attributes of Clinical Trial Sites

The ASCO statement addresses the minimum requirements for sites conducting quality clinical trials as well as the attributes of exemplary sites. Both minimum requirements and exemplary attributes were based on a review of the literature, current regulatory requirements, and consensus among community and academic clinical researchers. To conduct quality clinical research, sites should meet the minimum requirements. The exemplary attributes are voluntary and suggested as goals, not requirements. Not all attributes will apply to all clinical trial sites, and many sites may be able to conduct high-quality clinical trials without accomplishing all attributes.

that it is possible for a program in a community hospital to do clinical trials and get the benefit of these trials for patients and themselves without any cost to the practice,” Cohen says. “In some situations, it is even possible to get additional funding that might capitalize other endeavors.” There is no question that there will be additional costs starting off, and it could take a couple of years to achieve neutral conditions, he observes. Conducting clinical trials is worth it for a site, because the benefits include allowing patients access to state-of-the-art treatment modalities, and may well increase the visibility of a practice as the community recognizes the site as being involved in research.

“Clinical trials need to be done well, or you can’t do them,” Cohen explains, observing that one should not think of doing them as cheaply as possible, but rather, they must be done as well as possible. Budgets need to include all costs (eg, hourly wages, benefits such as health insurance, computers, use of software, dedicated space, and Internet access). He points out that there are hidden costs that need to be included in the budget such as additional time with the IRB if amendments to trials occur. The longer a trial is active, the more it will cost. Other time costs include customizing an EHR system for research use.

Sites need to allocate space for the clinical trial staff, and to consider whether trial records will be stored on site, which takes space, or off site, which can be expensive. Lyss calls personnel salary and benefits the “tip of the iceberg.” He says that space dedicated to research personnel needs to be a place where they can think, focus on their work, and communicate without disturbing others. Research personnel need to have access to technology, including telephones, fax equipment, and computers with Internet access, all of which are obvious budget items.

Clerical and front office support need to be considered in budgeting for the research program. Clinical trials require cost accounting to ensure that the site does not bill for expenses solely

related to research activities because these costs must be paid by the sponsor. Routine clinical costs, however, can be billed to the patient’s insurance company. If insurance companies reject the costs associated with clinical trials, it will then take nurse or physician time to appeal that decision. Some states have laws that require insurers to cover patient-care costs of clinical trials. Additional Resources provides information on state laws. The trial mix can also affect the budget. Lyss estimates that phase I and II trials take about twice the personnel time and effort than do phase III and IV trials, and industry-sponsored trials are also about twice as labor intensive as National Cancer Institute Cooperative Group-sponsored trials.

“One thing we made a mistake with was underestimating data management for trials already closed,” says Lyss. “We were not looking at the big picture of how long monitoring would take, how long patients would live and continue to report.” His practice has a full-time CRA dedicated to follow-up of a trial initiated in the 1990s, which will require monitoring and toxicity updates sent to the IRB as long as enrolled patients live. “We never estimated this. It’s good for the patients, and uplifting. It’s wonderful that the patients are doing well and are ambassadors for other patients.” He says his practice also initially did not appreciate the burden of some of the requirements of industry-sponsored trials (eg, maintaining screening logs for patients who were not eligible or who opted out of a study). Site initiation meetings also have a time-cost burden. The sponsor’s monitoring visits, sometimes conducted by Contract Research Organizations on behalf of sponsors, can take a lot of personnel time, and can be disruptive, particularly if they occur quarterly and a practice has multiple trials ongoing simultaneously. Additional time costs include physician attendance at investigator meetings, which a pharmaceutical sponsor may require. Lyss acknowledges that it is possible to negotiate per case reimbursement for industry-sponsored trials that helps cover these costs, and he finds companies are generally reasonable about those costs, if sufficient documentation of the anticipated expenses is provided.

Diversifying the Trial Mix

Both Cohen and Lyss recommend starting out with a few clinical trials for the diseases a practice commonly sees, and to make sure a majority of the physicians in the practice heartily endorse those trials. For example, if a practice sees a lot of patients with lung, breast, or colon cancer, it might make sense to have two or three trials for each disease. Cohen thinks it would be possible for everyone to know all those trials well, and that one CRA could recruit for seven or so studies. Lyss agrees that each practice has to look at its particular patient population and select trials that reflect commonly seen malignancies.

It is also important to consider the capability of the practice’s pharmacy when selecting trials. Some experimental drugs are difficult to manage, and in some areas there might not be reimbursement. Some practices might not have the wherewithal to administer intravenous medication 7 days a week, so should not consider trials that require it. Both Lyss and Cohen suggest

starting with phase III trials. Cohen says, “No one will give you a phase II trial if you haven’t shown you can collect phase III data.” Phase IV (postmarketing) trials are always sponsored by the pharmaceutical industry, he observes, suggesting that these trials are also a good way for a practice to get started because they are less labor intensive than are phase I to III industry trials. “Starting with less labor-intensive trials allows a practice to get its sea legs,” explains Lyss.

As practices expand their research programs, they should consider a mix of trial phases that includes trials for both early and late disease and for symptom control. Patients enrolled onto trials for early disease may go on another trial for symptom control, or for late disease, should they experience a relapse. A good mix of ongoing trials will also provide additional opportunities for patients who may have previously passed up enrolling onto a trial.

Increasing Accrual

Sites need to know how to increase accrual in a cost-effective manner. This topic will be addressed in greater depth in the next article in this series, which will cover marketing and outreach. Cohen suggests that it may be worthwhile to find donors, such as pharmaceutical companies, foundations, or local community organizations, to pay for general educational materials that explain the utility of clinical trials and can be used to generate interest among patients. If these materials relate to accrual to a particular trial, an IRB will want to review them. Lyss suggests tracking accrual for all physicians

involved in trials, and focusing attention on those who are intermediate in accrual. The physicians with high accrual are already in a good position, and it will likely take a lot of effort to get the physicians with lowest accrual to increase their activity. For the intermediate group, focus should be on how they can be more effective, what they need to get to the next level—whether it be a different trial mix, more personnel, attendance at research-based meetings, or mentoring to improve their techniques for discussing participation with patients.

“Once a practice is involved in the business of clinical research, it will need to continually review the process,” Lyss advises. “It’s a constant reassessment to make the practice as efficient as can be. The faster a practice can activate a study, the more patients it can accrue before the study closes.”

Upcoming Events

ASCO will hold conference calls in 2009 during which content providers to the series will discuss these topics in more detail and be available for discussion. See ASCO’s Web site at www.asco.org/researchresources for more information or e-mail researchresource@asco.org to be kept up to date with new content.

The next article in this series, to be published in the May 2009 issue of *Journal of Oncology Practice*, will discuss marketing and outreach to increase patient, referring physician, and public awareness and trial accrual.

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Additional Resources

Model Contract Language

- Use of the language proposed in the recommendations is not mandatory but rather was designed to be a starting point for clinical trials contract negotiations.
- The Proposed Standardized/Harmonized Clauses for Clinical Trial Agreements are available on the NCI download site at: <http://cancercenters.cancer.gov/downloads.html>

States With Clinical Trial Laws or Agreements

- www.cancer.gov/clinicaltrials/ctlaws-home

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