

Incorporating Cancer Clinical Trials Into Your Practice

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Module 1: Becoming a Cancer Clinical Trials Investigator

1. Introduction

Clinical trials are essential in developing new therapies and advancing cancer care. Many clinical trials can lead to novel therapeutic options in certain diseases. To complete clinical trials in a timely manner, both competent investigators and more rapid patient accrual are necessary. Only 3% of adults diagnosed with cancer participate in clinical trials annually while over 50% of pediatric cancer patients participate. To facilitate clinical trial implementation and completion, more investigators are needed.

This module helps you evaluate the option of becoming an investigator yourself by providing you with practical considerations and responsibilities associated with becoming an investigator. Methods for how to become a clinical trials investigator are also discussed.

Upon successful completion of this module, you will be able to:

- Identify the roles and responsibilities of a clinical trials investigator
- Identify potential benefits and challenges associated with clinical trials in your practice
- Identify sources for becoming a clinical trials investigator

Parts of the content in this module are compiled from works of the following authors.

Abrams, J., & Cohen., G. (2002). "Identifying clinical trials and implementing them in your practice". Podium presentation at the American Society of Clinical Oncology Conference, May, 2002, Orlando, Florida.

Berg, D.T. (2000). Sponsoring Agencies: Industry. In Klimaszewski, A.D., Aikin, J.L., Bacon, M.A., DiStasio, S.A., Ehrenberger, H.E., & Ford, B.A. (Eds.), *Manual for Clinical Trials Nursing* (pp. 33-35). Oncology Nursing Press, Inc. Pittsburgh, PA.

Cohen, G.I. (2003). Clinical Research by Community Oncologists. *CA: A Cancer Journal for Clinicians*, 53(2), 73-81.

Ginsberg, D. (2002). *The Investigator's Guide to Clinical Research*, third edition. Center Watch, Boston, MA.

National Cancer Institute (2001). *Cancer Clinical Trials: The In-Depth Program*. Available: <http://oesi.nci.nih.gov/series/cted/indepth.html>.

Individual references are not made in the text. See the bibliography in the Resources section for more information.

2. The Role of a Clinical Trials Investigator

A healthcare professional who is considering becoming involved in clinical research should consider the pros and cons.

2.1. *Potential Benefits From Becoming a Cancer Clinical Trials Investigator*

Becoming a clinical trials investigator represents the following potential benefits to a health professional:

- Self-satisfaction that he or she is contributing to the advancement of cancer care
- Ability to access new treatments and attract more patients
- Being more aware of cutting-edge therapies and current accepted standard care recommendations
- Continuing medical education from sources such as the National Cancer Institute and Cooperative Groups
- Enhanced opportunity to consult with experts in the field
- The chance to be a source of "second opinion" for both patients and health professionals in the community
- Enhanced opportunity to be appointed a part-time faculty position at an academic center

2.2. *Are there potential benefits for my patients?*

Clinical trials have associated risks and benefits. While many cancer patients (85%) were unaware of clinical trials as a treatment option, 75% of patients were willing to consider a clinical trial.

As a healthcare professional who participates in clinical trials, you may feel more prepared to discuss clinical trials as a treatment option. Having trials available within your practice setting allows patients another treatment option that may be in the forefront of evolving cancer treatment options.

For example, paclitaxel was offered to ovarian and breast cancer patients at research centers before it was approved by the FDA. A number of other therapies, such as monoclonal antibodies, radio-pharmaceuticals, and biologic response modifiers, have also been available to clinical trials participants, providing interventions for patients who had little hope with their advanced or aggressive cancers.

Many clinical trial participants express satisfaction and appreciation over the attention they received in clinical trials. As evidenced by these statements, many participants felt safer receiving protocol treatments than non-research treatments because they were much better monitored:

"For me, participating in a trial was receiving treatment but with a lot of special attention. I got a whole lot of extra attention every time, and I felt that I really benefited from that, because there were more people looking at my case than if I had just been in there in a standard treatment situation." (Diane)

"They treat you as a human being; and they care for you a lot; and it seems that you are much more important than their experiment. They give you more attention because this is experimental. And they try to make sure everything's going well, so they have to keep a closer eye; they have to monitor my body more, my blood work more." (Ariceli)

2.3. Are there potential risks for participants?

Safeguards are built into the clinical trial process to protect participants. Prior to accruing participants, a trial must be IRB-approved. The research protocol ensures consistency in study procedures and helps minimize potential risks for patients. Strict adherence to the protocol and close monitoring and timely reporting of adverse events are two important human participant protection measures.

2.4. Can clinical research participation positively affect my practice?

Experienced cancer clinical researchers believe that a clinical practice may grow as a result of clinical trial participation. One reason is that the practice may be viewed in the community as one that offers cutting edge cancer treatment and care options. As indicated by Dr. James Atkins, an oncologist who practices in Goldsboro, NC:

"Well, since the practice has grown, when I originally came to this town, I was actually told that this town could not support an oncologist, that it wasn't big enough, and now - you know we now have four medical oncologists and a radiation oncologist, and the radiation oncologist is extremely active in our GOG clinical trials, he's putting as many as 20 to 25 people on RTOG trials a year, so he is extremely active in clinical research in our group as well, so it has, it has been very good for our practice, for the community.

I started off with a half time person doing data management, then we got two half time people, then full time and right now we actually have one full time data manager per doctor. Because we've put that many people on clinical trials that we need that."

Experienced researchers may also recommend that there are some potential changes you need to plan for in order to facilitate your research effort.

The first is balancing your work time between conducting clinical trials and your regular and customary duties. As an investigator, you have the responsibility for supervising each trial, interacting with the IRB, developing budgets, dealing with audits and inspections, and performing other duties. Some traveling may also be required. One estimate is that after you've become familiar with the regulatory, scientific, and fiscal components, you can be quite successful by allocating 10% to 15% of your time to conducting trials.

You may be concerned about the administrative burden that is associated with conducting clinical trials. Will it be overwhelming? Will my time be compensated?

Dr. Atkins and Dr. Gorsch both conduct clinical trials in the community setting. Their opinions of administrative burden and compensation are presented on the next page.

<p>Dr Atkins</p>	<p>About administrative burden - "To me, it doesn't take any extra time to treat them on a clinical trial as it does off a clinical trial, so I don't see a time factor in having somebody on a clinical research trial. The administrative time is primarily going to the IRB meetings and presenting a clinical trial or answering questions that they may have. But otherwise from an administrative point of view at the community level, I don't see a lot of extra burden.</p> <p>There is some administrative burden for the clinical research professionals, the data managers - somebody obviously has to work with the protocols and get them through to the IRB and get them approved and keep up with the paperwork, so there is an administrative component that other people are also involved with, but for me as a physician, I don't see a significant administrative burden."</p> <p>About compensation - "Your time can be compensated in many, many ways.</p> <p>The monies that we are reimbursed technically cover part of data management and technically there's nothing there to really cover physician time and effort but, my compensation comes from taking care of my patients, my compensation comes from the typical clinical oncology that we all do.</p> <p>Word of mouth and the fact the people know that we're involved in clinical research is an extremely important issue in maintaining your referral base."</p>
<p>Dr. Gorsch</p>	<p>About administrative burden - "The administrative burden is really on making sure that you're collecting all the information that you need to be collecting for this study. Initially there's a steep learning curve. As time goes on, if you have a good data manager there's really not a lot that you need to do. I think it's worth it knowing that you're doing the right thing for the patient.</p> <p>Another challenge may be preparing your current staff and hiring new staff if needed. Every member on your staff contributes to the success of your studies, though they play different roles. It is important to educate them about conducting research trials. If new members are brought in, such as a data manager or a clinical research associate (CRA), the dynamics and interpersonal relationships in your office will change. Efforts made to help the staff understand each other's roles and responsibilities will help build a cooperative work team."</p>

2.5. Investigator Comments

Health professionals become cancer clinical trials investigators for a variety of reasons. Ultimately they all want to help advance science and provide better cancer prevention and treatment to the public.

When trying to sort out your own reasons for whether to participate, it may be helpful to hear from colleagues who have been there. We've included the comments from two experienced clinical trials investigators. They not only share with you why they decided to become involved in cancer clinical research, but they also offer some recommendations for those new to research.

James Atkins, MD, Oncologist, Southeastern Medical Oncology Center, Goldsboro, NC

Why did I become a cancer clinical trials investigator?

"After I got out into practice, I decided that it was very important to be involved in the clinical trial system. I knew that the most exciting advances that were going to occur in oncology were probably going to occur in the next 20 years. Here we are 18 years later, and I was right - we are at a very exciting time in oncology, and so I wanted to be in the action. I wanted to be involved in the clinical research and what was going on nationwide; I didn't want to get left behind.

Being a part of the clinical trial system, I'm involved with new protocols, new concepts, new ways of looking at things, from the very beginning. I think there's a lot going on right now in the grassroots efforts to educate patients. We're going to see more and more patients requesting clinical trials and the doctors who are not in the system are going to lose market share."

Recommendations

"If a new researcher wanted to...a new person wanted to get involved, then you can say okay, I'm only going to open two clinical trials. They can say I'm only going to open up two. I'm going to open one up for colon cancer; I'm going to open one for breast cancer. And I will put every single one of my new colon cancers on that clinical trial, and I will put every single one of my new breast cancers on that breast cancer trial. And just by doing that, I would expect that most clinical oncologists should be able to put 10 people anyway, if not more, on clinical trials a year.

The bottom line is you need doctors who are interested in doing the clinical trials, who want to answer the questions, who want to be a part of the system, because it costs money to get the system - a community up and running. It will cost probably \$5,000 - \$10,000 and so you don't want to put \$5,000 - \$10,000 into developing a community and then have them not put anybody on.

One of the things that I would recommend is that they have their own data manager. It doesn't mean the person has to be full-time. They can be half time. I think that one of the errors that people make is not taking the commitment.

It has to be a philosophical commitment too. They need to make the commitment that clinical trials represent the cutting edge of medicine. I'll look at the clinical trials as the very best...that the best cancer minds in our country have put together.

I think that they need to be willing to say I don't know which treatment is best and therefore I am going to do this clinical trial, and they have to believe that. They may have biases, okay, and I had biases. And we have to acknowledge what our biases are when we do clinical research."

Stephen Gorsch, MD, Oncologist, Martha Jefferson Hospital, Hope Inc., Charlottesville, VA

Why did I become a cancer clinical trials investigator? "There have been some classic examples in oncology where we have done the wrong thing because we didn't have the data and people were reluctant to get the data.

For years in the treatment of lymphoma, it looked like newer regimens were better than the older regimens. And it made sense intuitively.

When the studies looking at a comparison directly between the newer and the older regimen were finally done, we found that the older regimen was just as good and less toxic than the newer regimens.

So if we're going to do our patients a service, we need to know that what we do works. And the only way we really know is by participating in clinical trials. And I love being able to offer patients clinical trials and say to them, look this is to our knowledge, the state-of-the-art -- the best that we have. Only by doing these studies are we really going to know what is really the best treatment. That's the principal reason we decided to participate."

Recommendations "The single best thing they could do is to hire a good data manager. If you have a good data manager, she can support you and do the lion's share of the paperwork in terms of scheduling the appropriate tests, filling out the right forms, checking the eligibility on patients.

Being a participant through a major university as a sponsor is helpful because then you have their resources as well as a backup. It's not very difficult to do. When you come right down to it, having - offering clinical studies, clinical trials is really not difficult, provided that you have someone helping you with the paperwork."

3. Responsibilities of an Investigator

Another question you may ask when considering involvement with clinical trials is "What are the responsibilities of clinical trials investigators?"

Here is a list of some of these responsibilities:

- Expertise in therapeutic area
- Protocol management
- Maintain an adequate rate of patient accrual to studies
- Ability and willingness to train staff for project management
- Willingness and ability to comply with federal regulations

- Provide informed consent to patients and maintain compliance with all human participants protection regulations
- No financial conflict of interest
- Maintain a role in the auditing and quality assurance process

4. How to Become a Clinical Trials Investigator?

There is more than one way to become a clinical trials investigator.

You can join:

- One of the NCI's Clinical Trials Cooperative Groups Affiliates (formerly known as Community Group Outreach Program or CGOP) via an academic center or community hospital,
- NCI-sponsored Community Clinical Oncology Program (CCOP), or
- NCI-sponsored Cancer Trials Support Unit (CTSU)

Your institution can become part of the Cancer Centers Program.

Through a peer-reviewed application process, the National Institutes of Health (NIH) also supports various research grants that clinical researchers can apply for.

And finally, you can also serve as investigator for clinical trials sponsored by pharmaceutical companies.

Information about how to become involved with clinical trials sponsored by the above NCI programs or the industry is provided in this section. More in-depth information about the NCI programs is available in Module 3 of Section I: Cancer Clinical Trials Basics. Web links are also available for you to explore more resources.

4.1. NCI's Clinical Trials Cooperative Group Program

The Clinical Trials Cooperative Group Program, sponsored by the National Cancer Institute (NCI), is designed to promote and support clinical trials (research studies) of new cancer treatments, to explore methods of cancer prevention and early detection, and to study quality-of-life issues and rehabilitation during and after treatment.

Cooperative groups are composed of academic institutions and cancer treatment centers. They differ in structure and research focus. Some groups concentrate on treatment of a single type of cancer; some study a specific type of cancer therapy and focus on a group of related cancers.

One way to enroll patients into clinical trials sponsored by one of these cooperative groups is to become its affiliate member (formerly known as the Community Group Outreach Program or CGOP). Health professionals in the community can join cooperative groups through the sponsorship of one of the main group members, such as a university medical center. For instance, you can contact your training institution and request the sponsorship, provided that it is a main member of a cooperative group. A good resource for your research regarding application requirements and joining criteria is the Web sites of these groups. These URLs are available on www.cancer.gov.

You can also become affiliated with a cooperative group via the Community Clinical Oncology Program (CCOP). This is discussed in the "CCOP" section.

4.2. Community Clinical Oncology Program

The Community Clinical Oncology Program (CCOP), sponsored by the Division of Cancer Prevention (DCP), was established by the National Cancer Institute (NCI) in 1983. Through this program, community physicians work with scientists conducting NCI-supported clinical trials.

Participation in the CCOP benefits patients and physicians in the community and scientists in research centers. The program helps in the transfer of the latest research findings to the community level.

Facilities participating in the CCOP are required to affiliate with at least one research base. (A research base may be an NCI-supported clinical cooperative group or cancer center.) The CCOP participants use research protocols developed and provided by the research bases.

To apply to become a CCOP, you can access information on procedures, forms, and suggestions for organizing information on applications at <http://prevention.cancer.gov/programs-resources/programs/ccop/apply>.

For other information, visit the CCOP home page at <http://prevention.cancer.gov/programs-resources/programs/ccop>.

4.3. Cancer Trials Support Unit

The Cancer Trials Support Unit (CTSU) is a pilot project sponsored by the NCI for the support of a national network of physicians to participate in NCI-sponsored phase 3 cancer treatment trials.

Health professionals affiliated with any NCI Cooperative Group are eligible to register with the CTSU. As of May 2002, CTSU has opened its protocol menu to qualified healthcare providers who are not affiliated with an NCI-sponsored adult Cooperative Group. All individuals (MDs, RNs, Clinical Research Associates [CRAs], Data Managers, Secretaries) who will be participating in the research process are encouraged to participate.

CTSU members can access the following information and material on the CTSU Web site:

- Protocol-related documents (the protocols, all study forms, education and training materials, etc.), protocol updates, and safety information
- Information on CTSU operations and how sites and the CTSU work together
- Information related to the conduct of phase 3 clinical trials
- Links to patient education resources

While Cooperative Group members can register with the CTSU by completing a form, non-member health professionals need to meet standards similar to those for Cooperative Group members before they can enroll patients. They will first fill out an online interest

form. Staff from the NCI and the CTSU will evaluate the application following these criteria categories:

- Investigator qualification
- Experience in conduct of clinical trials
- Site infrastructure

For more information, including registration information, visit the CTSU home page at <https://www.ctsu.org/>. Choose the "Non-Group Investigator" tab at the top of the screen if you are not affiliated with a Cooperative Group.

4.4. Cancer Centers Program

The Cancer Centers Program of the NCI supports major academic and research institutions throughout the United States to sustain broad-based, coordinated, interdisciplinary programs in cancer research.

Requests from eligible institutions for cancer center support are subjected to a competitive peer review process that evaluates and ranks applications according to scientific merit. Successful applicants are awarded a P30 Cancer Center Support Grant (CCSG) to fund the scientific infrastructure of the cancer center. Each institution receiving a CCSG award is recognized as an NCI-designated Cancer Center.

A list of NCI-sponsored cancer centers is on the Cancer Information Service Web site at <http://www.cancer.gov/cancertopics/factsheet/NCI/cancer-centers>.

Policies and Guidelines Relating to The Cancer-Center Support Grant is also online at NCI's Web site at <http://cancercenters.cancer.gov/>.

4.5. Private Industry

In the past, the NCI was the major sponsor of new anticancer drug development. Pharmaceutical companies are now the major developers of cancer drugs. Most of their studies are done independently of the NCI. Pharmaceutical companies are active in new drug development in four different ways:

- Initial exploration of an agent for clinical activity with the NCI's Cancer Therapy Evaluating Program (CTEP)
- Collaboration with a cooperative group
- Industry-designed protocol with a selected research base of one or more institutes
- Institutional protocol with industry support

There are many ways in which you can locate industry-sponsored clinical trials that interest you:

- Visit the FDA Web site at <http://www.fda.gov/>
- Visit the Web site for Pharmaceutical Research and Manufacturers of America at <http://www.phrma.org/>
- Attend your own specialty meetings
- Attend industry meetings and conferences

- Write to the Contract Research Organizations (CROs), an independent contractor that assumes one or more of the obligations of a sponsor such as design of a protocol and selection monitoring of investigation

5. Summary

This module discussed a list of considerations when deciding whether to become involved in clinical trials.

- Are there any potential benefits involved in becoming a clinical trials investigator?
- Are there any potential benefits for my patients?
- Are there any potential risks for participants?
- Can clinical research participation positively affect my practice?

If you decide that clinical trials participation is for you, there are many ways in which you can become involved with clinical research. Clinical trials are sponsored by the National Cancer Institute (NCI), which sponsors a variety of programs, and the private industry. You should study all of these alternatives of participation and choose one that works best for your particular setting.

Program	Purpose	Participation
Clinical Trials Cooperative Groups Program	Promote and support clinical trials (research studies) of new cancer treatments, to explore methods of cancer prevention and early detection, and to study quality of life issues and rehabilitation during and after treatment.	<ul style="list-style-type: none"> • Group and affiliate membership available • Membership criteria and application requirements vary from group to group • Visit http://www.cancer.gov/cancertopics/factsheet/NCI/clinical-trials-cooperative-group for a list of cooperative groups
Community Clinical Oncology Program (CCOP)	<ul style="list-style-type: none"> • Enable community physicians to work with scientists conducting NCI-supported clinical trials • Increase the number of participants and physicians who can take part in clinical trials operated simultaneously in major research centers and in the community 	<ul style="list-style-type: none"> • Visit http://prevention.cancer.gov/programs-resources/programs/ccop/apply for application information • Facilities participating in the CCOP are required to affiliate with at least one NCI-supported clinical cooperative group or cancer center as its research base

Program	Purpose	Participation
Cancer Trials Support Unit	<ul style="list-style-type: none"> • Reduce regulatory/ administrative burden on Cancer Cooperative Groups • Increase physician and patient access to NCI-sponsored clinical trials • Streamline and standardize information collection and reporting 	<ul style="list-style-type: none"> • Active members of an NCI-sponsored adult Cooperative Group can complete the online CTSU Registration Form to register as CTSU members • All individuals who will be participating in the research process are encouraged to register • Health professionals who are not affiliated with a Cooperative Group can become CTSU members and enroll patient in NCI-sponsored clinical trials if they meet all the evaluation criteria • Visit www.ctsu.org for registration information
Cancer Centers Program	Sustain broad-based, coordinated, interdisciplinary programs in cancer research.	<ul style="list-style-type: none"> • Applications for the P30 Cancer Center Support Grant (CCSG) are subjected to a competitive peer review process • Visit http://www.cancer.gov/cancertopics/factsheet/NCI/cancer-centers for a list of NCI-supported cancer centers • Visit http://cancercenters.cancer.gov/ for the Policies and Guidelines Relating to The Cancer-Center Support Grant

Module 2: Setting Up the Cancer Clinical Trials Site

1. Introduction

Participation in clinical trials requires preparation of your office. This includes:

- Registering with the FDA
- Establishing the research team
- Educating your staff in protocol use and compliance
- Funding the clinical trial endeavor
- Identifying a responsible IRB
- Allocating space

Upon successful completion of this module, you will be able to:

- Describe procedures for investigator registration with the FDA
- Identify the key members of a research team and define their responsibilities
- Identify strategies in educating staff involved in a clinical trial
- Identify sources of funding and other resources for new cancer researchers to begin clinical trials
- Recognize the need to identify an IRB and to acquire additional space

2. Investigator Registration With the FDA

Before a clinical trials site is permitted to begin conducting a trial for a new drug or device, the principal investigator must complete the Statement of Investigator Form (1572 form) that the sponsor files with the FDA. A copy of this form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/FDA-1572.pdf>.

The 1572 form provides the FDA with the following information:

- Name, address, and CV of the principal investigator
- The name and code number, if any, of the protocol(s) in the Investigational New Drug (IND) (if available) identifying the study(ies) to be conducted by the investigator
- Names of all sub-investigators who will be assisting in the research
- Name and address of any medical school, hospital, or other research facility where the clinical investigation(s) will be conducted
- Name and address of the IRB that is responsible for the review and approval of the study(ies)

On the back of the 1572 form is a set of commitments that the investigator makes by his or her signature on the form. These commitments are as follows:

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 investigations.

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 an 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 312.66.

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.

I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

3. Research Team

The multifaceted dimensions of research protocols require the collaboration of people who have diverse expertise. In the experience of many community researchers, the research team is the entire office staff from the front-desk receptionist, insurance claim specialist, to the oncologist. Every one has a role to play in the research process.

Each team may be set up differently, depending on the staffing and resources of the research sites. Many research teams in the community are comprised of staff in an oncologist's office with the addition of the data manager and/or the clinical research coordinator. Some clinical trial investigators recommend separating the duties of clinical trials personnel and office employees. This will be dependant upon the size and needs of the research program.

Typical team members and their responsibilities include:

Team Member	Responsibilities
Principal investigator (PI)	<p>Accountable for the scientific integrity of the protocol and the compliance with regulatory and reporting requirements. S/he is approved by the reviewing IRB and oversees all aspects of a clinical trial. Specifically, a principal investigator in the community oversees:</p> <ul style="list-style-type: none"> • Protocol submission for local institutional review board approval • Participant recruitment • Informed consent • Protocol adherence • Data collection and analysis <p>The PI for most clinical protocols is a physician who understands the science of the protocol and has the clinical expertise to manage the potential side effects and possible adverse experiences that may arise throughout the treatment process.</p>
Co-investigator or associate investigator (AI)	<p>In the absence of the PI, a co-investigator, or associate investigator (AI), acts as a designee to make decisions regarding major issues. The AI is selected during protocol development and is also IRB-approved. The AI may address the following issues:</p> <ul style="list-style-type: none"> • Evaluating response • Stopping therapy • Removing a patient from a protocol <p>The AI should have a medical or related advanced degree appropriate for the responsibilities of the role, and have a 1572 form on file with the IRB if he/she makes any decisions regarding protocol interventions.</p>
Clinical research associate (CRA) and/or research nurse	<p>Plays a key role in the implementation and overall management of the protocol. Certification is available through SoCRA (the Society of Clinical Research Associates). A certified CRA has passed an exam documenting the education they have received about the clinical trials process. The main functions of this role often include:</p> <ul style="list-style-type: none"> • Working with referring physicians • Assistance in screening patients or directing the details of recruitment • Assuring the test procedures are scheduled • Completing IRB and other paperwork and receiving

Team Member	Responsibilities
	<p>reports</p> <ul style="list-style-type: none"> • Monitoring test results for necessary treatment adjustment • Organizing the collection of specimens • Facilitating the informed consent process • Developing data collection tools and maintaining study files • Educating research staff and patients • Alerting the PI to significant trends in the data • Acting as a resource person to staff and patients • Assuring proper chart documentation of response and side effects • Providing a quality assurance plan for data checks <p>In the office setting the staff nurses may also assume some the above functions.</p>
Data manager	<p>Major functions of a data manager include:</p> <ul style="list-style-type: none"> • Handling the management of clinical trial data, including data entry • Collaborating with the principal investigator and research coordinator in identifying what participant data will be tracked • Preparing data to be provided to monitoring agencies
Staff nurses	<p>Both inpatient and outpatient staff nurses play an integral part in the implementation of a protocol. They:</p> <p>May, with proper education/training, administer the intervention to participants as specified in the protocol</p> <p>Assess and record toxicity, drug tolerance, and adverse events</p> <p>Collaborate with the principal investigator and research coordinator in observing and reporting clinical trends</p> <p>Provide clinical management and participant education</p>

Research sites vary in what members they put on the research team and how they set up the roles and responsibilities of each member. For example, a site may decide that one team member will play the roles of both the research study coordinator and the data manager, and the staff nurses are responsible for drug dispensing and inventory.

Depending on the protocol's requirements and a site's policies and resources, a multidisciplinary team may also include:

- Pharmacist support
- Nutritional Services staff
- Social worker

- Clinical trial recruitment specialist
- Bioethicist
- Chaplain
- Biostatistician

Here are a few practical tips from experienced clinical trials investigators in the community:

- Existing office staff can take on new responsibilities if properly trained and supported. For example, a chemotherapy nurse may also do data management. In this case, make sure that the roles and responsibilities are clearly defined to avoid confusion. As a program grows, additional staff may be necessary
- Nurse practitioners and oncologists can complement each other in their work with protocol patients. Nurse practitioners make patient education a high priority, and they can spend time with patients and their families to answer questions regarding a clinical trial
- Your insurance claim specialists need to pay more attention to cases of protocol patients, and make sure that their insurance companies will pay for the drugs and procedures required by the protocol

All members of the multidisciplinary team work together to enroll patients into clinical trials and ensure protocol integrity and patient safety.

4. Staff Education

The key to the conduct of a successful clinical trial is a well-trained clinical research staff. Education ensures that your staff understands the importance of clinical research in advancing cancer care, and provides them with the knowledge and skills in implementing the protocol in compliance with regulations and quality assurance measures. For example, a front-desk staff who understands the importance of strictly following the protocol treatment schedule will make sure that correct appointments are given to protocol patients at the right time and for the right purpose.

A successful education program takes detailed planning, a trainer knowledgeable in the protocol, and effective training tools.

For most clinical trial sites, the principal investigator and the clinical research associate (or the data manager) serve as trainers.

Additional information about clinical trials is available at:

- National Cancer Institute - <http://www.cancer.gov/>
- NCI Clinical Trials Education Series - <http://www.cancer.gov/clinicaltrials/resources/clinical-trials-education-series>
- The American Society of Clinical Oncology (ASCO) - <http://www.asco.org/portal/site/ASCO>
- The Oncology Nursing Society (ONS) - <http://www.ons.org/>

4.1. Planning & Tools Development

Effective planning of an educational program requires that the trainers have a thorough knowledge of the protocol. This knowledge assists in analyzing the trial's impact on the responsibility of the research team members.

Based on the protocol, the trainers need to identify:

- The guidelines for the responsibilities of each staff member
- The equipment necessary to perform the trial
- Any new skills that are required of the staff

Then an assessment can be conducted to understand the staff's level of knowledge of clinical trials and of the skills required for the trial.

Based on the gap between the staff's current level of knowledge and skills and the level required for protocol implementation and compliance, the trainer designs a training program that will bridge this gap.

Planning of the program also includes the development of training tools. The most valuable instrument in a clinical trial is the actual protocol itself. This document is a detailed written plan of a clinical investigation and provides step-by-step guidelines for the safe conduct of the trial.

If an approved protocol needs modification due to emerging scientific information, toxicity issues, or any other reason, a formal amendment must be submitted to the approving IRB. The protocol amendment will contain the necessary alterations and any associated information for example a changed informed consent form, to be used with all newly accruing participants.

Besides the protocol, other instructional materials, such as drug fact sheets, common toxicity criteria, and schematics of a treatment cycle, can also be used to provide accurate, concise, and easy to read information about the protocol for quick reference.

Fact sheets: use as a quick reference guide to summarize essential information and identify the staff's responsibilities

Summaries: identify the daily requirements of the protocol and provide practical solutions that will facilitate the achievement of the trial's outcome

Calendars and schema: list standard instructions for the daily requirements of the study.

4.2. Training

A staff training program needs to achieve the following goals:

- Motivate the staff to actively and responsibly participate in the research effort
- Explain the conduct and requirements of the protocol
- Explain relevant regulations and guidelines
- Provide the skills necessary to implement the protocol
- Provide tools to assist job performance
- Provide continuous support to the staff in updating their knowledge and skills

Both formal and informal training can be used to achieve these goals.

Formal in-house training sessions are used to help the staff to develop or improve skills and to obtain any certification required by the trial. Such sessions include:

- Explanation of the importance of clinical research
- Presentation of protocol, scientific rationale, and objectives
- Description of dose and administration of treatment
- Review of expected and unexpected toxicities and procedures for managing and reporting adverse event responses
- Monitoring and management of side effects
- Instruction on use of specialized equipment necessary for implementing the study
- Review of tests required by study
- Review of instructions on processing ancillary tests (e.g., pharmacokinetics)
- Review of questionnaires to be completed by the research participants
- Review of names and telephone numbers of the clinical trial staff
- Review of handouts (e.g., articles on agent, protocol abridgment or summaries, calendar of events)
- Review of order forms that will be used for the protocol
- Review of any forms that will require completion by the staff

Besides formal training sessions, weekly staff meetings, phone conversations with research participants, and observation of an informed consent session conducted by the PI are all examples of informal training.

Continued training efforts after the protocol opens to enrollment are important to ensure protocol compliance and patient safety. Make sure to:

- Keep a copy of the protocol in every department and unit involved in the trial
- Share frequent updates on new findings and trends, especially with the staff providing direct care
- Identify and correct any deficiencies noted in implementation of the study
- Address any areas of concern

5. Funding Clinical Trials

5.1. Costs

Participation in clinical trials requires start-up capital. For an oncologist who has set up his or her regular practice, he or she will still need to put the staff and infrastructure in place to run clinical trials. The infrastructure consists of varied costs, some more obvious than others.

Potential costs for community physicians include:

Personnel	Nurse, Certified Research Associate (CRA), Secretary, Pharmacist services
Office Expenses	Workspace, computer access, phone, fax, mail
Physician time	Reviewing potential studies, IRB requirements, patient discussions, monitoring and assuring protocol compliance

Meeting time	With research staff, referring physicians, travel to and from
Less obvious expenses	Assessing insurance issues, IRB fees, audits, chart storage fees, non-covered protocol requirements

Experienced community investigators recommend the hiring of a dedicated nurse or CRA to keep your site's study coordination and data management at peak performance. These team members play a key role in the success of implementing trials into your practice. Whether this research team member is hired full-time or part-time, it is important that his or her work priority is always the protocol patients, versus other office duties.

5.2. Sponsor Reimbursement

Financial reimbursement is provided to research sites to cover the research costs of clinical trials. Amounts of reimbursement vary with study sponsors. For instance, if a research site participates in an NCI-sponsored phase 3 cancer trial through the Cancer Trials Support Unit (CTSU), the CTSU pays a defined amount per patient registration.

Trial sponsors usually pay a percentage of the total budget as an upfront payment. The amount of start-up funds is decided by the sponsors. Some sponsors provide 5% of the total budget, yet some may not pay anything until the first patient is enrolled. Based on contractual negotiations, the CTSU, for example, will pay a certain amount in advance of the site enrolling a patient, up to a certain amount. For more information on the CTSU and reimbursement for patients enrolled in clinical trials, visit www.CTSU.org.

In many community investigators' experience, the financial reimbursement from sponsors for enrolling patients may be used to pay research team expenses.

5.3. Insurance Reimbursement

Another issue related to the finance of your clinical research enterprise is patients' insurance payment for protocol drugs and procedures.

There are two types of costs associated with a trial:

Patient care costs

Usual care costs include costs for doctor visits, hospital stays, clinical laboratory tests, x-rays, etc., which occur whether the patient is participating in a trial or receiving standard treatment. These costs have usually been covered by a third-party health plan, such as Medicare or private insurance

Extra care costs are associated with clinical trial participation, such as additional tests required to evaluate the study interventions. These may or may not be fully covered by the clinical trial sponsor and/or research institution. The sponsor and the participant's health plan need to resolve coverage of these costs for particular trials

Research costs Associated with conducting the trial, such as data collection and management, research physician and nurse time, analysis of results, and tests purely performed for research purposes. Such costs are usually covered by the sponsoring organization, such as the NCI or a pharmaceutical company

Health insurance companies and managed care companies decide which healthcare services they will pay for by developing coverage policy regarding the specific services. In general, the most important factor determining whether something is covered is a health plan's judgment as to whether the service is established or investigational. Health plans usually designate a service as established if there is a certain amount of scientific data to show that it is safe and effective. If the health plan does not think that such data exist in sufficient quantity, the plan may label the service as investigational.

For some health plans, clinical trial participation may result in a denial of coverage. However, some health insurance plans make case-by-case decisions about clinical trials, and some health insurers, such as Medicare, now cover the usual patient-care costs in clinical trials.

A health plan may define specific criteria that a trial must meet before extending coverage, such as:

- *Sponsorship*: Some plans may only cover costs of trials sponsored by organizations whose review and oversight of the trial is careful and scientifically rigorous, according to standards set by the health plan
- *Trial phase and type*: Some plans may cover patient care costs only for the clinical trials they judge to be "medically necessary" on a case-by-case basis. Trial phase may also affect coverage; for example, while a plan may be willing to cover costs associated with phase 3 trials, which include treatments that have already been successful with a certain number of people, the plan may require some documentation of effectiveness before covering a phase 1 or 2 trial.

While health plans are interested in efforts to improve prevention and screening, they currently seem less likely to have a review process in place for these trials. Therefore, it may be more difficult to get coverage for the care costs associated with them.

Some plans, especially smaller ones, will not cover any costs associated with a clinical trial. Policies vary widely, but in most cases the best bet is for the investigator's office to initiate discussions with the health plan

- *Cost "neutrality"*: Some health plans may limit coverage to trials they consider cost-neutral (i.e., not significantly more expensive than the treatments considered standard)
- *Lack of standard therapy*: Some plans limit coverage of trials to situations in which no standard therapy is available
- *Facility and personnel qualifications*: A health plan may require that the facility and medical staff meet specific qualifications to conduct a trial involving unique

services, especially intensive therapy such as a bone marrow transplant (high-dose chemotherapy with bone marrow/stem cell rescue)

5.4. Medicare Coverage

For evolving information about Medicare coverage of clinical trials, go to the Web site for the Centers for Medicare & Medicaid Services (<http://www.cms.hhs.gov/>). The following are some frequently asked questions (FAQS) about Medicare and clinical trials.

What will Medicare pay for a participant of a clinical trial?

Anything normally covered is still covered when it is part of a clinical trial. This includes test, procedures, and doctor visits that are ordinarily covered

Anything normally covered even if it is a service or item associated with the investigational treatment. For example, Medicare will pay for the intravenous administration of a new chemotherapy drug being tested in a trial, including any therapy to prevent side effects from the new drug

Anything normally covered even if it resulted from the participant's being in the clinical trial. For example, a test or hospitalization resulting from a side effect of the new treatment that Medicare would ordinarily cover

What costs are not covered?

Investigational items or services being tested in a trial. Sponsors of clinical trials often provide the new drug free

Items or services used *solely* for the data collection needs of the trial

Anything being provided free by the sponsor of the trial

What kinds of clinical trials are covered?

NCI's Cancer Information Service has provided a fact sheet for Medicare beneficiaries (see <http://www.cancer.gov/cancertopics/factsheet/support/medicare>). In general, cancer treatment and diagnosis trials are covered if:

They are funded by the National Cancer Institute (NCI), NCI-designated Cancer Centers, NCI-Sponsored Clinical Trials Cooperative Groups and all other federal agencies that fund cancer research. Other trials may be eligible for coverage and the investigator can ask Medicare to pay the patients' costs

They are designed to treat or diagnose the participant's cancer

The purpose or subject of the trial is within a Medicare benefit category. For example, cancer diagnosis and treatment are Medicare benefits, so these trials are covered. Cancer prevention trials are not currently covered

See www.cancer.gov for strategies and initiatives related to reimbursement.

6. Identify a Responsible IRB

In the United States, a federally funded clinical trial is conducted under the close supervision of an Institutional Review Board (IRB) that has jurisdiction over it. An IRB protects the rights, safety, and welfare of human research participants.

If an investigator is affiliated with an academic medical center or a hospital, it is likely that the institution will have its own IRB. The investigator will submit all relevant documentation to this IRB for review.

Multi-center clinical trials like those sponsored by the NCI are routinely reviewed by hundreds of different IRBs. This is why the Clinical Trials Review Committee at the NCI proposed a Central Institutional Review Board (CIRB) to eliminate redundancy, provide quality reviews, and speed up approvals. This pilot project is currently being evaluated.

The CIRB has been created to:

- Improve access to clinical trials for patients and their physicians by enabling local IRBs to rapidly approve NCI-sponsored multi-site trials through the use of a facilitated review process
- Enhance the protection of research participants by providing consistent expert IRB review at the national level before the protocol is distributed to local investigators
- Collaborate more effectively with local IRBs
- Reduce the administrative burdens on local IRBs and investigators associated with IRB submission

The NCI CIRB doesn't replace local IRBs. Instead, it interfaces with local IRBs that provide assurance that "local context" requirement is fulfilled under the Common Rule. The CIRB process is as follows:

- CIRB approves protocol
- CIRB sends approval package to local investigator & local IRB
- If local investigator wants to enroll patients, submits CIRB approval packet to local IRB
- Local IRB chair or subcommittee performs a "facilitated review" and decides whether to accept CIRB review.
- If accepted:
 - Local IRB notifies CIRB
 - CIRB becomes the IRB of record
 - CIRB handles amendments, continuing reviews, adverse events, etc.
 - Local IRB is responsible for conduct of study within their institution, including review of adverse events that occur at their site

For more information about the NCI CIRB, see http://www.ncicirb.org/CIRB_FAQ.asp.

7. The Facility

A good facility should have all the necessary components for conducting clinical trials. The good news is that most oncology practices already have most of these components in place. These components include:

- **Locked drug storage:** Federal regulations require a clinical investigator to have secure, lockable storage area for trial drugs. Some professional sites have built-in storage rooms for study drugs that are guarded by alarm systems. Issues regarding a safe mixing area for agents, radiation areas if necessary, and FDA compliance to standards, are critical for the safe implementation of a trial.
- **A dedicated study area:** A specific and spacious area should be dedicated to data management. Set it up with computer, printer, phone, fax, and sufficient data storage area.
- **A monitor work area:** Monitors conduct regular visits to your site. Their job is to make sure that the conduct of the study is in compliance with protocol and regulations. Depending on the number of patients enrolled in the study and the complexity of the protocol, they may spend a lot of time reviewing case report forms, the drug inventory, and the source documents. A comfortable work area enables them to work efficiently.
- **Conference room:** This is a good facility to have if your space allows for one. This room will get frequent use at study initiation visits, study close-outs and during sponsor audits.
- **Record storage area:** Once a trial is completed, it is a good idea to clear out the documents of this trial to allow room for ongoing and new trials. Documents from closed trials can be stored in a remote storage facility. Remember that these documents should be retrievable within a few days notice in case of an audit, or if questions should arise about how the research was conducted.

8. Summary

A research team is crucial to the success of your clinical research endeavor. You start your effort by establishing a multidisciplinary team. All of the team members and your staff need to be educated on the conduct of the trial and compliance with the protocol. The clinical research associate, or the research nurse, is a good candidate to take on the educator role. Funding your research efforts is not an easy task, but there are many sources of reimbursement, including sponsor reimbursement, insurance reimbursement, and Medicare coverage. Identifying a responsible IRB is also important because the quality of its supervision determines the quality of the research data your site turns out. Finally, you need to make sure that your site has the appropriate infrastructure for conducting clinical trials. Additional space may need to be acquired if your current office space is not enough to accommodate your research needs.

Module 3: Conducting Cancer Clinical Trials

1. Introduction

Once the clinical trials site and research team have been established, the details of trial implementation must be addressed. This module describes the major tasks involved in conducting clinical trials:

- IRB approval of protocol
- Patient enrollment
- Creating source documents and case report forms
- Quality assurance
- Maintaining pertinent forms and study records

Upon successful completion of this module, you will be able to:

- Describe procedures for verifying patient eligibility and initiating enrollment in a trial
- Describe the record keeping and reporting requirements in conducting clinical trials
- Describe the clinical trials monitoring requirements
- Describe applicable federal regulations and quality assurance procedures

2. IRB Review and Approval of Protocol

Before enrollment for a trial can begin, the IRB must review and approve:

- The protocol
- The investigator and sub-investigators
- The site(s)
- Informed consent form
- Advertisements (if applicable) and/or investigator brochures

Until the investigator receives written IRB approval, no participant can undergo any procedures designed to determine eligibility for the study

The IRB is concerned about a broad range of issues ranging from scientific validity of the research question to the risks and benefits for study participants.

Besides the initial review, there are also three other types of IRB review: continuation or annual review, modification review, and adverse reaction review.

Continuation or Annual Review: If a clinical trial goes on for more than one year, or other specified periods, it must undergo continuing IRB review for as long as the trial continues. This will consist of documentation of the IRB's annual review and continuing approval of the protocol.

Modification Review: Modification of the protocol, its informed consent form, and/or the advertisement is required when new information, such as a new telephone number or new drug dosing, becomes available. All modifications must be listed separately from the original protocol, attached to the original protocol, and resubmitted to the IRB. If necessary, new review will be conducted and re-approval granted.

Adverse Reaction: The IRB also reviews reports of adverse reactions and unexpected events involving risks to study patients or others.

For more information on IRB approval, visit the NCI-sponsored Web-based course "Human Participant Protections Education for Research Teams" (choose the course from the curriculum menu).

3. Patient Enrollment

After obtaining IRB approval for the study, you can start enrolling patients. This involves three tasks:

- Screening patient eligibility
- Obtaining informed consent from the patient. The informed consent document must be presented to, and signed and dated by the study patient **prior to** the performance of any study-related procedure
- Patient registration/randomization

3.1. Eligibility Screening

The eligibility criteria, including inclusion and exclusion criteria, are stated clearly in the study protocol and establish the parameters and guidelines that define the appropriate patient population.

- Basic components of eligibility criteria include:
 - Evidence of a specific cancer or hematologic diagnosis
 - The level of overall health of the patient
 - Age limits
 - Major organ system functioning
 - Prior medical history, especially related to other malignancies
 - Prior treatments for cancer
 - Establishment of a baseline disease state from which to measure disease response
 - Stipulation regarding exclusion of certain concomitant illnesses/medications
 - Protection for offspring of patients of childbearing age
 - Establishment of a psychological or mental status that presumes compliance with the study

Example of Eligibility/Pretreatment Worksheet

Protocol: _____ Primary Nurse: _____

Name: _____

Unit #: _____ Pts Home Phone: _____

SS #: _____ Pts Medical Record #: _____

DOB: _____ Attending Physician: _____

Sex: _____

Race: _____ Fellow: _____

Primary Tumor Site: _____

Stage of Disease: _____

Eligibility Criteria	Comments	Prestudy Evaluation (<i>Within 1 Month</i>)	Result	Date	Remarks
Older than age 18					
Path confirmed cancer		Complete H&P			
Disease radiologically measurable		Height & Weight			
CBC/Chemistries suitable for treatment		Vital signs			
No investigational agent within 3 weeks prior to treatment		CXR			
Karnofsky >=50		EKG			
Written consent		MUGA/echo			
No pregnancy/lactation; effective birth control		Tumor measurements			
Another uncured malignancy		Performance Status - Karnofsky			
History CHF		Beta HCG			

Sign/Sym CHF		<i>Performed within 5 days</i>			
Consent signed/dated		WBC (4.0-10.0)			
Date of confirmed metastasis		ANC			
Prior treatment for metastasis/date		Hgb (M 14-18, F 12-16)			
		Hct (M 40-52, F 37-47)			
		Segs/Bands			
		Lymphs			
		Platelets (150-350)			
		PT/PTT (<13; <1 sec contr/25-38)			
		Glucose (70-105)			
		BUN (8.0-18)			
		Creatinine (0.5-1.2)			
		CO ₂ (22-30)			
		Chloride (96-106)			
		Sodium (135-145)			
		Potassium (3.5-5.0)			
		Calcium (9.1-10.6)			
		Phosphorus (3.1-4.5)			
		T. Protein (6.0-8.0)			
		Albumin (3.5-5.0)			

		Bili D/Total (<0.2/<1.2)		
		SGPT/SGOT (0-35)		
		LDH (118-242)		
		Alk Phos (30-114)		

Reproduced from Anderson (2000 in Klimaszewski et al.)

All eligibility criteria must be met prior to enrolling a patient in a trial. To determine eligibility, the following testing and screening are often done besides interviewing the patient and reviewing the medical record.

3.1.1. Required Testing

All laboratory testing and scans must be completed and documented **prior** to enrolling the patient. All studies must be completed **within the time frame specified in the protocol**. If no time frame is identified, a good rule of thumb is to have all laboratory testing completed within seven days of initiating the investigational therapy.

Tests and schedules are described in the sample eligibility/pretreatment worksheet shown above

3.1.2. Staging

A specific stage of disease is usually one of the protocol eligibility criteria. The staging system describes the extent of disease and therefore enables the physician to determine treatment options and prognostic indicators. The stage of the patient's disease should be determined **before** the patient is enrolled into the study.

3.1.3. Pathology Review

Pathology reports are crucial in determining patient eligibility, particularly in phase 2 and 3 studies. Generally, the protocol provides detailed information on pathology review. Additional informed consent may be required from the patient if additional pathology studies need to be done.

Screening and confirming a patient's eligibility is crucial in ensuring the successful conduct of a clinical trial. All criteria must be met and documented as part of the patient's source documents. Patients must not be enrolled in any clinical trial unless all of these criteria are met. A patient sample letter is shown on the next page.

An Example: Letter to Patient Scheduling an Eligibility Screening Visit

March 05, 2002

Mary Jane Patient
222 Buckyway Ave.
Utica, NY 45278

Dear Mary Jane:

As we discussed during your recent office visit, in view of your medical history and personal interest, you may be a candidate for the _____ clinical trial. An appointment for a comprehensive eligibility screening has been scheduled for you for March 13, 2002 at 1:00 with the clinical trials nurse, Josephine Hershey.

During this visit, several things will take place. Josephine will ask you several questions that are important for determining your eligibility for the study. She will also explain the purpose of the study, the things you will be required to do if you decide to participate in the study, possible side effects of the drugs, and the written consent form. Feel free, Mary Jane, to discuss any concerns or questions you have with her, at that time. Should any medical tests be required to determine your eligibility for enrollment, she will also make the necessary arrangements.

If it is determined that you are eligible and you decide to participate, Josephine will be the nurse who will be working with you throughout the study. If, at any time, you have questions or concerns please feel free to contact her at _____. Thank you, Mary Jane, for your interest in participating in this research and we are looking forward to working with you.

Sincerely,

Sally E. Doctor, MD

3.2. Comprehension Screening

One important aspect of screening is comprehension screening. During the initial encounter between a research team member and the patient and his or her family, the research team member needs to consider the following questions:

- Does the patient understand the treatment options?
- Is the patient capable of following the instructions necessary to comply with all aspects of the study? Some studies are very tedious in their scheduling and there is a lot of follow-up involved, and it can be overwhelming
- Can the patient fully understand the informed consent and the dangers or risks involved with the study?

- Will the patient be responsible in reporting symptoms and warning signs to the appropriate medical personnel?

It is not ethical to put a patient on a study if he or she is not able to comprehend what's involved. In order to make sure, the research team member can ask patients to repeat back what they understand they need to do, what the potential risks are, etc.

3.3. Obtaining Informed Consent

The investigator must obtain informed consent from patients participating in a study. A research team member should discuss clinical trials participation and the informed consent process with the patient. Patients must also be told that they will have the right to leave the study at any time.

Dr. Stephen Gorsch and nurse practitioner Kathleen Haden, RN, MSN, ANP-C have developed a "routine" for presenting a clinical trial and explaining the informed consent process to patients.

<p>Dr. Gorsch</p>	<p>"In terms of actually presenting the study to the patient, I have a sort of fixed routine. One of the concerns that patients have is whether they're in fact a guinea pig when they're being offered the study. And I tell them that there's several reasons why they might want to be on a clinical trial. The first reason is that it's a way of getting a national second opinion. It's not what Dr. Gorsch thought of, it's what the best colon cancer doctors in the country or the best breast cancer doctors in the country, sat down, they hammered this out they said how are we going to advance the treatment? This is the national second opinion they say this is the best we have.</p> <p>Another reason is it's quality assurance. I can tell patients that if you're on this clinical trial, everything I do is reviewed. Your x-rays, your blood work, the doses of chemotherapy. You know that what I'm doing is being done the right way, and that's something that is, I think reassuring to patients. And then ultimately, of course there's the altruistic motivation of providing information that will be useful for future patients."</p>
<p>Kathleen Haden</p>	<p>"We always give the patient options.</p> <p>I try to explain it as best I can. There are some patients I know that are just not going to understand it. They don't understand the disease, you try to get them through step by step, and sometimes the first meeting is very overwhelming. You know it takes two or three meetings before a patient may understand the prognosis of a terminal illness if that's the case, or just the emotions of developing cancer. And then from there.</p> <p>We talked about dispelling the myths about the guinea pig. I tell people, you're getting the best treatment, and try to explain what it is and step by step in terms of the follow-up and what we do. And there's been plenty of studies that people on clinical trials rate that</p>

	<p>their quality of care is much higher than the ones that aren't on clinical trials because you have to dot every 'i' and cross every 't' and you have to follow this protocol, and you're following them a little closer maybe so they think that the quality is much better. And we work as a team. We have a clinical research associate that tries to keep us on track, that helps with the data monitoring and that we're doing everything that we have to do...and I tell the patients that, too. You know not that we wouldn't give you good care anyway, but that it may be superior or better. And especially when you're allowing the patient to get a drug that isn't even commercially available. And I tell them that you're not only going to help yourself but you're going to help millions of other people in the world by going on this study. And of course, the most important point - they understand and that they know that they can stop at any time, you know that they're not married to the protocol."</p>
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As mentioned in Kathleen Haden's comments, cancer patients undergo strong emotions when they are first diagnosed with the disease. You may be trying your best in explaining different treatment options, but the message may not get across to them if fears are not overcome.

To enhance the quality and efficiency of the communication, most providers encourage a potential participant to bring a friend or family member along for support and to listen, and provide written information for people to refer back to.

- The consent form must be signed and dated by the patient and a witness. A family member or the coordinator can serve as a witness
- The original of the form should be filed with the patient's source documents
- A copy of the form should be given to the patient

The activity of obtaining patient informed consent must be documented in the patient's medical record in a note that is signed and dated by the investigator.

For information on the process of informed consent see www.cancer.gov/clinicaltrials/conducting/informed-consent-guide.

3.4. Registration/Randomization

Patients usually are registered with the study sponsor or the centralized registry within the institution responsible for gathering data. Forms for registration collect demographic information and data regarding eligibility.

If the clinical trial is a randomized study, patients are randomized into a specific treatment arm to reduce patient, physician, or researcher bias to the minimum and to maintain the scientific integrity of study results. Such randomization is often computerized, and done by an institution independent of those providing the treatment.

Prior to beginning a study, a research team member is responsible for registration and for obtaining the randomization arm assignment. The treatment assignment is documented as part of the patient's source documents.

4. Source Documents and Case Report Forms

Source documents include all observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

The case report forms (CRFs) are designed by the trial sponsor to capture trial data that will make it possible to assess the safety and efficacy of the investigational [agent](#).

In a clinical trial, all information entered on a CRF must be supported by and consistent with source documents.

4.1. Source Documents

The International Conference on Harmonization (ICH), and Code of Federal Regulations (CFR), and Good Clinical Practices (GCPs) require the following:

- Written, informed consent by all participants prior to the implementation of any study-related procedures
- Accurate, complete, and appropriate clinical research documentation

Source documentation is the foundation of all clinical studies. It provides a paper or electronic trail of any observation made or data generated about a study participant during her/his participation in a clinical trial. Source documents:

- Verify the completeness and accuracy of data collected on the CRFs
- Show evidence that the study was conducted in compliance with the protocol, Good Clinical Practice, and relevant regulations
- Permit the entire reconstruction of the data in the unlikely event of losing the CRF

If it is not documented, it did not happen!

The following are examples of source documents for every trial participant:

- Medical history, including demographics data and documentation of inclusion/exclusion eligibility
- Physical examination results
- Current medications
- Medications discontinued in the past 30 days
- Original, signed, and dated Informed Consent Form
- Screening and intake forms
- Progress notes
- Telephone logs
- Appointment books
- Screening logs
- Study-specific flow sheets
- Study-specific checklists
- Adverse event list
- Participant diaries
- Site visit monitoring logs

Medical Reports: There are different types of medical reports that are generated while a patient is enrolled in a study:

- Laboratory: serology, chemistry, hematology, microbiology, urinalysis
- ECG reports
- MRI/CT scan reports
- Radiology reports
- Pathology reports
- Admission summaries
- Discharge summaries

Progress Notes: Progress notes record what happened during a patient's visit as part of a clinical trial. It should list completed study procedures, treatments received by the patient, and any adverse experiences, illnesses, or problems reported by the patient.

Screening Log: Besides recording the names of patients who are screened and enrolled into a study, research team members must also document the names of those who are screened but do not meet the eligibility criteria, or who simply decide not to participate. Reasons must accompany the entry if the patient decides not to participate.

Anyone involved in the clinical study can create source documents. This may include, but is not limited to:

- Principal investigator
- Sub-investigators
- Data manager
- Research coordinator
- Floor nurse if an in-patient study
- Pharmacist who records the dispensing of the study drug
- Research participant who complete study-specific diaries

No source documents should be discarded during the trial and for a period after the trial has ended. Source documents are routinely compared to CRFs at audits to make sure that what you say happened did happen. This is an important measure to prevent fraud.

The *Compliance Program Guidance Manual* used by the FDA to audit an investigative site is an excellent resource for source documentation.

4.2. Case Report Forms (CRFs)

Based on data collected in source documents, the principal investigator, the research coordinator, or the data manager completes CRFs for each patient. CRFs enable the transfer of data regarding demography, efficacy, safety, medication use, and other aspects of the study to the trial sponsor.

The data on the CRFs must be consistent with the source documents.

- The principal investigator (PI), research coordinators, or the data manager fill out CRFs
- The PI or a sub-investigator named on Form 1572 signs and dates all CRFs

- Only the PI or the designee listed on the Authorized Representative Signature Record (for more information, see Module 5) may enter corrections on original CRFs
- Any discrepancies or missing data noted by the coordinator, the data manager, or the monitor during a site visit should be resolved before the data are forwarded to the trial sponsor

Traditionally, CRFs are preprinted pages. The use of electronic CRFs is becoming more and more common as it speeds up the collection and analysis of data. The computerized data can also be submitted to the sponsor on a regular basis throughout the study.

5. Quality Assurance

Good Clinical Practices (GCPs) are based on Federal regulations and define the responsibility of individuals involved in the clinical research process:

- Sponsor and its employees
- IRB
- Principal investigator and those who work at the site

In the process of conducting a clinical trial, Good Clinical Practices require the investigator to:

- Obtain informed consent from every study volunteer
- Maintain accurate documentation showing that patients met eligibility criteria
- Maintain accurate case histories for all study participants
- Maintain accurate records detailing the receipt, dispensation, and final disposition of the study drug
- Maintain accurate records showing that treatment was given and response was assessed according to the protocol
- Notify the IRB of all amendments to the study protocol
- Report all adverse events to the sponsor, and immediately report all "serious and unexpected" adverse events to the sponsor and IRB
- Maintain a record of accreditation for all laboratories used during the study

Standard Operating Procedures (SOPs) standardize the way typical research processes, such as consenting patients, drug dispensation, and IRB interaction, are conducted at a research site. The research team should establish SOPs, train team members in their use, and keep them at the site to provide reference and guidelines.

As discussed earlier under Patient Enrollment, informed consent is obtained from a patient before any study-related procedures can be performed. After obtaining the signed informed consent, but before enrolling a patient into a study, the research staff conducts testing, staging, pathology review, and compliance screening according to protocol-specific criteria to determine eligibility. All of these procedures must be accurately documented.

During the treatment phase of a clinical trial, all of the guidelines and procedures specified in the protocol should be strictly followed and precisely documented. The medical record should be monitored regularly to ensure that compliance with the protocol

is documented accurately. Moreover, clear documentation of response to the investigational therapy should also be kept.

In the remainder of this section, we are going to take a closer look at some of the measures that are taken by the research site and the study sponsor to ensure the quality of data from a clinical trial:

- Adverse event reporting
- Ongoing informed consent
- Drug accountability
- Sponsor quality assurance monitoring

5.1. Adverse Event Reporting

An adverse event may be described as a decline from baseline conditions and may or may not be attributed to the study drug. During the study, the investigator must report all adverse experiences to the sponsor.

All unexpected adverse events must be reported to both the sponsor and the governing IRB within 24 hours. An unexpected adverse event is defined by the FDA as one that is not identified in nature, severity, or frequency in the current investigator's brochure.

All serious but expected adverse events must be reported to both the sponsor and the IRB within 10 days. A serious adverse event is defined as any experience that suggests a significant hazard, contraindication, side effect, or precaution.

There is a mechanism for rapidly reporting adverse events in clinical trials. Adverse event expedited reporting system (AdeERS) is a Web-based program that enables researchers using NCI-sponsored investigational agents to expedite the reporting of serious and/or unexpected adverse events directly to the NCI and the FDA. For more information about AdeERS, see <http://ctep.cancer.gov/reporting/adeers.html>.

Clinical toxicity is graded uniformly across trial sites using the Common Toxicity Criteria (CTC). CTC is a Web-based, interactive application that uses standardized language to identify and grade adverse events in cancer clinical trials. For more information about CTC, see <http://ctep.cancer.gov/reporting/ctc.html>.

All adverse events should be documented in patients' medical records. Paper trails should be maintained of the proper reporting of such events. The investigator also needs to document the treatment and resolution of adverse events. All of these documents are part of the source documentation.

A research site needs to clearly define who has the responsibility of reporting adverse events to whom, so there is no confusion or delay in reporting that arises from the confusion.

After receiving reports from an investigator, the sponsor must notify the FDA in written reports of any serious, unexpected adverse events.

A clinical trial sponsor carefully tracks and reviews reports submitted about adverse events and considers whether the new findings affect the safety of participants enrolled in a trial. This is why if you have particular concerns about any adverse event, you need to state it in your report or letter to the sponsor.

If the safety of participants is affected, the sponsor is responsible for notifying the FDA. In addition, the sponsor may also take one or more of the following corrective measures:

- Communicating the new information by sending written notices directly to investigators
- Modifying the protocol or discontinuing or suspending the trial
- Initiating special clinical or preclinical studies to investigate the adverse reaction
- Modifying existing informed consent forms and informing participants of new findings

5.2. Ongoing Informed Consent

Informed consent is a process that begins with the initial discussion, between the patient and a research team member, about participating in a trial and it doesn't stop until the patient's trial participation ends.

When new information about the investigational agent becomes available, or if changes are made to the protocol, the informed consent form must be revised accordingly and submitted to the IRB for approval. The new approved informed consent form must be shared with the patient in the same manner the first consent form was presented.

The new, signed, and dated consent form is filed along with the previous consent form(s).

A patient has the right to withdraw from a trial at any point. If the patient withdraws consent, proper documentation should be made in the medical record concerning this withdrawal, contact data should be maintained for future contact if necessary, and the referring clinician should be notified.

5.3. Drug Accountability

The principal investigator or his or her designee is accountable for dispensing and returning investigative agents used in a clinical trial. This accountability is carefully documented on the Drug Accountability Record (DAR) or an equivalent form provided by the trial sponsor.

The typical tasks involved in handling research study drugs include:

- | | |
|------------------------|---|
| Receiving study drugs | <ul style="list-style-type: none">• Verify the study drug against the protocol• Review and file the drug receipt• Record drug shipment on DAR• Label and securely store the drugs |
| Storing study drugs | <ul style="list-style-type: none">• Store the drugs in a locked place with limited access• Store drugs for different protocols separately• Keep a daily temperature log for the drug storage such as the refrigerator and the freezer |
| Dispensing study drugs | <ul style="list-style-type: none">• Record the preparation and dispensing of the drugs on DAR• Label the drug with "Investigative Drugs" |

- Returning or disposing of study drugs
- Return or dispose of the drugs as required by the protocol
 - Fill out and file the Return Drug List or an equivalent form supplied by the trial sponsor
 - Record the return or disposal on DAR

5.4. Quality Assurance Monitoring

Quality assurance and monitoring are concerned with the execution of a clinical trial and the quality of data that support the scientific conclusions.

The purpose of an audit is to evaluate clinical trial conduct and compliance with the study protocol, good clinical practices (GCPs), institutional standard operating procedures (SOPs), and applicable regulatory requirements.

An audit of a clinical study site can be conducted by one or all of the following:

- The FDA
- The study sponsor, such as the NCI, a cooperative group, and a pharmaceutical company
- An internal auditing group, such as an office of quality assurance.

5.4.1. Trial Sponsor Site Visits

Clinical trial sponsors implement different measures to ensure the quality of the data collected from a clinical trial. One of the most important measures is the periodic on-site visits conducted by monitors.

Monitors review trial procedures, documents, and data on his or her visit. An understanding of the areas of review will help you prepare for such visits. Monitors perform the following tasks:

- Check for compliance with IRB and informed consent requirements
- Inspect shipping, storage, inventory, and use of drugs and other agents
- Inspect Case Report Forms and related source documents. Check for consistency between the two and conformity with the protocol
- Inspect collection, handling, and storage of specimens

5.4.2. FDA Audits

FDA audits are conducted to verify that data submitted by a trial sponsor in support of the New Drug Application (NDA) are accurate, and that the data were collected ethically. There are two types of FDA audits: routine audits and for-cause audits.

A **routine audit** is conducted for clinical studies that are pivotal to the review and approval of a New Drug Application.

A **for-cause audit** of a research site is conducted for a specific reason. Such a reason may be one of the following:

- An investigator has conducted a large number of clinical trials
- A clinical trial is outside of an investigator's field of specialty

- The study data submitted by an investigator are inconsistent with those from other investigators conducting the same study
- The number of participants enrolled is high compared to the expected numbers of such patients in an investigator's practice

An FDA audit has two parts. In the first part, auditors focus on the conduct of the study, and in the second, they inspect source documents for the research data turned out at the site.

When studying the facts of the conduct of a study, auditors look at who did what during the clinical trial, how and where data were recorded, how investigational drug accountability was achieved, etc.

Then auditors examine all the source documents for that particular study and compare them to the research data submitted to the FDA and/or the study sponsor.

An exit interview is conducted with the principal investigator (PI) at the end of the audit. There are three possible outcomes from an FDA audit:

- No significant deviations were found and no response is required from the PI
- Deviations were found and response may or may not be required from the PI
- Significant deviations were found and prompt correction is required of the PI. In this case, regulatory, legal, and/or administrative sanctions may follow

5.4.3. Preparation for an Audit

To prepare for an audit, the following documents need to be ready:

- All of the source documents such as physicians' office records, hospital records, laboratory test results, participant medical history, participant follow-up data, and the appointment calendar
- All of the case report forms (CRFs)
- All of the regulatory documents

If the monitors or auditors need to inspect certain documents, they usually communicate their request in a letter prior to the visit.

Tagging the charts and x-rays appropriately or color-coding the materials will help the monitors find the source documents.

The following information may also be requested:

- The degree of delegation of authority by the PI
- How and where data were recorded
- How test article accountability was administered and maintained
- How the sponsor communicated with the PI and evaluated the study program
- Certification of service/calibration for study-related equipment

The data manager and/or the investigator is present at the audit or the site visits to help locate documents and provide explanations. It is better to let auditors go through and find what they want and provide help only when asked to.

Conducting clinical trials is a complex task. Negative comments from monitors or auditors are almost inevitable. Try not to take them personally. Look at them as constructive feedback and improve your efforts based on them.

5.4.4. DSMB Monitoring

The NIH requires all phase 3 clinical trials to undergo monitoring by a data and safety monitoring board (DSMB). A DSMB may also be appropriate and necessary for phase 1 and 2 clinical trials that are blinded, take place at multiple clinical sites, or employ particularly high-risk interventions or vulnerable populations.

The DSMB is an independent committee whose membership includes, at a minimum, a statistician and a clinical expert in the area being studied. Other members are experts in all scientific disciplines needed to interpret the data and ensure participant safety. Members may also be clinical trial experts, bioethicists, or other clinicians knowledgeable about the trial's subject matter.

The objectives of data and safety monitoring plans are to:

- Ensure that risks associated with participation are minimized to the extent practical and possible
- Ensure the research results are reviewed appropriately while maintaining confidentiality of study data
- Stop a trial early if unacceptable safety concerns arise or if its objectives are met

6. Keeping Records

Complete and meticulous documentation and record keeping are vital to the success of a clinical trial. Besides creating and maintaining source documents and case report forms (CRFs) for every patient, the research team also needs to complete, compile, and maintain the regulatory documents and other study-specific forms and records such as the drug accountability record and the site visit log.

6.1. Regulatory Documents

Every clinical trial site is required to compile and continuously update all the regulatory documents for each of the trials it conducts. These documents must be kept in the study binder or regulatory binder provided by the sponsor of the trial. It is important that new, relevant documents be included in this binder as the trial progresses.

Regulatory documents to be included in the study binder include:

- A signed, original copy of the protocol and all amendments
- An original 1572 form and any revisions
- Updated copies of signed and dated CVs for the investigator and sub-investigators
- Laboratory certification (updated every 1 to 2 years) and the laboratory normal ranges list (updated each time calibration tests are completed)
- Copy of the investigator's brochure
- IRB approval letter

- Original IRB-approved patient informed consent form and any IRB-approved revised informed consent forms
- IRB-approved advertisements used in the study
- Copy of the IRB membership list
- All study-related correspondence, in particular with the IRB and the trial sponsor
- Serious adverse event reports and correspondence with the sponsor and the IRB
- Investigational agent receipts, records, and inventories
- Site visit log
- Telephone log
- A study close out or final report to the IRB

6.2. Pertinent Forms and Records

Drug Accountability Record: Provided by the study sponsor, this form records the receipt, storage, dispensing, return, and/or disposal of the investigative agent(s) used in the trial. See the "Drug Accountability" section for more information.

Authorized Representative Signature Record (Site Signature Log): Only the principal investigator or his or her designee(s) can make changes to the case report forms. Their full name, handwritten signature, and initials should be documented in the Authorized Representative Signature Record.

Adverse Events Form: This form is supplied by the sponsor. It records events that the investigator considers adverse experiences. Careful review of the source documents may reveal unreported complaints. The principal investigator decides whether to record these complaints as adverse events. See the "Adverse Event Reporting" section for more information. For samples of:

- Single agents - Adverse Event Expedited Report, see http://ctep.cancer.gov/forms/34-AdEERSv4_SAT.pdf
- Multiple agents - Adverse Event Expedited Report, see - http://ctep.cancer.gov/forms/34-AdEERSv4_MAT.pdf
- The MedWatch Adverse Experience Form – see <http://www.fda.gov/medwatch/safety/3500.pdf>

Specimen Handling and Submission Forms: Most protocols involve collecting and shipping biologic specimens to a reference-testing laboratory. Instructions for the collection, storage, and shipping of specimens are provided by trial sponsors, as well as submission forms to be completed at the time of shipment.

Participant Enrollment Form: This form records that the patient meets the eligibility criteria for the trial.

Site Visit Log (Monitor Log): When the sponsor's monitor pays a visit to the research site, he or she signs the Site Visit Log. This log must be kept in the study binder with all the other regulatory documents.

Telephone Log: This log records all the telephone contacts related to the study. It should document the date and time of the call, items discussed, action taken, and follow-up

required. This log must be kept in the study binder with all the other regulatory documents.

Delegation of Authority Log: This log is an International Conference on Harmonization (ICH) requirement. It documents the study-specific tasks that are delegated by the PI. A sample log for PI delegation of responsibilities is available for your reference.

7. Summary

Looking from the outside, one may feel that conducting clinical trials is a daunting task, with a million things that need to be attended to. After you've studied this module, we hope that you now see that it is really not that difficult, as long as you have a good system established and a good staff that takes clinical research seriously and pays meticulous attention to details.

The major tasks involved in conducting clinical trials include:

- IRB approval of protocol
- Patient enrollment
- Creating source documents and case report forms
- Quality assurance
- Maintaining pertinent forms and study records

Module 4: Patient Recruitment

1. Introduction

Besides the scientific integrity of the research protocol and the compliance with the protocol and related regulations, another factor that determines the success of a clinical trial is patient recruitment. All trials require the enrollment of a sufficient number of patients to ensure the statistical power and the generalizability of study results. The sooner a trial can reach its enrollment goal, the faster data are collected, analyzed, and shared in the medical community to improve cancer care.

Successful patient recruitment starts with a well-designed plan that maps out all the steps, methods, and research team member responsibilities for the recruitment efforts. While building such a plan, attention should be given to issues regarding research ethics and under-representation of women and ethnic minority groups in the study population.

Upon completion of this module, you will be able to:

- Identify major elements of a recruitment plan
- Describe methods for recruiting patients
- Identify special issues of consideration in patient recruitment for cancer clinical trials

Parts of the content in this module are compiled from works of the following authors:

Barrett, R. (2002). A Nurse's Primer on Recruiting Participants for Clinical Trials. *Oncology Nursing Forum*, 29(7):1091-1098.

Brown, D.R., Fouad, M.N., Basen-Engquist, K., & Tortolero-Luna, G. (2000). Recruitment and Retention of Minority Women in Cancer Screening, Prevention, and Treatment Trials. *Annals of Epidemiology*, 10(S8):S13-S21.

Flaskerud, J.H. & Nyamathi, A.M. (2000). Attaining Gender and Ethnic Diversity in Health Intervention Research Cultural Responsiveness versus Resource Provision. *Advances in Nursing Science*, 22(4): 1, 15.

Ford, B. (2000). Recruitment and Promotion Strategies for Clinical Trials. In Klimaszewski, A.D., Aikin, J.L., Bacon, M.A., DiStasio, S.A., Ehrenberger, H.E., & Ford, B.A. (Eds.), *Manual for Clinical Trials Nursing* (pp. 77-78). Oncology Nursing Press, Inc. Pittsburgh, PA.

Giuliano, A.R., Mokuau, N., Hughes, C., Tortolero-Luna, G., Risendal, B., Ho, R.C.S., Prewitt, T.E., & McCaskill-Stevens, W.J. (2000). Participation of Minorities in Cancer Research: The Influence of Structural, Cultural, and Linguistic Factors. *Annals of Epidemiology*, 10(S8):S22-S34.

Harden, J.T. & McFarland, G. (2000). Avoiding Gender and Minority Barriers to NIH Funding. *Journal of Nursing Scholarship*, 32(1):83-86.

Outlaw, F. H., Bourjolly, J.N., & Barg, F.K. (2000). A Study on Recruitment of Black Americans into Clinical Trials Through a Cultural Competence Lens. *Cancer Nursing™*, 23(6):444-452.

Spilker, B. & Cramer, J.A. (1992). *Patient Recruitment in Clinical Trials*. Raven Press, New York, NY.

Underwood, S.M. & Alexander, G.A. (2000). Executive Summary: Participation of Minorities and Women in Clinical Cancer Research. *Annals of Epidemiology*, 10(S8):S1-S2.

Individual references are not made in the text. See the bibliography in the "Resources" section for more information.

2. Recruitment Plan

For most clinical trials, patient recruitment follows this process:

- Recruitment effort by which the research team informs the community of the clinical trial
- Initial patient eligibility screening on the phone or at the study site
- Obtaining informed consent
- More detailed eligibility screening at the study site
- Patient registration
- Administering the protocol

A detailed plan for patient recruitment should be developed **before** a clinical trial starts. Because patient recruitment takes concerted efforts from every one on the research team, it is important that all research team members be actively involved in developing the plan and that they all agree to the strategies and methods to be used. This creates ownership of the recruitment plan among team members and promote adherence to the recruitment procedures.

There are seven steps in developing a recruitment plan.

2.1. Step 1 - Identify the number of patients to be recruited

This first step requires an estimate of the pool of patients in the recruitment area who would qualify for enrollment. Note that the number of patient to be recruited should be larger than the number that needs to be enrolled. This is because not all the patients recruited will meet the eligibility criteria, they may not sign the informed consent, or they may drop out of the trial, rendering their data unusable.

2.2. Step 2 - Identify potential referral base(s)

Potential participants in a clinical trial can come from different sources:

- The investigator's existing patient pool
- Physician referrals
- Patients who learn about the trial from information channels such as the newspaper or the Internet
- Referrals from non-medical sources, such as family and friends of current patients, professional societies, and lay organizations

Unless required by the sponsor to use only one or two sources, the research team should make efforts to reach out to as many patient sources as possible. It not only speeds up the patient enrollment process, but also ensures that the research results can be generalized to a broader variety of patients.

It is particularly important to use multiple participant sources in cancer prevention or screening trials. Participants in such trials are individuals who do not have a diagnosis of cancer. Primary care physicians and family physicians are one important referral source because they have direct access to this participant population.

2.3. Step 3 - Determine methods for approaching each source

There are a variety of ways to inform potential patients of the clinical trial. Which methods to use should depend on the phase and type of the clinical trial. The following are some ideas for recruitment methods:

- Newspaper stories or advertisements
- Radio or television stories or advertisements
- Internet stories or advertisements
- Talks at local and state medical societies
- Seminars in hospitals
- Notices on bulletin boards

2.4. Step 4 - Determine the process for patient enrollment

As discussed in *Conducting Cancer Clinical Trials*, informed consent must be obtained and eligibility screening must be conducted before a patient is enrolled into a clinical trial. For a large study, a complicated small study, or a study where multiple staff members are involved in enrolling patients, it is necessary to:

- Delineate all the tasks in the enrollment process
- Define team member roles and responsibilities
- Design proper tools to assist in task fulfillment

Such tools may include a:

Form for initial screening on the phone that includes columns for name, date, critical demographic information, telephone number, answers to critical inclusion answers, and interest in the trial

- Sheet of instructions for telephone interviewers
- Pamphlet describing the clinical trial to be handed out to interested patients
- Training manual that instructs staff how to present the scope and purpose of the clinical trial in a consistent manner when obtaining informed consent
- Manual of instructions for patients to help retain compliant patients. Decreasing patient drop-out rates reduces the need to recruit more patients

2.5. Step 5 - Document the recruitment plan

Systematic documentation of the recruitment plan enables the research team to follow the plan in recruitment efforts and to review and discuss the strategies and methods both

prior to the start of the study and periodically in the course of the study. Such documentation also provides good basis for publishing recruitment practices and experiences.

2.6. Step 6 - Define evaluation criteria for recruitment plan

To ensure the efficiency of a recruitment plan, it should be reviewed both prior to the clinical trial and during the trial. It is important to define your criteria for the "success" of the recruitment plan prior to its implementation. One criterion can be the number of patients your site is required to enroll by the sponsor or the research base with which you are affiliated.

A timeline should be set for the periodic review of the plan. If recruitment falls short of the evaluation criteria, problems should be identified and corrected.

2.7. Step 7 - Administer recruitment plan and review the plan regularly

The last step in the recruitment plan is to administer it. All staff members should adhere to their roles and responsibilities specified on the plan, and perform their respective tasks.

The research team should systematically evaluate the achievement of recruitment and retention goals. Problems need to be identified and corrected. The effectiveness of different recruitment methods should be studied. Increase the use of the effective methods and adopt these methods in other trials that are similar in size and in the target patient population.

The above seven steps are commonly seen in well-designed clinical trial recruitment plans. Depending on your study, you may or may not incorporate all the steps in your development process, and each of the steps can be simple or complicated.

3. Recruitment Methods

In their effort to recruit participants for a clinical trial, research team members can reach potential patients directly by means of posters, mailing, talks, and the media. In many studies, in particular cancer prevention and screening trials, they can, and should, reach out to physicians and medical professionals in the community for patient referral.

Enrollment of a patient is only the first step toward the successful completion of a study. The research team needs to pay special attention to retaining study patients.

It is crucial that the research team bear in mind the implication of the Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy Rules. According to these Rules, research recruitment is neither a marketing nor a healthcare operations activity. Under the Rule, a covered entity is permitted to disclose protected health information to the individual who is the subject of the information, regardless of the purpose of the disclosure. Therefore, covered healthcare providers and patients may continue to discuss the option of enrolling in a clinical trial without patient authorization, and without an IRB or Privacy Board waiver of patient authorization. However, where a covered entity wants to disclose an individual's information to a third party for purposes of recruitment in a research study, the covered entity first must obtain either authorization from that individual or a waiver of authorization as permitted at Sec. 164.512(i) of the Privacy

Rule. See <http://privacyruleandresearch.nih.gov> for useful information researchers need to know.

3.1. Direct Approaches

There are several direct approaches that can be used to include:

- The Internet
- Brochures and Posters at Various Sites
- Talks to Various Groups
- Stories and Advertisements in the Media (radio, television, newspapers, magazines, the Internet)
- Discussions at clinics
- Health fairs

3.1.1. Internet

With the rapid growth of Internet use, it's becoming more and more important that a research site have a presence on the World Wide Web. A larger site can consider putting up its own Web site with detailed listing of all the trials it conducts. Other sites that do not have the resources to maintain their own Web sites can still take advantage of the Internet to recruit patients:

- The Physician Data Query (PDQ[®]) sponsored by NCI provides information about research sites conducting NCI-sponsored cancer trials
- Web sites of cooperative groups, cancer centers, and Community Clinical Oncology Programs contain listings of clinical trials they sponsor and the participating research sites
- If the PI is affiliated with a local hospital, the hospital's Web site can advertise the clinical trials the PI conducts
- The CenterWatch Trials Listing Service on www.centerwatch.com maintains a list of industry-sponsored trials
- Pharmaceutical Research and Manufacturers of America (PhRMA) on www.phrma.org publishes a list of new cancer drugs in development

3.1.2. Brochures and Posters at Various Sites

Brochures and posters are widely accepted as the first-choice method of advertising for clinical trials. They are relatively easy to produce, usually done on computers and printed locally, at low cost, and easy to distribute.

Containing any message or amount of information as desired, brochures and posters are displayed in areas with high patient traffic, such as the waiting room or a health fair, and are given to patients who are interested in learning more about the trial or want to recommend the trial to people they know.

All brochures and posters must be approved by the IRB overseeing the trial before they can be used.

3.1.3. Talks to Various Groups

Another excellent way of recruiting patients is speaking to various groups in the community. Informative talks increase the awareness of cancer clinical research in the community and generate interest in participation. Speaking opportunities also establish your reputation in the community as a cancer clinical investigator who provides cutting-edge cancer care. There is a wide range of target audience groups. Local cancer patient support groups, black coalition groups and church groups are good examples.

3.1.4. Stories and Advertisements in the Media (radio, television, newspapers, magazines, the Internet)

News stories and advertisements are two useful types of media publicity. They are designed to disseminate information about a particular clinical trial either locally or nationally.

News stories in local newspapers, radio, or television are an excellent way of drawing attention from the local community to the clinical trial. They provide information such as the objectives of the trial, types of patients sought, and more importantly, the expected benefits for patients. News stories are free, but the opportunity doesn't come often nor is it repeatable.

Although expensive, paid advertisements on radio, television, and magazines generally generate a steady stream of inquires from prospective participants. In order to be more cost effective, ads can be placed in the news section instead of the classified section. Ads placed in a newspaper after a news story will maximize the benefits of the news story. Newspaper and radio ads are more effective when used for a cancer prevention trial than for a treatment trial because these ads can reach a large population of otherwise healthy individuals.

Besides the high-cost involved, another downside to advertising in general media outlets is that many of the people who respond don't qualify for the study. The message in the ad therefore needs to be carefully crafted to communicate as much as possible about the therapeutic category involved.

All advertisements must be approved by the IRB overseeing the trial before they can be used.

3.2. Indirect Approaches

The principal investigator and the research staff don't have direct access to the entire potential patient population for a clinical trial. Therefore, patient referral from other physicians and healthcare professionals becomes an important source of participants. Indirect approaches may include:

- Letters to solicit referrals
- Seminars in hospitals
- Notices on bulletin boards
- Notices in journals
- Letters to journals
- Talks at local and state medical societies

- Talks at professional societies
- Exhibits at conferences

The support of primary healthcare professionals is crucial for the success of cancer prevention and screening trials. Participants for these trials are healthy individuals and are not seen by oncologists, who traditionally conduct the clinical trials. They may be at high risk for developing cancer but they do not have as urgent a need to seek treatment as patients diagnosed with cancer. Primary care healthcare professionals play an important role in influencing preventive health behavior; a discussion between the primary care physician (PCP) and the patient about attending a clinical trial will positively influence a patient's decision.

Direct, personal contacts by the principal investigator have been found effective in informing the local health community of research efforts. These contacts often provide an opportunity to reduce some of the sense of ambiguity surrounding cancer control research among many healthcare professionals in the community.

A referral network with other cancer clinical trials investigators in the same community allows investigators to most appropriately refer patients so more patients can be enrolled in the appropriate studies. It benefits patients and the recruitment efforts of all the investigators involved.

Any one or more of the methods shown in the graphics here can be used to reach the local health community. One most important point to keep in mind is that you need to educate your audience about the importance of cancer clinical research. If they do not believe in research, they won't refer their patients to your trials.

3.3. Retaining Patients

All clinical trial participants have the right to drop out of the study at any time. If a patient chooses to drop out or fails to show up for follow-up visits, some of the data collected for this patient may be rendered unusable. This is why retaining patients throughout the study is as important as enrolling them.

There are many ways in which a site can encourage its participants to remain in the study until the end. Here are a few practical tips:

- Show the participant they are respected and valued for their commitment throughout the study and the follow-up
- Be flexible when scheduling visits and testing
- Keep participants informed of study progress and results
- Keep referring clinicians informed of participants' treatment, progress, and adverse events, so they can help provide emotional support to participants and answer participants' questions
- Be sensitive to participants/small children and provide toys and books for children if possible
- Make reminder phone calls and/or send written reminders regarding upcoming appointments or follow-up visits.

A sample on-going study visit letter is shown on the following page.

An Example: Reminder Letter to Patient During the Study

April 22, 2002

Mary Jane Patient
222 Buckyway Ave.
Utica, NY 45278

Dear Mary Jane:

I wanted to remind you that your next appointment for the _____ clinical trial is scheduled for May 2 at 1:00. As it is very important for you, and to the study, that we see you as scheduled, please call me right away if you have any concerns about being able to keep the appointment. We may be able to assist you in keeping this time, or if necessary, I will arrange another suitable time.

Please remember that it is important that you do the following:

- Keep a record of any unpleasant symptoms that you may experience, when they start, and when they end.
- Take the medication according to the instructions that I gave you.
- Keep your patient diary current, as we discussed.
- Bring your patient diary with you to each office visit.
- Bring any unused medication with you to each office visit.

If you have any questions or concerns that you would like to discuss with me before your next visit, or you experience troubling symptoms and don't feel you should wait, don't hesitate to call me at _____.

Sincerely,

Josephine Hershey, RN
Clinical Trials Nurse

4. Avoiding Under-Representation of Women and Minorities in Clinical Trials

Women make up about 52% of the population in the United States, and ethnic groups other than Whites account for 28%. Women and minority populations experience a disproportionate share of the country's cancer burden, suffering higher rates of cancer morbidity and mortality. For example, African-American males are diagnosed with cancer approximately 15% more frequently than white males, and have the highest overall cancer mortality rate; disproportionate rates of cervical cancer are also observed in many minority women.

In order to improve gender and ethnic diversity in health intervention research, the NIH Revitalization Act of 1993, Public Law 103-43, requires recruitment of women and minorities and their subpopulations in all clinical research studies, especially clinical trials. Guidelines include:

- Ensure that women and members of minorities and their subpopulations be included in all human subject research
- For phase 3 clinical trials, ensure that women and minorities and their subpopulations be included so that valid analyses of differences in intervention effects can be accomplished
- Not allow cost as an acceptable reason for excluding these groups
- Initiate programs and support for outreach efforts to recruit these groups into clinical studies

This section presents the typical challenges for the research team in its effort to recruit and retain women and minorities in clinical trials, and strategies to overcome these challenges.

4.1. Challenges in Recruitment and Retention

Access availability and affordability: Women and ethnic people of color are more likely to live in poverty than men or Whites. Lack of or insufficient health insurance limits their access to primary health care and to clinical research studies that require third party payment. They are less willing to participate in clinical trials because they can't afford to take a considerable amount of time off work or incur out-of-pocket expenses.

Lack of knowledge about benefits: People choose to take part in clinical trials if they think benefits associated with the participation outweigh burdens. Women and minorities face more financial and logistic burdens, but they often are unaware of the benefits of clinical trials.

Language, literacy, and cultural barriers: For ethnic minorities who speak a language other than English, understanding the informed consent and compliance with protocol requirements may pose major problems. The use of medical language further excludes people with low literacy ability. The different cultural values that ethnic minorities hold may prevent them from participating in clinical trials. For example, many people think that disease and death are natural occurrences and not something to fight against.

Other challenges include:

- Distrust of the scientific and the medical community as a result of historical experience
- Failure of researchers to adequately consider recruitment of a diverse population
- Alienation and failure to collaborate with minority scientists and healthcare professionals

4.2. Recruitment Strategies

To successfully recruit women and ethnic minorities into cancer clinical trials, the research team needs to provide resources to these groups and also be culturally responsive.

Low-income persons are least likely to participate in research and most likely to drop out. Providing resources to women and minority groups helps to reduce or eliminate the various barriers, and thus empower them to participate in research. Such resources range from transportation, child care, health insurance, and monetary incentive to education and social integration and status.

Cultural responsiveness attempts to encourage women and minority communities to participate in research by achieving shared knowledge, attitudes and values, and collaborative practice of researchers and participants. Matching research team members and potential participants in gender, ethnicity, and language should increase understanding and trust between the two groups and facilitate recruitment.

The use of culturally targeted mass mailing and media presentations are among the most effective recruitment strategies. Here are some more strategies you can use to increase the representation of women and ethnic minorities in your studies:

- Provide a welcoming office environment for participants' families
- Assist participants in accessing available medical insurance, disability insurance, and drug assistance programs
- If possible, recruit people in their communities and conduct interviews in their homes or shelters
- Involve minority members actively in the research from the outset of the project to instill a sense of project ownership
- Match gender, language, or ethnicity of research team members and participants. This will enhance the communication between the research staff and the participants about clinical trial benefits, informed consent, and protocol compliance
- Send follow-up letters acknowledging the patient's time and effort
- Obtain support from local community leaders

5. Summary

Patient recruitment and retention in a clinical trial determine how efficiently research data can be produced. A well thought-out recruitment plan helps direct the efforts of a research team. This plan should include such elements of the target number of patient recruitment, patient sources, and ways to reach these sources. It is also important to build in a system to document, evaluate, and revise the plan both before and after the trial starts.

There are a variety of methods to inform patients and the medical community of the clinical trial you are conducting, such as the Internet, brochures, talks, and the media. These methods all have their advantages and disadvantages in terms of costs and efficiency in disseminating the information. You choose the best methods for your study according to your available resources and the audience you are trying to reach.

The last topic we examined in this section is how to attain gender and ethnicity diversity in your clinical trials. Proportionate representation of women and ethnic groups in research samples ensures that study results can be generalized to and benefit a broad population. Two keys to success in recruiting and retaining these groups are cultural responsiveness and resource provision.

Module 5: Working With Referring Clinicians

1. Introduction

Besides medical procedures required by the study protocol, a research participant also receives medical care for any side effects that may arise from the protocol drug. The principal investigator can manage these symptoms if the patient lives in a nearby area and can travel to the research site easily. For patients who live far away, the referring clinicians play an extremely important role in interpreting and clinically managing patients when they are home. This is especially true in rural areas where there is limited access to cancer clinical researchers and therefore a greater reliance on the referring professionals working in the community.

This module presents a model for a collaborative working relationship between the research team and the referring clinicians. Effective communication is the key in this relationship.

Upon completion of this module, you will be able to:

- Identify key patterns of responsibilities in an effective referring clinician-research team working relationship
- Describe the types of communication that can facilitate increased accrual to clinical trials

Parts of the content in this module are compiled from works of the following authors:

Kaluzny, A.D., Lacey, L.M., Warnecke R., Morrissey, J.P., Sondic, E.J., & Ford, L. (1994). Accrual of Patients to Randomized Clinical Trials: Factors Affecting Cancer Prevention and Control Research. *International Journal of Technology Assessment in Health Care*, 10(3):506-516.

Mansour, E.G. (1994). Barriers to Clinical Trials, Part III: Knowledge and Attitudes of Health Care Providers. *CANCER Supplement*, 74(9):2672-2675.

National Cancer Institute (2001). *Cancer Clinical Trials: The In-Depth Program*. Available: <http://oesi.nci.nih.gov/series/cted/indepth.html> .

Williams, P.T. & Peet, G. (1994). Differences in the Value of Clinical Information: Referring Physicians versus Consulting Specialists. *J Am Board Fam Pract*, 7:292-302.

Individual references are not made in the text. See the bibliography in the Resources section for more information.

2. Research Staff - Referring Clinician Working Relationship

The working relationship model we are going to show you here is also presented in Section I, Module 4 "The Referring Clinicians' Role in Cancer Clinical Trials." If you have studied that module, you can skip this topic and use the "Communication" link to proceed.

As the referring clinician works closely with a research team, a pattern of responsibilities emerges:

- Determine eligibility and feasibility of this patient enrolling into a clinical trial
- Discuss the trial with the patient
- Establish initial contact with the clinical research team (this is preferable to direct communication by the potential participant as he or she may not have sufficient information on their medical conditions and prior treatment to determine eligibility)
- Determine preliminary eligibility over the phone or via the Internet
- Schedule appointment and share appropriate clinical data with the research team

If the person is accepted onto a trial, the referring clinician:

- Continues to provide clinical care of their patient
- Communicates with the research team regularly regarding patient's condition and any significant changes
- Provides emotional support to their patient
- Helps answer questions

Referring clinicians play several important roles throughout the clinical trial process:

- Supply information to the clinical trial team enabling it to care for the trial participant
- Provide shared care for the participant while the patient is on the study and upon patient's completion or removal from the clinical trial
- Facilitate participant retention in the clinical trial by providing participants with continuity of care, emotional support, and answers to their questions

The referring clinician, research team, and participant should develop a clear understanding of responsibilities for optimizing the participant's care.

The research team in turn:

- Provides care for the participant in compliance with the study protocol
- Updates the referring clinician regularly regarding the prescribed intervention, expected symptoms, and suggested management of any unexpected symptoms
- Seeks input from the referring clinician on standards of care, future protocol development, and any methods to promote trial efficiency and participant safety and well-being

3. Communication With Referring Clinicians

The research team's communication with referring clinicians is an essential element in maintaining the referral pattern and assuring the provision of the best care to the patient:

- A survey of primary care physicians suggests that the timing, specificity of information, and perceived support from a research site influence the level of the family physician's satisfaction with their supportive care role
- Studies have also shown that there is a direct correlation between patient satisfaction and the quality of communication between involved healthcare professionals

The research team can play a key role in educating potential referring clinicians about clinical trials. In doing this they can directly impact patient referrals and speed patient accrual. This education can take many forms, including:

- Presenting at meetings and hospital rounds
- Written articles or newsletters
- Newspaper articles in health-type sections
- Utilizing CME venues to address issues related to trial referrals/participation

Before the trial: Provide detailed inclusion and exclusion criteria for referring clinicians so they can adequately evaluate a patient's clinical situation. If appropriate, a list of references on the therapy modality to be investigated is also helpful.

During the trial: To make referring clinicians at ease and comfortable with participating in the care of the patient, it is essential to provide them with adequate information regarding:

- Prescribed treatment
- Expected side effects
- Suggested management of any adverse events
- Progress the patient is making
- Adverse or unexpected situations regarding their patients
- A report of each encounter between the research team and the participant is also deemed important by referring clinicians

The above communication from the research team also enables referring clinicians to answer participants' questions and therefore facilitates participant retention for a study.

After the trial: Provide referring clinicians with a contact person so they can communicate information such as long-term side effects or death of participants. If appropriate, provide referring clinicians with information regarding how to manage the participant after the clinical trial participation.

Ongoing support: Unlike in a traditional consultation-referral process, the research team needs to go one step further to ensure that the referring clinician has a good understanding of clinical research.

Help referring clinicians understand the basics of clinical trials and the importance of research in the advancement of cancer care. After the initial conversation with a research team member, patients often return to their referring clinicians and ask for advice whether to participate in the clinical trial. The referring clinicians need to understand the basics of clinical trials to be able to assist the patient in this decision. They play a key role in helping patients see clinical trials as one way to get the state-of-the-art treatment and believe in the importance of research.

Send a copy of the informed consent document. Patients often want to review this document with their referring clinicians before making a decision.

Emphasize the importance of record keeping and adverse event reporting. It is crucial that referring clinicians understand the importance of recording and prompt reporting of

such events to the research team. They should also inform the team of any changes they may have initiated in the care of the patients.

Research has shown that satisfaction of referring clinicians increases when the consulting physician, the research team in a clinical trial, provides information of educational value.

4. Summary

Healthcare professionals who refer patients to clinical trials can be the patients' primary care clinicians or their oncologists. They play a supportive but indispensable role in the patients' total care during a clinical trial. This is why it is important that the research team effectively communicate with referring clinicians about patients' treatment, progress, and expected side effects from the investigational drug.

Referring clinicians are more likely to assist in patient recruitment and retention in clinical trials if they believe in the clinical research process. Efforts by the research team to educate referring clinicians on the importance of research and the basics of clinical trials will pay off in the long run.

Comments from Dr. James Atkins, an accomplished cancer clinical investigator, sum up the importance of good communication:

"Communicating with the family doctors or the referring doctors is extremely important whenever you're dealing with a medical practice that's based on referrals. It's very important that referral physicians keep their referring doctors informed.

It's amazing, because I sort of think that when I talk with my patients that um, that I have the answer to all their questions and they're happy and they're satisfied and all this and then they go to their family doctor and say well what about this and this and this.

That is a real issue and so they do talk with their family doctors and so their doctors do need to be in the loop and we need to talk to the doctors about clinical trials, they really do need to. They need to be as knowledgeable as you can have them."

Module 6: Starting Your Clinical Trials

1. Introduction

In the previous five modules, you were introduced to the major issues involved in offering clinical trials in your practice. We hope that you are now motivated to set up some studies on your site. The first half of this module assists you in coming up with a plan of action for setting up clinical trials; the second half assesses your understanding of implementing study protocols with a case study.

2. Action Plan

After carefully considering all the practical issues concerning offering clinical studies in your practice, you've decided that you will become involved in clinical research. Go through the following questions and make your choice of actions you would like to take to set up the research infrastructure.

Becoming a Cancer Clinical Trials Investigator

Clinical trials will be offered at my site through the following channel(s):

- Joining one of NCI's Cooperative Groups with sponsorship of one of its members.
- Joining an NCI-sponsored Community Clinical Oncology Program (CCOP)
- Registering with the NCI-sponsored Cancer Trials Support Unit (CTSU)
- Offering pharmaceutical company-sponsored clinical trials

Building a Research Team

Members I desire for my research team:	Those team members I need to hire:	Those team members I need to re-train:
<input type="checkbox"/> Principal investigator (PI)	<input type="checkbox"/> Principal investigator (PI)	<input type="checkbox"/> Principal investigator (PI)
<input type="checkbox"/> Co-investigator	<input type="checkbox"/> Co-investigator	<input type="checkbox"/> Co-investigator
<input type="checkbox"/> Clinical research associate or research nurse	<input type="checkbox"/> Clinical research associate or research nurse	<input type="checkbox"/> Clinical research associate or research nurse
<input type="checkbox"/> Data manager	<input type="checkbox"/> Data manager	<input type="checkbox"/> Data manager
<input type="checkbox"/> Staff nurses	<input type="checkbox"/> Staff nurses	<input type="checkbox"/> Staff nurses
<input type="checkbox"/> Pharmacist	<input type="checkbox"/> Pharmacist	<input type="checkbox"/> Pharmacist
<input type="checkbox"/> Member from Nutritional Services	<input type="checkbox"/> Member from Nutritional Services	<input type="checkbox"/> Member from Nutritional Services
<input type="checkbox"/> Social Worker	<input type="checkbox"/> Social Worker	<input type="checkbox"/> Social Worker
<input type="checkbox"/> Clinical Trial Recruitment Specialist	<input type="checkbox"/> Clinical Trial Recruitment Specialist	<input type="checkbox"/> Clinical Trial Recruitment Specialist
<input type="checkbox"/> Bioethicist	<input type="checkbox"/> Bioethicist	<input type="checkbox"/> Bioethicist
<input type="checkbox"/> Chaplain	<input type="checkbox"/> Chaplain	<input type="checkbox"/> Chaplain
<input type="checkbox"/> Biostatistician	<input type="checkbox"/> Biostatistician	<input type="checkbox"/> Biostatistician

Educating the Research Staff

Education for the research staff will be:

- Formal training sessions.
- Informal training such as conversations between the PI and the nurses, observation, and recommended readings for the staff.
- Both formal and informal training.

Staff education will be conducted:

- Before a protocol is open to patient enrollment.
- Throughout the time when the protocol is open.
- Both before and after a protocol opens for enrollment.

Identifying an IRB

Study protocols to be conducted at my site will go through review and approval by:

- The IRB of the hospital I'm (or the PI is) affiliated with.
- A national centralized IRB offered by the trial sponsor, if available.
- The hospital that I'm (or the PI is) affiliated with doesn't have an IRB. Research conducted at my site will be reviewed by an IRB in another site.

Preparing the Facility

The following work needs to be done to prepare the facility at my site:

1. Prepare a lockable drug storage cabinet.
2. Put in new office areas for the data manager (or the clinical research coordinator)
3. Prepare an area where study monitors or auditors can work without interruption.
4. Prepare space for storing study files and records.

3. Exercise - Implementing Clinical Trials

Oncologist Dr. Neal practices in Augusta, Georgia. She recently learned about the opportunity to offer cancer clinical trials in the community and became an investigator through the NCI-sponsored Community Clinical Oncology Program (CCOP). Her first study is the Study of Tamoxifen and Raloxifene (STAR) for the Prevention of Breast Cancer. Answer the questions as you read through this case study (see <http://www.cancer.gov/clinicaltrials/digestpage/STAR>).

1. Before opening the study for patient enrollment, Dr. Neal sends the trial package to the IRB at her affiliated hospital for approval. Which of the following components must Dr. Neal include in the IRB package?
 - A. The protocol
 - B. Identity of the investigator(s)
 - C. Location of the research site(s)
 - D. Informed consent form
 - E. A form letter to be mailed to primary care physicians and OB/GYNs in the community.
2. The chair of the IRB is a friend of Dr. Neal's and he told Dr. Neal that the study had been approved and a letter would go out to Dr. Neal within the coming few days. Dr. Neal:
 - A. Waits until she has received the written IRB approval before she starts to enroll patients.
 - B. Starts to enroll patients into study before she receives the written IRB approval
3. Dr. Neal receives the written IRB approval from the IRB. She puts the approval letter, as well as the approved informed consent form and advertisements, in the study binder, where she will keep and continuously update all the regulatory documents regarding this trial.

Patients and referring clinicians have started to call Dr. Neal's office to find out more about the trial since advertisements came out in the local newspaper a few days ago. Among them is family physician Dr. Levinson. He calls to find out whether one of his patients is eligible for the trial.

Karen, Dr. Neal's data manager, talks with Dr. Levinson on the phone and goes over the eligibility list with him. At the end of the conversation, Karen obtains the contact information from Dr. Levinson for the patient.

Karen contacts the patient, Ana, and schedules an appointment with her for an office visit to further screen Ana's eligibility. Among all the eligibility requirements, the protocol requires a blood test to determine the complete blood count, differential, and platelet count.

Karen contacts Ana, and schedules an appointment with her for an office visit to further screen Ana's eligibility. Among the eligibility requirements, the protocol requires a CT scan to determine if Ana's disease is measurable.

Before Ana can receive the protocol treatment, there are several tasks that the research team needs to perform.

Place these tasks in the correct order in which they should occur:

1. Register Ana with the Cooperative Group that sponsors the study.
2. Perform protocol-related procedures on Ana to confirm eligibility.
3. Ana signs and dates the informed consent.
4. Explain the informed consent document to Ana and answer Ana's questions.

A. 1, 2, 3, 4

B. 2, 3, 4, 1

C. 4, 3, 2, 1

D. 3, 2, 1, 4

4. After Ana's visit, Karen, the data manager, fills out the screening and intake forms and keeps them on file with Ana's signed and dated informed consent form. In the same file she will also keep other records such as Ana's current medication and medical history to be received from Dr. Levinson, Ana's primary care physician. These documents are called source documents. Of the following, which are considered source documents?

- A. Laboratory results
- B. Screening log that records all the patients who are screened for the STAR trial
- C. Appointment books
- D. Patients' case report forms
- E. Adverse event list

A, C, D, E

A, B, C, E

B, C, D, E

All of the above

5. Karen regularly completes case report forms (CRFs) based on data on various source documents, and submits the CRFs to the NCI Cooperative Group that sponsors the

STAR trial.

Which of the following is a correct action after the CRFs are submitted to the trial sponsor?

- A. With data from source documents transferred to the trial sponsor in CRFs, Karen discards the source documents from the previous months to make room for source documents to be generated in the coming months.
- B. Karen keeps copies of all the CRFs and maintains records of all the source documents.

6. On Ana's third visit, Karen finds that Ana's renal function tests are unexpectedly elevated.

What is the correct action Karen should take?

- A. Karen should report this as an adverse event.
- B. Karen thinks the symptom is mild and doesn't need to be reported as an adverse event.
- C. Karen doesn't think the abnormal renal function tests are related to the protocol treatment, and therefore don't need to be reported as an adverse event.

7. Karen confirms with Dr. Neal that abnormal renal function tests are considered an adverse event.

What are the correct actions that Karen or Dr. Neal should take in reporting this adverse event?

1. Report the event to the NCI Cooperative Group that sponsors the study.
2. Report the event to the IRB.
3. Report the event to the FDA.
4. Report the event to the site monitor during a site visit so that the monitor can report it to all the parties concerned.
5. Document this adverse event and keep the record with other source documents.
6. Document all the communication generated while reporting this adverse event.

- A. 1, 2, 5, 6
- B. 1, 2, 3
- C. 4, 5, 6
- All of the above

8. Thanks to effective advertising strategies, the patient enrollment for the STAR trial at Dr. Neal's site has been increasing steadily. Half a year after Dr. Neal started to offer the study, a monitor from the NCI sponsoring Cooperative Group pays a site visit to Dr. Neal's office.

What are some of the things Dr. Neal and Karen can do in preparation for the visit?

1. Make available copies of all of the case report forms (CRFs) that have been submitted to the sponsors so far
2. Make available all of the source documents
3. Color code all the materials to facilitate the monitor review
4. Prepare the binder that collects all the regulatory documents related to this trial
5. Make sure that at least one of Dr. Neal and Karen is available during the site visit to answer questions and assist the review

- A. 1, 2, 3, 5
- B. 2, 3, 5
- C. 1, 2, 3, 4
- D. All of the above

9. To provide high-quality healthcare to patients and also to maintain the referral base, Dr. Neal believes that clinical investigators and referring clinicians should work closely together and keep each other updated on the patient's status.

What is some of the information that a clinical investigator can share with the referring clinician in order to aid him or her in the management of symptoms?

- A. Prescribed protocol treatment.
- B. Expected side effects of the study drug and suggested management of any toxic reaction.
- C. Adverse events experienced by the patient.
- D. All of the above