

The benefits and challenges of conducting clinical trials

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This is the first in a series of articles *Community Oncology* will publish about conducting clinical trials in your community-based oncology practice. No matter what stage you are at—whether you are just thinking of dipping your toe into this revenue stream, or you are looking for ways to better manage your trials already under way—this series will provide practical information to help you more effectively care for patients and more efficiently run the business end of your research program. In this first article of the series the author weighs the benefits versus the potential difficulties of running clinical trials—an enterprise not to be taken lightly.

Currently, there are more than 650 anticancer drugs being studied in clinical trials. Traditionally, such trials have been conducted in academic settings. But over the past 20 years, community-based oncology practices have leapt ahead, with more than 3,100 investigators in over 800 practices recruiting more than 60% of all cancer patients. One advantage of this trend is that community practices can offer a much more realistic picture of the efficacy and safety of a drug. An institution, with all its support systems, may not present a real-world view of how these drugs actually work in patient populations. Another advantage is for the patients themselves, allowing them easy access to the latest clinical trials within their own community under the supervision of their local physician.

Among the benefits for practices:

- Clinical trials offer access to the latest in cancer therapy, thus providing your patients with state-of-the-art quality care.
- Private practitioners have the opportunity to learn about the latest therapies before they come to market. This experience provides you first-hand knowledge of safety concerns, raising your level of confidence in treating your patients.
- Clinical trials give you a competitive edge, serving as a marketing tool, not only for increasing referrals but also for maintaining your patient base.

Of course, your participation in clinical trials presents many challenges; running trials is not an enterprise into which you can venture casually. Like cancer, clinical trials are complex. Many practices begin a research program without understanding the basics, either from a business or clinical per-

spective. Most underestimate the time involved in establishing and maintaining a research program at their practice. It's important to remember that managing a successful research program isn't just about patient accrual. You and your staff need to fully understand the challenges involved *before* you begin a program and *while* you are implementing.

Practice commitment

Clinical trials are not conducted in a vacuum, and your decision to participate must be support-

KEY POINTS

Clinical trials in your practice give you a competitive edge and provide your patients with state-of-the-art care.

Practice-based clinical trials offer a real-world picture of the efficacy and safety of new drugs.

Deciding whether to conduct trials—or increase your participation—requires careful planning.

The entire practice must be committed to, and well versed in, the protocol.

Data must be submitted accurately and in a timely manner to ensure regular payment.

Documentation must be meticulous and infallible. Your reputation depends on it.

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ed by everyone in your practice including physicians, management, and staff. Too often, clinical research coordinators (CRCs) are expected to shoulder the entire burden, which sets up your research program for numerous challenges. Everyone in the practice has a role to play.

Three important elements of a committed practice are:

- **A coherent practice philosophy.** Within a practice, physicians are crucial to setting the tone of commitment to the overall goals of the practice. They must convey to the entire staff—from the nurses to the support staff—that involvement in clinical trials is important to the practice and important for patients. The CRC needs everyone's support and efforts to recruit, retain, and treat patients on clinical trials.

- **A willingness to invest for the long term.** Months before your practice sees any returns, you will have to invest time and money in staff, training, systems, and equipment. Every partner should support these investments, and the practice manager should feel comfortable that it makes good economic sense.

- **Good communication.** For your patients to feel comfortable participating in clinical trials, they must be able to sense that “the right hand knows what the left hand is doing.” Take the time to communicate regularly in staff meetings to make sure that everyone knows the plan, allowing a coordinated and systematic approach to trial conduct.

Cost

Clinical research is labor intensive. Most of the cost of a program is for research personnel expenses, including salaries and benefits. There are additional overhead costs for phones, computers, fax and copy machines, some of which you may need to dedicate exclusively to managing all the activities involved in clinical trials. You'll need ample storage space

Five essentials for trial participation

- **Effective screening process** Engage all staff members in this endeavor.

- **Adequate training and education** Includes knowledge of the protocol requirements as well as knowledge of good clinical practice.

- **Effective communication** All staff, physicians, and management must effectively and consistently communicate.

- **Oversight** Proper supervision by the principal investigator on site helps ensure involvement and adherence by everyone in the practice.

- **Local research standard operating procedures (SOPs)** SOPs ensure that everyone is “on the same page” when it comes to conducting the research.

for documents that must be kept on file for 10 years. You'll need space to store the trial drugs, which must be kept separate from other stock drugs, as well as a biosafety cabinet for drug admixture.

Effectively managing costs, accurately assessing ongoing staffing needs of your research department, and successfully budgeting/contracting will ensure the program's quality, efficiency, and financial success. Operating a clinical trial program within your practice rarely generates large profits. However, you should strive to bring in sufficient revenues to support the required efforts and increased staffing needs as your program grows. All in all, it's a balancing act.

Adequate and appropriate staffing

As a rule of thumb, each CRC should be able to manage 25–30 active patients. Of course, this level of staffing depends on a number of factors, including trial acuity, number of accruals per month, number of active

patients versus number of patients in follow-up, size of the practice, number of locations at which research is conducted, support by the ancillary staff, and local Institutional Review Board (IRB) requirements.

The key is to be realistic and to plan strategically for growth. There are many resources available that can assist you in developing your program, projecting your initial and ongoing staffing needs, and maintaining a current understanding of US Food and Drug Administration (FDA) requirements. (See the “Resources” box on page 167.)

Knowledge of and compliance with FDA regulations

The Code of Federal Regulations from the FDA outlines “Good Clinical Practice (GCP) Guidelines” for conducting clinical trials and can be ordered online at www.barnettinternational.com; the complete publications list includes the “2005 CFR/ICH GCP Reference Guide” for \$11.95. You and your CRC should be familiar with these codes and should be able to convey key elements to your staff. Additionally, training in the Protection of Human Research Subjects is mandatory for all research staff and investigators and is online at the National Institutes of Health (NIH) Web site <http://cme.cancer.gov/clinicaltrials/learning/humanparticipant-protections.asp>. The sponsors of any trials in which you participate will want documentation that you are trained and certified. Consult the listed resources; they focus on GCP, research training, guidance documents, and human subject protection tutorials.

Selection of appropriate trials

Although it may be tempting to start a number of different trials, you need to be selective and realistic, knowing that opening and conduct-

ing multiple trials costs time and money. The primary consideration is your patient population. If you only see 50 lymphoma patients per year, selecting a lymphoma trial may not be a good choice. It's better to focus on fewer trials and do them well. At International Oncology Network-Clinical Research, we recommend that you hire a clinical research coordinator dedicated to research and start with two or three solid tumor trials, such as lung or colon cancer. With high-incidence tumors, you'll have more opportunity to recruit sufficient numbers of patients and provide quality, timely data. Payment for research services is based on these two deliverables, allowing you to effectively manage your research costs.

Physicians are often attracted to a trial because they are interested in the drug under study. However, if your CRC examines the protocol logistics and operational details and determines that the trial is not feasible, we recommend that you exercise caution in the selection of that trial. An experienced and knowledgeable CRC is an invaluable asset and his or her

judgment should be respected.

Quality documentation

Successful research is measured not only by accruals and the number of open trials, but by meticulous source documentation, and timely and accurate data as well. Consequently, these data are critical for the financial welfare of your research department.

Typically, most data should be submitted within 2 to 4 weeks of the patient visit. However, that deadline can be as early as 2 to 5 days, depending on the needs of the sponsor or pharmaceutical company. It is in your economic interest—as well as in the interest of your reputation as a reliable researcher—to collect and submit data in a timely manner. Many, if not all, drug companies base payment on receipt of data. Without those payments, your costs to conduct the trials will keep mounting, negatively impacting your balance sheet.

Keeping good records isn't always easy, but it is possible, especially if you consistently utilize "prompting" tools such as source document worksheets. They ensure that you need not rely on memory to capture all the information. The CRC can develop these work sheets based on the data captured in the case report form, or they can be provided by a consultant, clinical research organization/network, or sponsoring company. Following a consistent routine makes for much better documentation and completion/submission of case report forms.

It's also a good idea for practitioners to get into the habit of writing detailed chart notes. These notes not only tell the "story" of your patients' experience while on the clinical trial, they also provide documentation of your oversight during this important phase of their care.

Ideally, when a patient is seen, the CRC should be present to assist the investigator in ensuring protocol

Five important factors to consider when adding staff

- Active and follow-up patient load
- Monthly accruals
- Trial acuity: does the site participate in phase I and/or pharmaceutical trials? How complex are the data?
- How many offices are covered by the staff?
- Are the trials handled by a central IRB or must trials go through the local IRB?

compliance and thorough assessment and documentation of adverse events. When the CRC is unavailable, other team members must be aware of the fact that this is a clinical trial patient (a flag on the chart works well for this purpose) and must know what needs to be collected and documented that day.

Creating accurate documentation for a research patient is really no different from what you already do for patients who are not taking part in a clinical trial. As with any patient, documentation for Standard of Care visits determines the code level at which you can bill insurance, as dictated by Medicare.

The wave of the future is electronic data capture. Some practices, as well as pharmaceutical companies are providing dedicated computers or a Web site address at which notes may be documented electronically.

With quality documentation you will have a well-managed program that fulfills the commitment you have made to patients and industry.

Understanding your roles

Whether you are preparing to develop a research program or managing an ongoing program, keep in mind that a successful program involves everyone in the practice to varying degrees. It must be a team effort to be a success.

Five "must haves" when choosing a trial

- **All physicians must support the scientific rationale;** if they don't, they won't accrue patients.
- **Adequate patient pool** from which to recruit.
- **Ability to conduct the required study procedures** within your practice's infrastructure; without that, adherence to the protocol is compromised.
- **Adequate staffing and ancillary support** You need to realistically assess the need for additional staff to manage all clinical trials at your site.
- **An understanding of your patients** Will they accept phase I/II clinical trials that may deviate from your standard of care?

Five biggest mistakes

■ **Failure to obtain informed consent** Protection of the human research subject is our first obligation. Obtaining informed consent and thorough documentation of that process is the most important component of that protection.

■ **Falsified data** Don't let your zeal for accruals trap you into falling behind and falsifying data.

■ **Inadequate source documentation** Your source documentation tells the story of your patient's experience while on trial and provides proof of your oversight.

■ **Protocol noncompliance** Failure to follow the protocol may compromise patient safety and does compromise the integrity of the study.

■ **Delinquent or inaccurate data submission** Multiple queries and late data lead to no payment or delayed payment for the hard work you and your staff have put into the study.

Committed physician investigators

To be effective, the physician must believe in the worth of the trial and be ready to convey his or her conviction, presenting it as a treatment option—in some cases, the best option. It is up to the physician to fully explain the trial so that the patient can give his or her informed consent. Patients are much more willing to participate in a clinical trial when they feel that their physician is confident that the trial provides one of the best treatment options.

However, physician obligations don't end with the recruitment of patients. At the beginning of a clinical trial, the investigator signs the FDA Form 1572, a legal document binding him or her to specific responsibilities when conducting the clinical trial at his/her practice. Failure to follow these obligations can lead to sanctions, including disbarment. The following is a list of these specific requirements stated within the FDA

Form 1572 for which all physicians are accountable:

I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

I agree to personally conduct or supervise the described investigation(s).

I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.

I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.

I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.

I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Physicians need to remain cognizant of these responsibilities throughout the development and management of a clinical research program.

Clinical research coordinators

The CRC is the pivotal point of any research program. In most programs,

the physicians delegate some of their 1,572 responsibilities to the coordinator. Under the supervision of the physician, the CRC is responsible for conducting research according to FDA regulations and the protocol. The CRC's daily responsibilities can include:

■ Screening charts to point out potential research patients.

■ Following up with patients after they talk to the doctor.

■ Following up the doctor's discussion about informed consent and ensuring that patients understand the safety risks.

■ Seeing that all protocols are followed correctly by meeting with and educating the staff, particularly chemotherapy nurses who will be responsible for administering the drugs.

■ Setting up patients' office visits to make sure they follow the protocol.

■ Making sure tests are ordered on the right day and patients come in on the right day for treatment.

■ Maintaining drug accountability for all study drug provided by the sponsor.

■ Making sure data are collected and available in the required time frame.

The CRC is a valuable and critical component in ensuring that your patients on clinical trials are treated appropriately and that your research program is successful.

Pharmacists

Sometimes pharmacists assist the CRC by maintaining drug accountability; in some instances, they actually function as the coordinators. Pharmacists log drug receipt and administration, ensure accurate drug calculation, and may assist with data. Research department management must be aware of the scope of the pharmacists' role and their labor costs to the research department.

Chemotherapy nurses

These practitioners are responsible for administering study drug within the guidelines of the proto-

col. They must be in constant communication with the research staff to ensure they have the most current information. Chemotherapy nurses are also responsible for assessing and thoroughly documenting any adverse events experienced during the course of study drug administration.

Practice managers/accounting

Accounting personnel must ensure that the research department is credited for all revenues received throughout the clinical trial. I always recommend that you account for the revenues and expenses as a separate line item, associating research revenues with research ex-

penses. In that way, your practice manager can see that you are covering your costs and can determine whether budgets should be increased. If research expenses are not being covered by research revenues, it's usually due to inadequate budgets, lack of accrual, and/or a trial selection inappropriate to your patient population.

Accounting personnel must also be aware of what may be billed as standard of care costs and what may be billed to the sponsor as part of protocol-covered expenses. "Double dipping"—that is, receiving payment from a sponsor and billing the same charge to insurance—is illegal.

Summary

Conducting clinical trials is a balancing act of accruing patients, ensuring protocol compliance, providing oversight, collecting and reporting quality data, and ensuring you have adequate staff to handle the job in a timely fashion. It is critical that you have the infrastructure to support this endeavor, for without it, some of the balls in the air will start to drop, compromising the success of your research program.

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Resources for conducting research

Publications:

Becoming a Successful Clinical Research Investigator, Dr David Ginsberg;

<http://www.centerwatch.com/bookstore/pubs.profsindex.html>

This publication takes you through the process of determining whether clinical research is right for you to understanding the industry, setting up your own clinical research site, and finding studies.

The CRC's Guide to Coordinating Clinical Research, Karen E. Woodin, PhD; <http://www.ons.org/publications/books>

This publication was designed as a training resource for investigative site

staff. It is filled with valuable information on the role and responsibilities of a clinical research coordinator (CRC) and explains in detail the research process from the site and CRC perspective.

Good clinical practice:

<http://www.fda.gov/oc/gcp/regulations.html>

www.GMPPublications.com

Research training courses:

Association of Clinical Research Professionals, <http://www.acrpnet.org/education/gcp/index.html>

Clinical Research Site Training, http://www.crstnet.com/html/basics_dates.htm

Research Dynamics

<http://www.resdynco.com>

Aureus Research

<http://www.aureusresearch.com>

The Society of Clinical Research Professionals

<http://www.socra.org>

Guidance documents:

<http://www.fda.gov/oc/ohrt/irbs/default.htm>

Human subjects

protection tutorials:

<http://www.cancer.gov/clinicaltrials/learning/page3>

<http://ohrp-ed.od.nih.gov/CBTs/Assurance/login.asp>

In upcoming issues of *Community Oncology*, we'll explore in more depth the practical information you and your staff need as you develop your clinical trials program. Among the topics we'll include:

- Accruing patients
- Codes of Federal regulation
- Good Clinical Practice
- Informed consent: educating patients
- Establishing internal quality standards
- Working with Internal Review Boards
- Managing drug accountability
- Regulatory paperwork
- Clinical nurse managers
- Budgeting
- Data management
- Managing, documenting, and reporting adverse events
- Preparing for an audit