

The Elements of Success

Conducting Cancer Clinical Trials

A Guide



Coalition of
CANCER COOPERATIVE GROUPS

Preface

In June 2005, The Lewin Group, in partnership with Lovett-Collins Associates, was commissioned by C-Change™ to conduct a study to determine the cost and time expenditures of cancer clinical trials. The Lewin Group published these findings and elements of success for cancer clinical trials in a document titled, “*A Guidance Document for Implementing Effective Cancer Clinical Trials, Version 1.2.*” http://www.c-changetogether.org/about_ndc/newsroom/default.asp¹

The following year, based on input from the Summit on Clinical Trials, C-Change and the Coalition of Cancer Cooperative Groups commissioned The Lewin Group, again in partnership with Lovett-Collins Associates, to produce two targeted follow-up documents: a policy document that summarizes the current economic environment of cancer clinical trials for policy makers; and a web-based resource and guidance document on how to conduct clinical trials for use by clinical trial personnel.

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¹ The document can be viewed by clicking on the link *Guidance Document* in the Reports section on this web page.

Commissioned by

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The Document

Section 1.01 Background

Clinical trials result in new and approved drugs and procedures for patients, and often result in changes to therapeutic options for patients with cancer. Since most adult cancer therapies do not result in cures, it is imperative for the scientific community to engage in clinical trials to improve outcomes such as survival, side effect profiles, combination therapies, and quality of life. According to the National Cancer Institute (NCI), about three percent of all adult patients will be enrolled in a cancer clinical trial.² However, a recent study at an academic center found that the overall accrual rate for screened patients was 14%.

Factors that contribute to low accrual rates included physician barriers, protocol or eligibility barriers, patient barriers, and resource or funding barriers. Physician bias that decreases the number of screened patients includes not knowing or not having an active trial for a particular cancer, and perception of patient performance (too old, too frail). Patients may refuse based on general desire to get another therapy, geography and travel, fear of randomization, and third-party payer issues.³ The proportion of qualified physicians who participate in studies is also small. Therefore, many patients are not being offered the treatment options provided by controlled clinical trials.

Coverage by payers for study procedures should also be considered during the protocol evaluation stage.

Section 1.02 Purpose

There is a wealth of resource information supporting the planning and conduct of clinical trials. This document is intended as a resource to provide general information on the conduct of clinical trials for new and prospective clinical trial investigators and sites. Different groups will use the document in different ways, but it is particularly intended for those participating in multi-center research studies.

In so doing, this document:

- 1) Highlights elements of success
- 2) Defines general areas of trial execution
- 3) Provides specific information in the forms of checklists, templates, and websites
- 4) Helps sites locate useful resources

This document/web site contains a representative sample of checklists, manuals, and forms developed by experienced clinical trial practitioners. For new sites, there is a section designed to encourage the thought process of those beginning clinical trials. For more experienced sites, there is information throughout the text and in the reference section that may be helpful in improving performance.

The tools and regulations referenced in this document are illustrative rather than comprehensive. They are provided as a guide and, in practice, it is ultimately the responsibility of the investigator and/or the institution to ensure that all study related activities meet local and federal regulatory requirements and comply with good clinical practice standards.

² Cancer Clinical Trials: The Basic Workbook. In *National Cancer Institute*. Retrieved June 26, 2006, from http://www.cancer.gov/PDF/091e02f3-5bb9-4ba6-a988-9ad35eab6a61/BasicsWorkbook_m.pdf.

³ *Prospective Evaluation of Cancer Clinical Trial Accrual Patterns: Identifying Potential Barriers to Enrollment*. Lara, P.N., Higdon, R, Nelson, L, Kwan, K, Nanaka M, Lau, D, Wun, T, Welborn, J, Meyers, FJ, Christensen, S, O'Donnell R, Richman, C, Scudder, SA, Tusciano J., Gandara, DR, Lam, KS. JCO Vol 19, No 6: pp1728-1733

⁴ *Enhancing Cancer Treatment through Improved Understanding of the Critical Components, Economics and Barriers of Cancer Clinical Trials*, prepared for C-Change by The Lewin Group, September 14, 2006. This document lists critical barriers to clinical trial participation in the Executive Summary.

Section 1.03 How to Use This Document

The document is divided into six sections that can be used independently as sources of information for research sites. Though some people may want to read the document from start to finish, others may want to refer only to those portions they find relevant.

Section I provides the six Elements of Success identified by the Summit Series on Cancer Clinical Trials. These are “how to” principles for successful research programs. Listed with each element is the applicable operational section of the document.

Section II lists the Functional Steps of Clinical Trials summarized from an initial survey of successful trial sites, and published by the Lewin Group as “*A Guidance Document for Implementing Effective Cancer Clinical Trials*” June, 2005. The functional steps refer to the process of evaluating, initiating, conducting, and closing a clinical trial. References to other document sections are included with each of these steps.

Section III is a detailed look at some selected elements of research, including investigator responsibilities, patient protection, and key procedural steps in a program development. References to template forms and web resources are included in this section.

Section IV addresses various issues involved in budgeting and includes a sample budget.

Section V is for sites new to research. There is some overlap with previous sections, but this section addresses specific areas of interest and concern (e.g., resource, time, and regulatory requirements) for those sites just beginning clinical trial participation and programs.

Section VI contains Internet resources and references and is organized by area of interest.

I. The Elements of Success

An Overarching Framework for Cancer Clinical Trials and Trial Sites

The Summit Series on Cancer Clinical Trials (<http://www.cancersummit.org/>) has identified “Elements of Success”⁵ that contribute to the development, execution, and longevity of a site’s ability to sustain clinical trials. These elements are relevant across all trial settings, including private practices, community hospitals, community cancer centers, and academic institutions.

The Six Elements of Success

1. Committed Staff

Since the work of supporting a clinical trial program is adjunctive to the work of providing care, the execution of a successful research program mandates that there is commitment both in time and adequate personnel to perform the research, as well. Such commitment includes a dedicated physician to act as investigator, ancillary personnel as required by the site (coordinator, data manager, pharmacy), and research training to ensure compliance with regulatory and patient safety requirements.

(Section III: 1.3, 2.1.1, 2.1.2, 2.1.6, 3.0, and 5.0.)

⁵ *A Guidance Document for Implementing Effective Cancer Clinical Trials*, prepared for C-Change by The Lewin Group, June 7, 2005. Section II, Cancer Clinical Trials: Elements of Success (pp 6-11), deals in detail with the findings from the survey.

2. Financial Resources

Adequate financial resources must be available to execute and sustain the research program and associated personnel. Operating systems should ensure that research staff is not diverted to perform routine clinical or other non-trial functions once studies are in place.

(Section III: 4.0 and 5.0.)

3. Accessible Ancillary Services

Oncology research is becoming increasingly complex, and successful sites effectively identify and utilize ancillary services. This may include services such as patient referrals from surgery or radiation colleagues, laboratory and/or pathology departments for specimen collection and storage, adequate treatment facilities with necessary equipment, and patient support systems. Sites should strive to make the provision of these resources appear seamless to potential clinical trial research subjects.

(Section III: 3.3)

4. Respect for Subjects

Patients must be treated ethically, and appropriate measures must be undertaken to ensure respectful contact and communication. Ongoing participation in ethics training, knowledge of requirements for patient privacy and consent issues, identification of potential conflicts of interest, and patient education are all important aspects of meeting the criteria for respect.

(Section III: 1.2, 2.1.3, and 2.1.5)

5. Host Institution

The research-setting supporting clinical trial participation and infrastructure may vary widely. It is important to meaningfully involve all interested parties in all appropriate activities, e.g., planning and budgeting, to ensure support for an enduring program.

(Section III: 2.1.4, 3.3, 4.0, 8.0, and 9.0)

6. Emphasis on Safe Patient Care

Ensuring patient safety requires 1) knowledge of good clinical practice guidelines, 2) applicable regulations that guide research, 3) an understanding of each protocol, 4) patient education, and 5) support for management during a study. All aspects of clinical trial execution must be delegated only to qualified individuals.

(Section III: 2.1.3, 2.1.5, 7.2, 7.3, and 7.4)

II. Functional Steps of Clinical Trials

The Operational Framework for Cancer Clinical Trials

1.1 The Seven Functional Steps⁶

The Elements of Success noted in Section I represent a conceptual framework of “how” to build a successful cancer clinical trial program. The success of any endeavor depends on commitment and understanding, identification of resources, implementation, and ongoing evaluation. However, there is also an operational framework: the “what” upon which the conceptual framework must be laid.

Listed below are the basic functional steps detailed in the initial survey document.⁷ Information related to these steps is addressed in the following section. Each investigator and research site will have unique needs within the framework of required activities. This information will aid trial personnel in understanding the meshing of the “how” and the “what.”

1. Protocol Selection
2. Study and Site Feasibility Assessment
3. Regulatory Submission
4. Legal and Financial Review and Approval
5. Site Activation
6. Study Execution (Accrual and Follow-up)
7. Study Closure

⁶ *Ibid.* Note that the original *Guidance* document listed Nine Functional Steps that were part of a data collection survey. This document has reduced those nine steps to seven, meshing “Preparation for Study Execution” into “Site Approval” and including “Data Review” in “Study Execution.”

⁷ *Ibid.* Section IV, Clinical Trial Functional Requirements (pp. 16-29), lists valuable data including Time and Cost Drivers for each element.

1.2 General Activities in each Functional Step

Activity	Comment	References and Supplementary Information
<p>1. Protocol Selection</p> <p>Principal Investigator (PI) identifies “gap” in study coverage</p> <p>Contact sponsor to obtain study information, or PI is approached by the sponsor for study consideration</p> <p>Confidentiality may need a disclosure agreement for certain sponsors</p>	<p>Identify a potential new therapy or patient group where clinical trial may be of benefit where there is no current trial.</p> <p>For public trials, information is available on the web at www.clinicaltrials.gov or from a national cooperative group. For private sponsors, there may be information available on the web as above, or a site may be approached by a sponsor or contract research organization (CRO), acting on behalf of a sponsor.</p> <p>Certain agreements and training are required for participation in publicly funded studies, for other sponsors an agreement will be required when potential proprietary information is shared.</p>	<p>Section III, 3.0 Choosing Trials</p> <p>Section III, 4.0 Contracts</p>
<p>2. Feasibility Assessment</p> <p>Obtain protocol from sponsor</p> <p>Summarize protocol requirements to ensure feasibility</p> <p>Review all elements</p> <p>Budget evaluation</p> <p>Pre-study visit by sponsor</p> <p>Site Approval</p>	<p>Obtain the protocol and any other supporting documents such as monitoring plan, case report forms, expected enrollment, etc.</p> <p>Estimate accrual, ancillary resource needs, site and space needs, personnel time estimates and cost estimate. Review study timeline and patient follow-up expectations.</p> <p>Scientific review by investigators/site, feasibility by research staff and ancillary (e.g., pharmacy or laboratory) with elements above. Ensure all parties are included in evaluation. Make final determination of interest.</p> <p>Budgets are fixed in public studies for patient accrual reimbursement. For privately funded studies, negotiation is up to the sponsor and the site. Some sponsors provide a one-time payment for regulatory and up-front costs, payable upon contract execution.</p> <p>Performed by private sponsors for site evaluation, generally takes 4-6 hours. For publicly funded studies, an accurate site assessment of the protocol and requirements should determine ability to perform the study within timelines and NCI requirements for investigators.</p> <p>Final site approval for privately sponsored studies will not occur until all regulatory documents are submitted, reviewed and approved, site training has occurred, and a contract is executed.</p>	<p>Section III, 3.1 Protocol Scientific Assessment</p> <p>Section III, 3.2 Feasibility Assessment</p>

Activity	Comment	References and Supplementary Information
<p>3. Regulatory Submissions</p> <p>Institutional Review Board (IRB) Selection</p> <p>Informed Consent Form (ICF)</p> <p>IRB submission and approval</p> <p>Regulatory documents to sponsor</p>	<p>Site requirements and obligations to IRBs are dependent upon research settings and affiliations. It is the PI's responsibility to know which IRBs can be utilized and to provide oversight:</p> <ul style="list-style-type: none"> * Local IRB (Institutional/Local IRB) * Central IRB (Commercial/Independent IRB) * Central IRB (CIRB) Only for cooperative group and CTSU (NCI) sponsored studies. <p>ICF templates are usually provided by all sponsors of multi-site trials and must be amended to include institutional and investigator information. Sometimes these must go back to the sponsor for approval before IRB submission.</p> <p>Determined by IRB requirements. At the least, the protocol document and consent form must be submitted. Any potential plan for advertising outside of listing the study on www.clinicaltrials.gov and all information given to patients must be submitted. Other necessary documentation required by IRB, e.g.: Synopsis of research, Curriculum Vitae (CV) for appropriate personnel, Form 1572 for the Principal Investigator, Health Insurance Portability & Accountability Act of 1996 (HIPAA), Legal Review of the submission, if applicable, and Peer Review, if applicable.</p> <p>Other required regulatory documents vary by sponsor-AAAAtype (public or private) and regulatory phase (IND or non-IND).</p> <p>CV of PI and sub-Is, FDA form 1572, financial disclosure forms, IRB-approved consent and protocol documentation, laboratory normal values, lab certification, licensure information of PI, certification of no debarment or research sanctions.</p>	<p>Section III, 2.1.4 IRB</p> <p>Section III, 2.1.3 Patient Protection</p> <p>Section III, 2.1.4 IRB</p> <p>Section IV - Budgeting for Clinical Trials</p>
<p>4. Legal/Financial Review and Approval Budget (exhibit)</p> <p>Send contract (agreement) for appropriate review</p>	<p>Budget review may be the responsibility of the investigator or other hospital staff. Know if there are any fixed research costs at the site. The person who reviews the budget and gives approval may be different from the person who reviews the contract</p> <p>Know who is responsible for contract review and signature. Legal contract review is based on individual practice or institutional requirements and the type of relationship between investigator/site/institution.</p> <p>Contracts among multiple parties require much iteration and may take months to complete, depending upon communication flow and layers of review.</p>	<p>Section III, 4.0 Contracts</p>

Activity	Comment	References and Supplementary Information
<p>Review protocol procedures for standard of care vs. research</p> <p>Determine workload requirements</p> <p>Negotiate budget, contract, and other agreements with sponsor</p> <p>Execute the contract</p>	<p>Standard of care is determined by usual and reimbursable costs. Sponsors will often identify and provide reimbursement language in contracts/agreements. It is the site's responsibility to provide an accurate assessment as local, insurance, and federal laws vary.</p> <p>Make an effort to include estimates of all potential costs.</p> <p>Contracts between multiple parties require much iteration and may take months to complete, depending upon communication.</p> <p>There are not study-specific legal agreements for publicly funded studies, but an overarching institutional agreement will be signed for cooperative groups or for performance of studies through the CTSU.</p> <p>Execution of private sponsor agreements is final once all signatures are obtained. Determine who has signatory authority. An original should be securely maintained in files separate from regulatory files.</p> <p>If the agreement is maintained in a legal office, ensure that the PI or coordinator has a copy, as agreements contain information on PI requirements and milestones for payments that will need to be referenced during the study.</p>	<p>Section III, 4.0 Contracts</p>
<p>5. Site Activation</p> <p>Assure that all paperwork is completed and submitted</p> <p>Site Initiation Visit</p> <p>Study Supplies</p>	<p>Keep regulatory files as above in a secure area and per sponsor requirements. Schedule of correspondence with sponsors should be determined and agreed upon (e.g., what is the preferred method of contact during the study, expectations such as screening log submission, filing methods, et.al.).</p> <p>Publicly funded studies do not require a site visit by the sponsor, so site protocol training is the full responsibility of the investigator.</p> <p>Private sponsors will either conduct a one-day visit on site, or have an investigator meeting, or both. Sites should prepare by reading the protocol and becoming familiar with other protocol documentation and procedures.</p> <p>If the sponsor provides supplies, they are usually shipped around the time of activation, or immediately after activation. Ensure there is space in a secure area and label supplies for study use only.</p> <p>Ensure process for re-supply and any site requirements for re-supply.</p>	<p>Section III, 6.3 Approval and Study Initiation</p>

Activity	Comment	References and Supplementary Information
Study Drug (Investigational Product) if provided	Study drug must be maintained in a secure area with limited access. Ensure proper handling, dispensing, and destruction procedures. Study drug dispensing should have oversight by the PI. Drug should be maintained separately from commercial supplies. Each sponsor will have requirements for drug procurement and re-supply.	Section III, 6.3 Approval and Study Initiation
6. Study Execution		
Complete site training	<p>Copy and distribute all study materials to study personnel (under confidentiality and designated tasks).</p> <p>Develop a training agenda for study staff not trained by the sponsor (including pharmacy, ancillary staff, and clinical staff).</p> <p>Prepare and educate administrative functions: legal, accounting, billing, and compliance.</p>	Section III, 5.3 Training
Establish billing and budget procedures	<p>Obtain account numbers to track research procedures as needed.</p> <p>Standard of care to accounting for billing purposes.</p> <p>Prepare study budget as per sponsor agreement for payment milestones.</p>	Section III, 8.1, Keeping Track of Studies
Notify all involved parties, i.e., the institution, participating practices, all study staff, that the study is open to enrollment	Studies may be opened upon receipt of sponsor approval. For public and private studies, site activation will include patient registration procedures. All required study documents must be on file and in good order with the sponsor before enrollment can take place and/or drug can be shipped. For privately funded studies, in most cases an agreement must also be executed.	Section III, 6.3 Approval and Study Initiation
Screen and recruit patients	<p>Sites should have an agreed upon screening method. Screening time for each study will vary by study eligibility and complexity.</p> <p>Develop a screening process to be used for every trial. Keep accurate logs of numbers of patients screened, reasons for failure, and number of patients enrolled.</p> <p>For studies where referrals or time is of importance, ensure the screening process is in place.</p> <p>Develop patient consent process, ensuring time for consent review. The consent should be reviewed and given to the patient early in the process and while other non-specific screening takes place. No study-specific (non-standard) procedures must take place until after the consent is signed.</p>	Section III, 7.0 Recruitment & Retention

Activity	Comment	References and Supplementary Information
Patient follow-up	<p>The time and procedures for patient follow-up will be by study endpoints (e.g., response, survival, and long-term survival). All patients will be followed for the times determined by the protocol and sponsor. Time for follow-up assessments and documentation must be made. Follow-up for adverse events is listed below.</p>	Section III, 9.0 Evaluating Your Practice
Adverse Event/Serious Adverse Event (AE/SAE) Management	<p>Procedures for handling adverse events will vary by sponsor and will be in the protocol document or other study manuals. Ensure that the proper reporting process (e.g., to a CRO or directly to sponsor) is known for each study, with mandatory reporting timelines and follow-up, including IRB notification.</p> <p>The PI or other qualified physician must determine adverse event causality regardless of severity. Before signing, the physician must review narratives and explanations for SAEs. Each sponsor will have different methods for following SAEs and responding to questions/queries.</p>	Section III, 2.1.5 Safety Reporting
Follow-up on billing	<p>Ensure that payments are made according to the contract and budget specifications. Ensure that all milestones (case report forms, completion of therapy, and query responses) are known and performed for each study so that payments can be made.</p>	Section III, 6.0 Study Execution
Case Report Forms	<p>Sponsors provide standards and case report forms. Publicly funded studies have sets of standards used across tumor types.</p> <p>Private sponsors each have differing forms and requirements for submission (monitored and collected or sent in by site). Set time aside to complete documentation on CRF from source documents.</p> <p>The sponsor for applicable studies will describe electronic data capture. The site must determine and understand all requirements before activation and approval.</p>	Section III, 8.0 Study Operations
Prepare for site Reviews and Monitoring	<p>Monitoring frequency will vary by sponsor and by study complexity. In general, publicly funded studies are reviewed via an audit process for a subset of selected data. Each public sponsor has independent but related processes that are available for sites to help prepare for scheduled visits.</p>	
7. Study Closure	<p>Private sponsors will visit on a predetermined schedule of frequency. Site visit length will be determined by accrual and the preparedness of a site. Find out ahead of time what is expected.</p> <p>Non-scheduled audits may be performed on sites for quality assurance or by federal agencies. All sponsors should be notified immediately if a site has been notified of an FDA audit. Each site should have a procedure for handling such audits.</p>	

Activity	Comment	References and Supplementary Information
Document retention	<p>Document retention requirements will vary by sponsor and regulatory requirements. Notify a sponsor when records are moved off site during a study. Also, keep accurate records of where all study documents are after study completion, including case report forms and all patient source data. Special provisions for expired patients and record retention must sometimes be made for long-term storage.</p> <p>Sites will be notified when studies are closed to accrual. Sites should then notify their IRB that patients will no longer be enrolled, but that the study is open to follow-up and requires continuing approvals.</p> <p>When all data are in and the sponsor has notified the site, the study can be closed at the site. The IRB will require a final report.</p> <p>Private sponsors often visit a site for closure activities that include ensuring all study documents are reconciled, all files are in good order, all data are clean, and that study files will be kept per the document retention policy.</p> <p>If provided, study drug will also be reconciled and either provision for destruction at the site will be given or drugs will be returned to the sponsor. Provision for other study materials will also be given.</p>	Section III, 8.5 Closeout
Conduct Study Closure Activities	<p>Budget review may be the responsibility of the investigator or other hospital staff. Know if there are any fixed research costs at the site.</p> <p>Know who is responsible for contract review and signature. Legal contract review is based on individual practice or institutional requirements and the type of relationship between investigator/site/institution.</p>	

III. Administration and Operation of Clinical Trials

Look for Resource Utilization suggestions in boxes such as this.⁸

1.0 Brief Understanding of the Regulatory Environment

1.1 Good Clinical Practice

According to the US Food and Drug Administration, Good Clinical Practice (GCP) is "...a standard for the design, conduct, and performance, monitoring, auditing, recording, analysis, and reporting of clinical trials."⁹ The impetus behind GCP is to protect both the human subjects in trials and the population who will use the products once they are on the market.

It is in the context of GCP that the regulatory environment has evolved. An appreciation of that environment is essential before undertaking a clinical trial. Despite the apparently burdensome amount of documentation and the multiple agencies producing rules and regulations, the over-arching goal of the regulatory environment is to provide safe, scientifically significant, financially responsible, and effective clinical trials that ultimately enhance the well-being of society.

GCP guidelines were further developed to provide standards for studies done in the European Union (EU), Japan, and the United States and to "facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions." Compliance with these standards provides public assurance that the rights, safety, and well-being of trial subjects are protected consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible (<http://www.ich.org/cache/compo/276-254-1.html>).

1.2 Background of Human Subject Safety Protection

Many examples of mistreatment of research subjects and outrage within the public, regulatory, and medical professional community have led to adoption and institution of overarching principles for the treatment of human subjects. Two documents, the Declaration of Helsinki (1964) and the Belmont Report (1979) constitute the backbone for human subject safety.¹⁰

The Declaration of Helsinki was developed by the World Medical Association after dissemination of the Nuremberg Code and presented in 1964. It has since had multiple iterations but is a central statement of ethical principles with respect to medical research involving human subjects. These principles guide the current informed consent process and protect vulnerable populations. It is this declaration that set the stage for implementation of the IRB process in the United States. (current version, 2004 <http://www.wma.net/e/policy/b3.htm>).

In 1974, Congress passed the National Research Act, which established a mandate for IRB review of all federally funded research. Before this act, review of research was voluntary at the site level. The National Research Act also established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, which was charged with developing guidance for research with human subjects.

In 1979, the Department of Health Education and Welfare (now Department of Health and Human Services [DHHS]) presented the report for the Ethical Principles and Guidelines for the Protection of Human Subjects of Research, now known as the Belmont Report (<http://www.hhs.gov/ohrp/>). The Belmont Report identifies three fundamental ethical principles for all human subject research: 1) respect for persons, 2) beneficence, and 3) justice. Those principles were the basis for the HHS human subject protection statutes in 1981, now FDA regulations 21 CFR Part 50 and PHS Regulation 45 CFR part 46, and for Institutional Review Boards, 21 CFR Part 56.

⁸ The Lewin document "A Guidance Document for Implementing Effective Cancer Clinical Trials, Version 1.2, June 2005, listed relevant "cost drivers," helpful hints provided by experienced clinical trial sites. In an effort to capitalize on this information, these hints are included in the relevant operational sections in outlined boxes.

⁹ The US Food and Drug Administration, accessed at www.fda.gov/oc/gcp

¹⁰ A subject is defined as, "an individual who is, or becomes, a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient (FDA 21CFR 312.3)"

While these reports were not legal requirements at the onset of their introduction, the codification of the principles into legal statutes or regulations has shown the importance placed on the medical community for ensuring oversight of clinical research, particularly involving human subjects.

1.3 Regulations

One of the most important aspects of working with Federal regulations is the appreciation that they change. New directives can supersede commonly understood regulations. It should be the custom of trial personnel to check for regulatory changes affecting their studies. An easy way to accomplish this is to subscribe to a listserv for immediate notification of pending and effected changes to regulations.

1.3.1 Federal

Regulations are acts of Congress (statutes) that, when considered permanent or public, are then “codified” into law. The official codification of Federal statutes is called the United States Code. The United States Code of Federal Regulations (CFR) is divided into “titles,” based on overall topics, and numbered 1 through 50. Investigator obligations and human subject protection are generally covered in Title 21, Parts 50, 54, 56, 312 and Title 45 for Public Health.

The Department of Health and Human Services (HHS) oversees all federally funded studies and is governed by the Federal Policy for the Protection of Human Subjects, known as the Common Rule. The Common Rule is codified at Subpart A of Title 45 CFR Part 46, [<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm>] and contains:

- The requirements for assuring compliance by federally funded research institutions
- The requirements for obtaining informed consent
- The requirements for IRB membership, function, operations, review of research and record keeping

The FDA concurs with most of the Common Rule but not all of its provisions; there are some significant differences.

The Office of Human Research Protection (OHRP) supports and strengthens the nation’s system for protecting volunteers in research conducted or supported by the HHS, including compliance, education, and the administration of IRB assurances [<http://www.hhs.gov/ohrp/>].

The Food and Drug Administration (FDA) regulates drugs, biologics, and devices for diagnosis, treatment, and prevention of disease in humans and animals. Many parts of federal regulations are applicable to companies and entities pursuing a marketing application or managing a product under an existing application [<http://www.access.gpo.gov/cgi-bin/cfrassemble.cgi?title=200121>].

For the purposes of this document, we will discuss activities that apply to clinical investigators and for oversight of patient protection.

- Federal Regulations for investigators: <http://www.fda.gov/cder/about/smallbiz/CFR.htm>
- Federal regulations for Institutional Review Boards 21 CFR Part 50 and 56
- Federal regulations for Financial Disclosure 21 CFR Part 54
- Federally funded studies follow 45 CFR Part 46. (A federally funded study for the FDA requires following BOTH sets of regulations.)

1.3.2 State and Local Laws

Regulations at the state and local level are developed to protect and uphold statutes specific to state law and constituency needs. State and local laws and regulations supersede federal regulations [See 45 CFR 46.101(f)]:

- When state and local laws are more restrictive than federal
- When state and local laws do not put the subject at increased risk

Investigators must be familiar with any state and local regulations that directly affect their research. State issues that commonly affect trials include licensure, e.g., who can draw blood, or who can do a physical. Medical personnel are usually familiar with these local requirements. However, some states have requirements about insurance reimbursement for trial care. The website (<http://www.ncsl.org/programs/health/clinicaltrials.htm>) details which states have such regulations. This information can be particularly important in recruiting patients.

It is the responsibility of the investigator to understand and abide by all applicable local regulations.

1.3.3 Guidelines

FDA Guidelines and Information Sheets represent the Agency's current guidance on good clinical practice and the conduct of clinical trials. They do not operate to bind the FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. However, in many places throughout the documents, specific regulations are cited and the enforceable requirements of the regulations are reiterated (<http://www.fda.gov/oc/gcp/guidance.html>).

The International Conference on Harmonization (ICH) promotes congruence of regulatory requirements (<http://www.ich.org/cache/compo/276-254-1.html>) in three regions of the world: the European Union, Japan, and the United States. In the Federal Register of May 9, 1997, the FDA adopted the ICH's "Good Clinical Practice: Consolidated Guidelines" without making them regulation (<http://www.fda.gov/oc/gcp/guidance.html-ich>). Trial site personnel should note that the ICH Guidelines are sometimes easier to understand than those from the FDA. Since the FDA considers the two sets of rules congruent, it is sometimes helpful to get clarification from the ICH.

2.0 Investigator Responsibility in Research

Note that the following sections contain references to sample forms and checklists. These are meant to be representative of what experienced research sites have developed. However, each research site should develop unique forms to meet site-specific requirements for Standard Operating Procedures (SOPs), regulatory requirements (federal and local), and individual sponsor requirements.

2.1 Regulations that Apply to Investigators

2.1.1 Oversight and Study Conduct

It is the sponsor's responsibility to select qualified investigators who will participate in clinical trials; however, certain responsibilities are solely the purview of the investigator, once he/she agrees to participate in a trial. The investigator must oversee the conduct of the study at the site level: 1) personnel supervision, 2) patient safety, 3) investigational product management, 4) patient rights, and 5) assurance of institutional review. All these activities are under the PI's oversight, whether or not the study is conducted under a US Investigational New Drug Application (IND).

Studies not performed under a US IND require investigator compliance with all applicable regulations, both local and federal, but certain federal obligations and reporting requirements differ. Section 4 of the ICH GCP Guidelines outlines standards of investigator conduct for all studies.

For studies performed under a US IND, investigator responsibility includes assurances to the FDA which are outlined in 21 CFR 312.53 and secured by investigator signature on an FDA Form 1572 (Box 9). (<http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>),

21 CFR 312.53(vi)(c): [the investigator] "will personally conduct or supervise the described investigations(s)."

2.1.2 Investigational Product

21 CFR 312.59, 21 CFR 312.61, 21 CRD 312.62(a), ICH 4.6.

Investigational product may or may not be provided by a study sponsor. In cases where the drug is supplied by either the NCI or by a manufacturer, product must be kept in accordance with regulations cited above.

It is the responsibility of the investigator to ensure that product is managed by qualified personnel, that storage facilities meet the requirements of the product, and that all product is maintained securely and separately from commercial supplies and dispensed only to patients on study.

This may require separate storage areas, site personnel training, and separate record keeping. Each sponsor or protocol will provide this information as well as information on re-ordering of drug, destruction, and or return policies.

Product storage requirements such as refrigeration, destruction and shipment, and other related costs of mixing and dispensing should be estimated (tubing, storage after mixing, labeling and product reconciliation) in the budgeting process. These requirements can be costly and should be accounted for with diligence.

2.1.3 Patient Protection - Informed Consent Form (ICF)

21 CFR 50, 21 CFR 56, ICH 4.8

Informed consent is an important aspect of assuring patient safety. The consent process begins with initial discussions regarding therapeutic options and continues for the duration of the study. Patient consent is initially assured by signature on the informed consent form (ICF), but a process must be in place to ensure continuing consent and understanding of any protocol or risk changes.

A sponsor for multi-site trials usually provides a template for the consent document. However, the site must usually amend the template to include specific information required by the IRB and by SOPs, e.g. HIPAA, insurance or liability, adverse event assessment and other risks. Consent documents must contain all elements required by regulations and/or guidelines¹¹ as required, and be easily understood by patients. The HHS website provides a guideline for elements of consent <http://www.hhs.gov/ohrp/humansubjects/assurance/consentckls.htm>. A checklist detailing the elements for writing publicly supported consent forms is provided in Appendix VII of the Investigator's Handbook on the NCI, Cancer Therapy Evaluation Program website <http://ctep.cancer.gov/handbook/index.html>.

The IRB, and sometimes the sponsor, must approve the ICF and any changes made to it during the trial before that version can be given to patients for consent. Informed consent must occur, with documentation of that consent on the approved form, before any specific protocol procedures can be performed. Standard of care procedures to determine patient performance can be done as usual in the provision of care.

The ICF may be updated frequently, based on product and regimen safety data. Sponsors may have requirement for submission to and approval of any changes. These changes to the ICF and IRB can be time consuming.

2.1.4 Institutional Review Board (IRB) Oversight

21 CFR 56, 21 CFR 312.66, ICH 3.0, ICH 4.8

An Institutional Review Board is required by Federal Regulations and the Department of Health and Human Services (DHSS) to review and monitor research involving human subjects, and is regulated by the Office of Human Research Protection (OHRP <http://www.hhs.gov/ohrp/>) within the DHSS. Requirements of IRBs are strictly regulated by 45 CFR 46 (the "Common Rule") with regard to composition, membership, and review and approval of documents.

¹¹ FDA, 21 CFR 50.25, ICH 4.8.10, and HHS 45 CFR 46

There are three types of IRBs:

- Local IRB: operated by a hospital or academic center
- Commercial/Independent IRB: used by sites without an affiliated IRB. Usually are for-profit organizations and typically used for industry-sponsored studies
- The Central IRB (CIRB), sponsored by the National Cancer Institute (NCI): designed for sites to use for approvals for cooperative, i.e. public, group clinical trials and to decrease the time and resources for approval <http://www.ncicirb.org/>

It is the responsibility of the Investigator to understand and abide by any local IRB requirements. When a hospital or center has a local IRB affiliation, the written procedures of that IRB or of the institution should define the scope of studies subject to review by that IRB. A non-local IRB may not become the IRB of record for studies within that defined scope unless the local IRB or the administration of the institution agrees. Any agreement to allow review by a non-local IRB should be in writing.

The process and requirements for submission of protocols and consent forms will vary by IRB, but in general will include:

- Protocol(s)/amendment(s)
- Written informed consent form(s)
- Subject recruitment procedures (e.g., advertisements)
- Written information to be provided to subjects
- Investigator's Brochure (IB) and/or available safety information
- Information about payments and compensation available to subjects
- The investigator's current curriculum vitae (i.e. evidence of qualifications)
- Any other documents that the IRB may need to fulfill its responsibilities

IRB submissions will be required at least yearly throughout the period that the study is open¹² and, additionally, for all safety data submissions. Safety data submissions can include, for example: 1) safety letters, 2) information from manufacturers, such as IB, 3) any protocol changes affecting consent, and 4) other IRB requirements specific to a protocol.

Note that there must be an adequate system for the retention of these records so that material can be easily retrieved and reviewed by a sponsor, and the Investigator should have a method to ensure that only current and IRB-approved versions of protocols and consents are being used. The investigator should be familiar with all IRB requirements regardless of which type is used to ensure that all documents are submitted for initial review, continuing approval within IRB timelines, and that all safety information is submitted within applicable safety reporting regulations.

Anticipate the number of IRB submissions for the duration of a study by estimating total accrual timelines and the duration of the study to meet all study endpoints. Studies that use drugs prior to marketing approval may have an increased number of changes, including amendments to the protocol and consent form and safety updates. Understanding all IRB requirements will ensure a timely review and reduce conditional approvals for missing information and questions.

2.1.5 Safety Reporting - Adverse Events (AEs)/ Serious Adverse Events (SAEs)

21 CFR 312.64(b), ICH 4.11

The process for investigator reporting of AEs and SAEs will vary according to sponsor and protocol requirements. It is the responsibility of the investigator to understand and report AEs as required. All SAEs should be reported immediately to the sponsor as per protocol requirements and available safety information. The timelines for reporting SAEs will also be outlined in the protocol or other related documents (e.g., process documents, study contract). Investigator compliance is important to ensure all applicable regulatory requirements are met. Investigators are also responsible for reporting SAEs to their IRB.

¹² Open in this instance means the study is still underway. Clinical trials are considered "open" so long as patients are being treated; enrollment may, in fact, have been "closed."

Sites should anticipate that SAEs will occur and have a procedure in place that includes assessment, treatment, and reporting (including sponsor reporting, regulatory reporting, and IRB reporting), and follow-up. The number of SAEs per patient will vary by study complexity and expected side effects.

2.1.6 Records

21 CFR 312.64, CFR 54, ICH E6 Guidelines Section 8

It is the responsibility of the investigator to follow the protocol and ensure that all required documents are collected, filed, and retained. These records include all regulatory documentation, source documentation, case report forms, and sponsor correspondence. Study files should be kept per site SOPs and sponsor requirements so that ease in source data verification can be performed at monitoring visits or sponsor audit visits.

Take into account how Case Record Forms (CRFs) and source data will be stored, accessed, and submitted to sponsor.

2.1.7 Investigator Obligation Summary

The following list summarizes investigator obligations:

Study Conduct

- Have adequate resources and qualifications (ICH GCP 4.2)
- Comply with the protocol (21 CFR 312.66; ICH GCP 4.5)
- Maintain source documents and comply with record retention (21 CFR 312.62, ICH GCP 4.9, 4.11)
- Report to the sponsor (21 CFR 312.64, Part 54; ICH GCP 4.9, 4.11)
- Manage investigational drug (21 CFR 312.59,61,62; ICH GCP 4.6)
- Manage IRB submissions (21 CFR 56; 21 CFR 312.66; ICH GCP 4.4, 4.13)
- Provide informed consent (21 CFR 56; 50; ICH GCP 4.8)

Safety

- Read the Investigator Brochure (IB) and inform other appropriate staff (21 CFR 312.53)
- Understand medical care and protection of subjects (21 CFR 312.60; ICH GCP 4.3)
- Report adverse events to sponsor (21 CFR 312.64; ICH GCP 4.11)

3.0 Choosing Trials

Sites should choose studies based on the study sponsor, scientific merit, applicability to the practice setting (i.e. therapy and complexity), and availability of patients. Other reasons to participate in the conduct of a trial may include providing treatment to patient groups with otherwise limited therapeutic options or with cancers where no standard of care is available. A site, especially one new to cancer clinical trials, should consider the time involved in opening a trial and the cost of managing a trial with limited enrollment potential.

All the above factors should be taken into careful consideration prior to the initiation of a trial since each has an effect on personnel and budget.

3.1 Study Sponsor

A study sponsor can be an “individual, company, institution, or organization that takes responsibility for the initiation, management and/or financing of a clinical trial.”¹³ This document addresses study-site participation in multi-site clinical trials where the individual or institution is not the sponsor. Study sponsors are either private sponsors, e.g., pharmaceutical companies, contract research organizations (CROs) acting on their behalf, networks or Site Management Organizations (SMOs), or publicly funded, e.g., National Cancer Institute (NCI) studies through national cooperative groups or the Clinical Trials Support Unit (CTSU).

¹³ ICH E6 Glossary 1.53

Sponsors are required to select qualified investigators to conduct studies for both new and approved drugs, including certification of investigator training, experience, and adequate resources to conduct the study. Investigators will be asked to agree to:

- Conduct the study in compliance with the protocol, GCP and regulations
- Ensure patient rights and safety by submission to and approval by the IRB
- Comply with procedures for reporting and data recording
- Permit monitoring and inspection
- Retain essential documents.

The methods and procedures for site approval by sponsors and for investigator qualification will vary, but will meet all appropriate oversight and regulatory requirements.

Investigators should understand their responsibilities for the study under review with regard to sponsor requirements. Is a CRO involved? How will communication occur? Who gets what correspondence? Study sponsors will often ask sites to undergo a screening process and ask general questions to elucidate whether the site and the study needs are congruent. Sponsors will want information about research staff, number of subjects, any storage or dispensing requirements, IRB and its frequency, and the contracting process.

For cooperative group studies, manuals and on-line materials describing oversight and procedures are available, as well as information on becoming members of each group (see Section VI: Oncology Information, General Sites).

Sponsor requirements vary. It is imperative that sites thoroughly understand sponsors' needs such as regulatory requirements, the process of data collection, and monitoring frequency. Establishing frequent communication, usually through a minimum number of people, from the outset of a trial can preclude costly and time-consuming delays later on.

3.2 Protocol Scientific Assessment

Each site is obligated to review protocols to understand whether the study parameters:

- Are congruent with the needs of the trial site's patient population in terms of risk and recruitment
- Are ethical and equitable with respect to subject selection¹⁴
- Are scientifically sound
- Can be accommodated by a site's capabilities

3.3 Feasibility Assessment

The site should also consider other factors in assessing feasibility. It is important to review both the entire protocol and sponsor requirements for a study. The following website contains a checklist for assessing protocols, which could be adapted for individual site use, research needs, and institutional practices.

<https://www.ctnbestpractices.org/sites/studyops/prestudy/protocol-feasibility-checklist-word>

Checklists are limited. Personnel need to make realistic assessments of budget needs identified in a checklist. Sites should then carefully review personnel responses to assure that staff members fully understand the budget implications of their responses to the checklist items.

Since a number of people will need to review a protocol, often it is helpful to have a routing sheet to keep track of pertinent information involved in the review process.

<https://www.ctnbestpractices.org/sites/studyops/prestudy/protocol-routing-information/>

¹⁴As noted in *Enhancing Cancer Treatment through Improved Understanding of the Critical Components, Economics and Barriers of Cancer Clinical Trials*, prepared for C-Change by The Lewin Group, September 1, 2006. C-Change is concerned that minorities be better represented as clinical trial subjects.

3.4 Ancillary Services

It is imperative that all site resources be considered during a protocol review. Pharmacy, treatment areas, laboratory, pathology, surgery, or radiation oncology are some resources to consider. Coordination of resources will allow patients a more seamless process. A long wait or a paper mix up can be disconcerting to trial participants. It is also important to capture resource utilization when addressing budgets (see Section V).

Assure all supporting departments can address needed study activities and have an understanding of protocol or reporting requirements as necessary.

3.5. Standard of Care versus Protocol Activities

Thorough review of a protocol for non-standard tests and frequencies of standard tests should occur as a study is considered. Sponsors may support non-standard tests or reimbursement, and this should be discussed during the consideration process. Investigators should use current guidelines for cancer therapy as benchmarks for this evaluation. *Reimbursement by insurers is also subject to local regulations and should be checked for each patient prior to enrollment.*

Note what protocol procedures are considered standard of care and which may be outside of reimbursement guidelines.

4.0 Contracts

The type of study sponsor will dictate what kind of research agreement or contract will be necessary. Publicly sponsored research through the NCI does not necessitate a separate agreement for each study. Private study sponsors may cover research at a site by a “master agreement” or require a separate agreement for each trial.

Research agreements cover legal responsibility of a study site and of the study sponsor. Each site will have policies and regulations that bind what is acceptable in a contract with a sponsor. Generally, these are designed to protect the welfare of enrolled subjects and define the responsibility and liability of each entity.

An incomplete study schedule at budget negotiations can present problems. Make an effort to include all costs, even if some are only estimates. Specimen handling is frequently specialized and can be expensive. The cost of and space for record retention are often overlooked; both can be vexing requirements, especially if dealt with “after the fact.”

Conduct an internal review so that all parties understand their obligations.

4.1 Review Time

Each research site will have different parties responsible for the review and approval of research contracts. The time for review and approval will depend on the numbers of parties who need to review and the number of iterations of the document. Careful tracking of the contract at the site can help to reduce the time frame investigators to approval. Reviewing the contract can be time consuming if inexperienced staff is involved. Even sites with contract specialists and attorney reviews should require review by the PI since contract language specific to investigator responsibility, time frames for accrual, and milestones for site deliverables all need to be approved by the research staff.

4.2 Interaction with Sponsor

Allocate time for one person to deal with the sponsor. Maintain timely communication so that issues do not escalate.

Private sponsors perform site evaluations (pre-study visits) to assess qualifications; these visits can take from one hour to one day. Though this investment of time might appear excessive, the site inspection represents an opportunity to learn about the sponsor and the sponsor's specific requirements and expectations.

4.3 Special Considerations

Most clinical trial agreements will be sent out as templates from each study sponsor. However, often contract areas, such as intellectual property, publication rights, medical care for research participants, and indemnification, are not clearly spelled out. A document, "Clinical Trial Contracts: A Discussion of Four Selected Provisions" published on the Association of American Medical Colleges website addresses these four areas. Information includes checklists and sample contract language.

https://services.aamc.org/Publications/index.cfm?fuseaction=Product.displayForm&prd_id=76&prv_id=75&cfid=1&cftoken=B515283C-50DD-493F-923496DA859A0AF1

It is imperative that site-specific requirements and policies with regard to contract negotiations be in place before any protocol participation.

5.0 Study Site Personnel

An adequate number of appropriately qualified personnel is essential to the successful conduct of clinical trials. However, when a site is just beginning the process of running a clinical trial, or when trials are run in community sites rather than large academic medical centers, it can take time for a site to learn the details of personnel requirements to conduct clinical trials.

At minimum, there must be a principal investigator and a research coordinator, also known as a study coordinator or data manager. In accordance with the Elements of Success, all personnel should have time dedicated only to research activities. This time will vary, depending on the number of open trials, the number of patients in active treatment versus follow-up, the complexity of each study, and the sponsor-type.

Whether personnel are full or part-time, their allocated time to research must be adequate for completion of all necessary tasks.

It is not uncommon for sites just beginning a clinical trial program to distribute research activities in a less efficient manner than those programs that have been in place and have multiple resources. For instance, a site may have the funds only to hire a Clinical Research Associate (CRA), leaving all of the tasks such as patient consent and toxicity assessment to the investigator. Later, that site may hire a Research Nurse to perform medical functions and, thus, free the investigator to see patients. In the same vein, a CRA may be performing all regulatory activities until an administrator can be hired, freeing the CRA more time to manage data more effectively.

5.1 Delegation

The PI can appropriately delegate research activities to qualified individuals. Such delegation should be in writing.¹⁵ Listed below are representative tasks that can be delegated. Note that this list is not comprehensive and delegation at each site will depend upon research infrastructure and available resources.

There is a range of tasks that the PI cannot delegate:

- Overall responsibility and accountability for the study
- The signature on FDA form 1572¹⁶
- Determination of the relationship or causality between an Adverse Event (AE) and investigational product
- Medical decisions, diagnoses, assessments, and physical exams (Note: Some states allow advanced practice nurses or physician assistants to perform physical assessments and medical histories.)

¹⁵ ICH GCP Section 4.1.5

¹⁶ The 1572 is the FDA form for Investigator Registration. It asks for all relevant information, such as names of investigators, copies of the protocol, CVs, host institutions, etc. The PI signs the form and thus accepts responsibility for the trial. Copies can be downloaded from <http://ctep.cancer.gov/forms/index.html>.

Activity	Investigator Oversight
Initially assessing protocol or procurement	Investigators will need to sign agreements or protocol signature pages of approval.
Assuring that all study staff are trained	Investigators will have ultimate accountability for ensuring training, but not actual performance.
Preparing and negotiating study budgets	Investigators may have signatory responsibility on agreements, to which the budget is attached.
Preparing and submitting documents to the IRB	Investigator is accountable to give assurance that the IRB selected has required assurances, and for sites with local IRBs when a central IRB is used, such agreements are in place.
Interacting with sponsor, IRB, office staff, providers, all department personnel	Investigators will need to be present at some training activities and at monitoring visits or audit visits.
Tracking study budget and payments	
Maintaining regulatory files	Investigator will have signatory responsibility for regulatory documents as required.
Documenting sponsor communication and study progress	
Resolving queries on study data	Investigator or sub-Investigator signature on queries is usually required to provide assurance.
Transcribing source information to Case Report Forms (CRFs)	Investigator or sub-Investigator signature on CRF is usually required to provide assurance.
Coordinating, preparing for, and participating in monitoring visits, audits, and inspections	Investigators will need to be present at some site selection, training activities, and at monitoring visits or audit visits.
Recruiting subjects	Investigator should agree on the recruitment plan for each study and oversight of all investigators' recruitment activities.
Screening subjects for eligibility	Except in cases where eligibility checklists must be signed by investigator.
Developing and coordinating advertising	Investigator and IRB approval is required, with the exception of clinicaltrials.gov listing. (Check with IRB for that requirement as well.)
Discussing study and conducting consent process	May in most states be performed by an RN and some other licensed professionals (PA).
Scheduling study assessments and visits	
Ensuring all visits, tests, and procedures are completed in required time intervals	This can be delegated but should be reviewed periodically.

Activity	Investigator Oversight
Interviewing and evaluating subjects at appropriate intervals	RNs and other licensed professionals may conduct toxicity assessments, and advance practice nurses and physician assistants may perform physicals, but should be listed as sub-investigators on the 1572.
Reviewing laboratory and clinical information for signs of adverse events	CRA's can conduct phone calls to subjects for follow-up, scheduling, etc.
Identifying, documenting, reporting and following up on adverse events	Investigators should be made aware of all SAEs and report as per requirements of each study. Causality assessment and final signature must be made by an investigator.
Maintaining drug accountability	Investigators should be made aware of all SAEs and report as per requirements of each study. Causality assessment and final signature must be an investigator.
Dispensing investigational product per protocol and under PI supervision	Investigators can delegate to appropriate staff such as nurses or pharmacists who are authorized by license to dispense and mix. Investigator should have procedure for periodic assessment of accountability.
Obtaining, preparing, and shipping biological specimens	Investigators can delegate to appropriate staff, such as nurses or pharmacists who are authorized by license to dispense and mix. Investigator should have procedure for periodic assessment of this accountability.
Coordinating study subject case reimbursement	As allowed by contract.

The list of activities includes a typical range of administrative functions. Failure to plan adequately for their completion could lead to subject and medical staff frustration. All delegation should be in writing.

It is helpful to delineate which tasks staff members can perform. Following are examples of two job descriptions from the *Clinical Trials Network Best Practices: NIH Roadmap*¹⁷ which highlight differences between skill levels and professional background. Other job descriptions for research personnel and associated responsibilities can be resourced online.

Clinical Research Specialist/Nurse

<https://www.ctnbestpractices.org/sites/siteoperations/job-descriptions/clinical-research-specialist-research-nurse/>

Clinical Trials Coordinator

<https://www.ctnbestpractices.org/sites/siteoperations/job-descriptions/clinical-trials-coordinator-word/>

¹⁷The Clinical Trials Network (CTN) Best Practices Network is one of the 12 contracts awarded by the National Institutes of Health (NIH) under the Re-engineering the Clinical Research Enterprise portion of their Roadmap initiatives. <https://www.ctnbestpractices.org/>

5.2 Specialized Resources

Laboratory

Specialized resources include laboratory and specimen management, including pathology and tissue sampling. These services should be assessed before study initiation with consideration given to available special equipment; e.g., freezers for specimens, centrifuges for processing, proper shipping containers, or dry ice. Since participation in clinical trials requires much sophistication, it is important to determine the ability to participate in trials where sampling is a requirement.

5.3 Training

There are numerous training venues available: books, seminars, and web-based courses. Representative examples are cited in the Reference section (Section VI) of this document. Since clinical research requires a good understanding of both the regulatory environment and study compliance, it is important to ensure all personnel are trained to their level of delegated responsibility.

The NCI mandates investigator training and documentation of completion prior to participation in Cooperative Group research. Individual Cooperative groups have CRA and Research Nurse tracks and also provides training opportunities. Guidelines and training for the investigator and site responsibilities, HIPAA requirements, patient protection, the scientific process, and misconduct for research are also available. Private sponsors often look for documentation of research training and may provide a required investigator course for participation in trials they sponsor.

Since the regulatory environment is constantly changing, it should be standard operating procedure to have annual site training. Requiring annual renewals is a good practice to ensure that all personnel remain current.

5.3.1 Site Personnel Training

The complex regulatory requirements for clinical research and individual sponsor requirements for specific studies mandate that all personnel have appropriate oversight and training.¹⁸ It can be demoralizing to competent professional people to be placed in situations where they know their knowledge is insufficient to perform duties. Insufficiently trained personnel also put study outcomes at potential risk.

Sponsors often provide training, and they require that it be documented. In many instances, they will provide ongoing training for changes in a study or for changes in study site personnel. When sponsors do not provide training, it must be conducted by qualified individuals at the site and should be documented in study files.¹⁹

Investigators should provide non study-specific training to all personnel. This training should be documented, required by job descriptions and SOPs, and be updated on a regular basis. Each site should have procedures in place that meet individual needs. The reference section of this document contains multiple references and websites that may be of interest.

Below, from the *Clinical Trials Network Best Practices: NIH Roadmap*, are two web pages containing documents that can be adapted for specific site use.

Sample log for tracking personnel training:
<https://www.ctnbestpractices.org/sites/siteoperations/edtrainlog/>

Coordinator Training Checklist:
<https://www.ctnbestpractices.org/sites/newtoresearch/coordtrainchk1st>

¹⁸ ICH E6 Section 4.2.4

¹⁹ ICH E6 Section 8.2

Other checklists can be found at:

Sample Site Roles and Responsibility Checklist http://www.researchpractice.com/r_checklist.shtml

Sample log for tracking personnel training <https://www.ctnbestpractices.org/sites/siteoperations/edtrainlog/>

5.3.2 Specialized Training for Research Coordinators/Research Associates

There are several professional organizations that provide training and certification for research personnel, including physicians, research nurses, and clinical research associates. Representative websites are listed in Section VI under "Certifications."

6.0 Study Execution

Maintain frequent and clear communication with sponsor.

Take inventory of all supplies required in a study; obtain any missing material; work with vendors to assure reliable replenishment.

Do not underestimate meeting time for PIs. There may be travel to other sites.

Check periodically to see that appropriate charges are getting to the billing office.

6.1 Standard Operating Procedures

It is a best practice to have all aspects of study conduct addressed in site standard operating procedures (SOPs). Study sponsors will often look to ensure they are in place. There are many resources available for SOP writing for investigative sites, including books and template examples. Professional societies are a good source for finding one that is right for each site if there is not a procedure in place. Web searches for SOPs for Investigative Sites or other similar criteria will provide further information. Currently, a guideline for writing SOPs is provided at:

<https://www.ctnbestpractices.org/sites/siteoperations/sop-guidelines-for-writers-word/>.

Make site-specific, department checklists. Include the obvious, which is often overlooked. Hand out the checklists and make sure that everyone knows that lists can be revised as circumstances require.

6.2 Patient populations and clinical trials accrual

Statistics for enrollment by sites to clinical trials are of interest.²⁰ When sites open a study to accrual:

- 15-20% of sites never enroll a single patient
- 30% of sites under-perform (i.e., enroll 5% of evaluable patients)
- 20% of sites are average performers (i.e., enroll 25% of evaluable patients)
- 30% of sites are high performers (i.e., enroll 70% of evaluable patients)

This means that 30% of sites do 70% of the work. Sites that under perform have to bear the same costs of study start-up, regulatory management, and study closure as sites that accrue well. Thus, low accruing sites have increased costs per-patient.

Since patient accrual is of paramount importance for a successful study, it is imperative to realistically estimate the number of available subjects for a trial and to reach the potential population with effective trial information. Sites can easily mislead themselves about the availability of patients. Too often there is an unrealistic generalization: "we have X number of people with condition y." Sites overlook the factors that diminish the number of available patients:

²⁰ *Budgeting at the Investigative Site*, University of North Carolina at Chapel Hill, Office of Clinical Trials Newsletter. July/August 2006.

- Screening methods: not screening every potential patient or investigator bias
- Eligibility criteria: homogeneity of the study is important for statistical value, but excludes many potential patients
- Patient unwillingness to participate

It is commonly considered that only 1 in 6-10 patients screened will be eligible and enroll to a study. Accurately estimating accrual potential during the study feasibility process will help sites plan resources and estimate costs. Sites should consider keeping accurate records of patients by tumor type and recurrence for a period of time, in order to accurately measure numbers of patients. Additional sources of information could be office billing codes and tumor registry information (if the registry is used by a single practice). Pathology departments are also a good source of estimating new diagnoses and surgical interventions. Screening logs, although time-consuming, are good research instruments. Examples of screening logs can be found at various websites. Formats can also be obtained from study sponsors.

As noted in the C-Change document, *Enhancing Cancer Treatment through Improved Understanding of the Critical Components, Economics and Barriers of Cancer Clinical Trials*,²¹ more attention needs to be paid to assuring adequate minority representation in clinical trials. Cultural norms and mistrust of the medical environment requires understanding and special provisions to provide adequate accrual to trials.²² Sites will need to assess patient populations and account for cultural needs during the protocol assessment process. There are patient and site resources provided by the NCI (www.cancer.gov) for certain minority populations. In addition, the government does provide general cancer and clinical trial information in Spanish.

6.3 Approval and Study Initiation

Final site approval and activation of the study at a site are dependent upon: 1) sponsor receipt and approval of regulatory documents, 2) execution of site agreements or, in the case of a public sponsor, investigator statements, and 3) site training. Sites are notified of activation and will receive all necessary materials, study drug if provided, and enrollment procedure activation.

Private sponsors, such as pharmaceutical companies, may conduct a site initiation visit or provide site training at an investigator meeting or, in certain cases, do both. Site training for publicly sponsored research is the responsibility of the investigator. Sites should prepare for activation by assuring that all personnel read and understand the protocol and all other related documents and requirements; e.g., Case Report Form (CRF), source document completion, study procedures, and other investigator responsibilities. Sites should require that the sponsor answers all questions before the site begins enrolling subjects.

7.0 Recruitment and Retention

7.1 Advertising

The Food and Drug Administration (FDA) considers that direct recruiting advertisements and patient information specific to a study are part of the informed consent, and are, therefore, governed by regulations in 21 CFR 50.20, 50.25, 56.111(a)(3). Regulations require that all advertisements must be reviewed and approved by an IRB prior to use to ensure that they do not contain information that is misleading to potential research subjects. The exception may include site listing on clinicaltrials.gov or other websites that cite that information. Some sponsors provide templates that can be used, once approved by the IRB. Sites should ensure that all study-related materials given to patients, if not provided by the sponsor, are both approved by the IRB of record for the site and by the study sponsor if required.

A helpful webpage, <https://www.ctnbestpractices.org/sites/studyops/enrollment/recruitretain/>, from the Clinical Trials Network website, details information about advertising and includes suggestions about other ways to make potential populations aware of clinical trials.

²¹ *Enhancing Cancer Treatment through Improved Understanding of the Critical Components, Economics and Barriers of Cancer Clinical Trials*, prepared for C-Change by The Lewin Group, September 1, 2006

²² *Reducing Cancer Disparities for Minorities: A Multidisciplinary Research Agenda to Improve Patient access to Health Systems, Clinical Trials, and Effective Cancer Therapy*, Deborah Watkins Bruner et. alia, *Journal of Clinical Oncology*, vol. 24, No. 14, (May 10), 2006: pp. 2209-2215.

7.2 Referrals

Though advertising is one method to reach individuals unfamiliar with available clinical trials, identifying potential populations within the practice and through referrals from related practices may also help enrollment. Sometimes timelines for study enrollment are so short that referrals between medical oncology, surgical oncology, or radiation oncology are required to meet enrollment timelines. For these studies, investigator involvement and communication with peers is important for success. Respondents to the survey conducted by The Lewin group in preparation for the *Guidance Document of June 2005* noted:

“The most effective trials are those where the investigator presents the trial as an integral part of an office encounter. The initial presentation of the study is typically followed by a discussion between the potential subject and study coordinator. The importance of the physician as a principal agent for patient accrual was strongly emphasized by most respondents.”²³

Increasing patient participation in clinical trials will take a “...group effort involving all practice staff, including treating physicians, advanced nurses and research nurses.”²⁴

7.3 Patient Screening and Record Retention

Creating templates for screening procedures is especially helpful. A detailed questionnaire, including all inclusion and exclusion criteria, can be key to finding site issues with the screening process. Screening logs are often used to document the screening process for some sponsors. Additionally, there may be requirements for keeping documentation of screen failures or ineligible patients. This will vary by sponsor and by the stage at which the patient falls out during screening. Check with each sponsor.

It may be helpful for a site to look at:

- Disease-specific screening issues (how many patients with lung cancer are actually screened versus seen)
- General site screening issues (what physicians participate in screening, or process issues)
- Protocol specific issues (difficult eligibility or timelines for a specific trial)

By assessing data accumulated on the above, a site can identify and evaluate trends in enrollment to specific trials and among all studies.

7.4 Talking to Patients

As detailed previously in the Elements of Success, respect for patients and concern for their welfare is key. The physician is usually the first point of contact and the person who communicates clinical trial availability. Respectful, friendly contact invites patient participation. Communication should be truthful and represent the potential risks and benefits of the study. This is often a difficult task for physicians. The rationale for patient participation and why a study was chosen is important to convey to patients.²⁵ The larger issues of patient privacy, consent, ethical guidelines, and patients’ rights in clinical trials previously addressed are the backbone of ensuring respect. However, It is not a good start if a patient calls for an appointment and there is no answer, or there is a harried and ill-informed voice at the other end of the line.

Some ideas for managing communication:

- Ensure research personnel time for patient contact, including visits and calls
- Plan ahead by creating patient calendars for study appointments and procedures
- Reschedule cancelled or missed appointments to keep studies on schedule
- Provide an efficient means for answering patient questions; e.g., a separate phone line that routes calls directly to study personnel. Timely response to patient questions minimizes fear.

²³ A *Guidance Document for Implementing Effective Cancer Clinical Trials*, prepared for C-Change by The Lewin Group, June 7, 2005.

²⁴ *Ibid.*

²⁵ Clinical research by community oncologists, GI Cohen. *CA Cancer J Clin.* 2003; 53:73-81.

Helping patients find general support information (see Section VI: References, Patient Education Services) about clinical trials and resources, advocacy groups, and patient support groups is essential to engendering trust.²⁶

When sites consider communication with patients, it is especially important that they be given a vehicle for assuring continuing consent. This element alone is one of the imperatives for patient retention.

7.5 Retention Issues

Choosing the right study and accruing patients is the first step in a successful clinical trial program. This insures that patients continue participation when possible, important to the successful outcome of each study. Subjects may discontinue participation for medical reasons (intolerable adverse event, patient's condition deteriorates), for compliance reasons (missed appointments, moves out of area), or for unexpected trial-related reasons (trial is terminated, investigator is no longer able to continue trial). But subjects also drop out for more "personal" reasons (requirements are too burdensome, transportation/childcare/time off from work are difficult to arrange).

Retention is important since it relates to the overall outcome of the study. It affects the statistical ability to answer questions regarding safety, efficacy, duration of therapy, and endpoints such as progression and survival. However, patients need to know that they may come off a study at any time without repercussion.

One secret to subject retention has been stated simply. "All site personnel have to be nice, treat subjects well, spend time with them, listen carefully to what they have to say, and communicate openly and often."²⁷

Here is a representative list of "small" things that discourage people and may cause them to drop out of a study.²⁸

- Having to wait for an appointment
- Not being treated nicely and with respect
- Not seeing the investigator or coordinator, but being seen by a "substitute" they don't know
- Not seeing the same person at each visit and developing a one-on-one relationship
- Being rushed and hurried through the appointment
- Feeling the investigator/coordinator doesn't really want to see them
- Not being asked how they feel and how the study is going for them
- Not having the opportunity or being afraid to ask questions
- Being made to feel dumb or silly when asking questions
- Being berated for doing something wrong

8.0 Study Operations

There are two distinct aspects of study operations: 1) study maintenance, e.g., regulatory and file management, and 2) patient/subject management; e.g., screening, enrollment, and follow-up, off study.

8.1 Study Maintenance

Ongoing record maintenance requires timely attention to detail for each trial, from pre-study to study closure and document retention. Regulatory requirements mandate the duration for document retention; site and IRB requirements mandate time frames for continuing approval of studies and where documents are kept. Management of this environment for each trial should be delegated to qualified individuals who have the time to complete activities.

Activities include:

- Initial submission and approval of protocol to IRB and sponsor
- Filing sponsor communication and regulatory documents

²⁶ Most general communication for clinical trials is not subject to IRB approval though some protocol specific information can be developed that requires approval. The IRB of record should give guidance to sites on this.

²⁷ *The CRA's Guide to Monitoring Clinical Research*, Karen Woodlin & John Schneider, CenterWatch Press, 2003.

²⁸ *Ibid.*

- Other study files (pharmacy, IB, etc.)
- Updates to IRB for safety and sponsor changes
- Protocol and ICF amendments
- Continuing (yearly or IRB-required) approval of protocols prior to initial expiration date
- Study closure
- Document retention policies and sponsor notification

Section 8 (see Reference Section), has a table listing relevant documents to be kept by investigators for every part of a study timeline. Document requirements for publicly sponsored studies may vary, and sites should keep those files appropriately as well. Each cooperative group and the CTSU have document requirements that can be found on websites or by contacting the specific group.

It is important to keep records of relevant information for each study such as:

- Initial IRB approval of protocol and consent
- Date of expiration. Re-submission to the IRB for continuing approvals needs to occur with enough time to ensure that there is no lapse in approval. IRB meeting dates will mandate when this re-submission should occur, but good practice is to note at least 2 months ahead (longer for IRBs that meet less frequently) to ensure time to collect all required documents for submission.
- Date of amendment approval (does not supersede continuing approvals) and version control for amendments and resubmissions
- Date of study activation by sponsor
- Date study is closed to enrollment (no more active patients allowed)
- Date study is closed to follow-up (date that IRB closure can occur and final report to IRB is required)
- Date of study closure by sponsor (as applicable)
- Date that all documents can be destroyed (ICH and FDA require 2 years from last marketing approval or per sponsor requirements);

For example:

Protocol #	Disease	IRB Approval	Exp. Date	Amend. 1	Consent Change	Closed to Enrollment	Closed to Follow-Up	Document Retention
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Spreadsheets or databases with this information are good tracking methods. However, investigators and sites are responsible for ensuring that studies are managed and that patients have consented with only current approved versions of consent forms for IRB approved protocols.

8.2 Keeping track of patients on study

Private sponsors often provide patient tracking logs for screening and enrollment, and sites must keep a record of the status of all patients on study. Sites should make a practice of keeping logs of all patients on studies and their status. Knowing who was screened versus enrolled and how long each patient stayed on study can provide valuable metrics over time. General screening logs can provide information on actual numbers of patients seen and issues with the screening process.

For individual studies, keeping a log, either on paper or electronically, of where each patient is in the process, and data due to sponsors or monitors, will help CRAs or other staff keep current on data and safety information on patients. A sample log follows:

- Screened versus enrolled
- Enrolled and treatment start date
- Treatment end date and follow-up timelines for data due
- Off study date and reason off-study
- Date of progression
- Date of death

This process is important as more studies are opened and accrual increases. This type of record helps staff members manage time and date efficiently and can be added to a spreadsheet or database covering multiple trials and sponsor-types. Investigator responsibility for providing access to monitoring and auditing require that source documents are kept for all patients in a manner congruent to this process.

8.3 Source Documentation

Source documents are “the original documents and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subject’s diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at the medico-technical departments involved in the clinical trials).²⁹

If source documents are electronic, they are also subject to 21 CFR Part 11 compliance.³⁰ Sites should know which systems in use are subject to these regulations and notify sponsors before visits.

Access must be given to sponsors or their representatives to source documentation for patients on study. Thus, storing such material so that it can be easily retrieved will be necessary. It is good practice to keep study files organized so that monitors can easily find what is recorded on Case Report Forms or in a database. It is helpful to separate pre-study information from on-study information.

8.4 Case Report Form Completion, Monitoring, and Query Handling

Source data are transcribed onto data collection forms or into electronic data collection systems. For multi-site trials, the sponsor is responsible for ensuring that data forms and the database will collect information required for statistical analysis and patient safety assurance.³¹ Sites are required to monitor data in a way that patient safety, data accuracy, and regulatory compliance can be verified.³² Monitoring frequency will vary by sponsor and by the complexity of a study. Sites should check with each sponsor for specific monitoring requirements. Public sponsors, such as cooperative groups, have manuals and training for sites to prepare for visits that can be accessed online or from the group. Private sponsors will cover monitoring requirements in supplemental procedures and during the study initiation process.

Not all protocol required documentation is transcribed, and monitors may look in source documents for data that are required but are not on case report forms (CRFs). It is imperative then that source data contain all elements required by the protocol and by applicable regulations, regardless of whether those data are transcribed.

CRF data are either monitored on site, remotely (Rapid Data Flow), or through a combination of both. Individual sponsor requirements will determine when and how data are submitted or monitored. In some cases, only a representative sample may be audited at a visit, and data are then evaluated upon data entry into the sponsor database. When data recorded on CRF or submitted electronically do not match required criteria, queries or questions to investigators are generated. A Query Form is generated by the sponsor or CRO that will note all pertinent information; e.g., protocol, sponsor, patient name, date, statement of the problem, corrective action taken, and timeline for submission. In addition, there is usually a complementary Query Resolution Form which notes in more detail what was done to rectify an error and why. Sponsor representatives are a good source of information for proactive questioning of CRF data before submission or for responding to queries.

It is unrealistic to assume that problems will never occur or that errors will not be made. What is expected is that problems are noted honestly and are recorded in full detail. Honest mistakes are a way to learn; deliberate falsification

²⁹ ICH Guideline for Good Clinical Practice, Glossary 1.52

³⁰ http://www.fda.gov/ora/compliance_ref/part11/PDA-conf-sum.htm

³¹ ICH GCP Section 5.5

³² ICH GCP Section 5.18

of records or other malfeasance is not tolerated.³³ It is good practice for sites to write procedures or SOPs for preparing for monitoring, handling data, and responding to queries.

Some web references for audit preparation are available, and each Cooperative group also has audit preparation guidelines for investigators. It is the sponsor responsibility to ensure that sites know what to expect at monitoring.

<https://www.ctnbestpractices.org/sites/siteoperations/audits/>
http://www.researchpractice.com/r_checklist.shtml

8.5 Closeout

As noted in the Lewin *Guidance Document of June 2005*, “the study closeout process varies, depending on the study type and data management requirements.”³⁴ Study closure timelines are determined by sponsors and are based on study statistical endpoints, or, when closed early, on sponsor or safety decisions. Whether or not a study closure visit is required by the sponsor, sites must give assurance that all regulatory and sponsor requirements are followed. For the most part, study closure at a site will not occur until all data are reviewed, all investigator files are in order, including IRB notification and documentation of closure correspondence, and study drug has either been returned or destroyed per protocol/sponsor requirements.

Often sites underestimate the amount of space for archiving essential documents which can require additional, sometimes unfunded, storage expenses.³⁵ Sites should find out from sponsors what document storage and retention requirements are, if possible, prior to study start. Sponsors may require additional visits after study closure and data is required. Storage and retrieval can be vexing problems if there has not been forethought on the subject.

9.0 Evaluating the Trial Site for Improvement

Quality improvement practices include periodic evaluation of the research enterprise. Only by honest evaluation of what was done can any process be improved. Reviews can be conducted: 1) after a monitor’s visit since valuable feedback, both positive and negative, will be provided by an outside source; 2) at the close of a trial; or 3) on an annual basis. All trial personnel should be allowed input to successes and areas for potential improvement. Disciplined group input improves processes.

IV. Budgeting for Clinical Trials

“A *Guidance Document for Implementing Effective Cancer Clinical Trials*,”³⁶ a companion document to this report, provides a great deal of information on the time and cost elements involved in budgeting. Section V: Staff Time and Labor Cost Benchmarks, details percentile and median data for functional elements and staff time. Since the information emanates from a survey of 14 experienced clinical trial sites, it is representative of well-established practices in mature sites. Less experienced sites should view the results of the survey as benchmarks for which to strive and not expect the same outcomes at the beginning of a clinical trial program.

1.0 Introduction

Research supports improvement in cancer care; clinical trials offer patients the opportunity to participate in new and innovative therapies, and to the physician, the opportunity to participate in scientific advancement.³⁷ The administration of clinical trials requires the planning and budget discipline normally found in business. The purpose of this section is to provide guidance on budgeting for the conduct of effective and efficient clinical trials.

³³ ICH GCP Section 5.2 and for publicly funded trials under 42 CFR Part 93 and the Office of Research Integrity <http://ori.dhhs.gov/>

³⁴ *A Guidance Document for Implementing Effective Cancer Clinical Trials*, prepared for C-Change by The Lewin Group, June 7, 2005.

³⁵ *Ibid.*

³⁶ (http://www.c-changetogether.org/about_ndc/newsroom/default.asp - The document can be viewed on this website by clicking on Guidance Document in the Reports section.

³⁷ *Setting Up a Clinical Research Program in the Community Hospital Setting*, Claudia Goggin Fredian, RN, BSN, CCRP, Alexian Brothers Medical Center, viewed on http://www.socra.org/pdf/200302_Clinical_Research_in_Community_Hospital.pdf

The conduct of research requires dedication of time and staff to ensure proper conduct. A physician leader who will assist staff to identify trials and provide effective oversight of the research process is imperative to a site's ability to sustain a clinical trials program. Commitment to provide necessary staff and infrastructure is necessary to initiate and sustain a program. Clinical research programs in the community setting are often introduced as a means to offer cutting edge therapies to patients and strengthen commitment to the community.³⁸ This dedication will take a steady commitment over time in order to assure that long-term objectives, whether altruistic or financial, are met. The business of clinical trial participation, including assessment, budgeting, and evaluation is discussed in this section.

One of the six elements of success for a clinical trial site cited in Section I is "adequate financial resources." The most important element in evaluating and projecting financial resources is the budgeting process.

There are six budgeting steps that, when properly and consistently implemented, can provide a process for estimating clinical trial cost impact collectively to a practice and individually per clinical trial:

- Step 1: Identify base costs and resources
- Step 2: Assess the protocol
- Step 3: Model the cost per patient
- Step 4: Negotiate the study budget
- Step 5: Conduct the study
- Step 6: Conduct a post-study evaluation

The cost to a study site for participation in clinical trials differs from costs of providing standard-of-care treatment to patients. These additional costs are associated with physician oversight of required regulatory obligations to ensure overall study compliance. The type of infrastructure, supplemental resources, and number of dedicated research staff also influence operations budgets.³⁹

There are also specific costs associated with performance of an individual study, which should be calculated prior to the decision to pursue and participate in the study. These estimates should be representative of the actual anticipated work to be done for a study.

2.0 The Six Budgeting Steps

2.1 Step 1: Identify base costs and resources

Since each clinical trial site has different available base resources, it is important to assess base resources in order to predict what kinds of costs are associated with each site that will be incurred, regardless of the number or type of studies opened.

When planning and projecting base costs, a 1, 2, and 5-year plan may help identify anticipated costs over time, and allow a projected growth rate to measure performance. The development plan should include site goals over time for:

- Number of studies and tumor types and stage
- Types of study sponsor (Pharma, NCI, other)
- Participation in correlative research or sampling (Will need access to centrifuge, freezer, and shipment or a supportive laboratory)
- Long-term document storage and retrieval facilities
- Resources noted below, such as space and personnel needs based on overall regulatory requirements and delegated tasks

³⁸ *Ibid.*

³⁹ Budget Tool Helps Investigative Sites Calculate the Cost of a Coordinator's Time for a Typical Outpatient Study Visit, Parts 1&2, Guy P. Johnson, CPA, MS, The George Washington University Clinical Research Administration Program, viewed on http://www.socra.org/pdf/Investigative_Site_Budget_Tool_by_Guy_Johnson.pdf

Resources

It is important to identify base resources available to a study site.

- Will the hospital or practice support the salary of research personnel?
- Will they provide space for clinical trial activities or will this need to be included in overhead? Does the hospital or practice have a local IRB and/or scientific review committee for clinical trials?
- Is there a research pharmacy or pharmacy where investigational products can be stored per regulatory requirements?
- Is there a willing physician to undertake research activities with appropriate qualifications?
- Are there any other “in-kind” gifts, grants, or endowments to support a research structure?

Space and equipment needs

Space and equipment needs include:

- Phone, fax, copy machine, computer with internet access, centrifuge (as applicable)
- Office space for research personnel and study files (should be locked and minimally accessible). Include office space for patient interactions as necessary
- Office rent and overhead as appropriate (electricity, plumbing, if not part of practice)
- Treatment area and Pharmacy area (must also be locked and separate with refrigeration as necessary)
- Examination rooms with appropriate equipment
- Long term document storage capabilities, study materials storage (case report forms, lab kits, etc.)

Research Personnel

As noted in the Elements of Success, Committed Staff is the first item on the list. Full time research employees are important to success. However, physician time should also be estimated as a consideration of protocol and regulatory requirements and delegated work. For instance, if a research nurse is hired as the FTE, physicians can delegate toxicity assessment and patient follow-up calls. If a CRA is hired as the FTE, an MD must retain all those responsibilities covered under a nursing license. It is important also to dedicate MD time for research activities such as weekly protocol reviews, patient assessments, accrual initiatives, case report forms, and pharmacy oversight. (General information on delegation of investigator responsibilities and applicable regulatory requirements is contained in Section III: 5.1.)

Investigator	Annual Salary + Benefits (est. @24%) / percent of time dedicated to research
Administrative	Annual Salary + Benefits (est. @24%) / percent of time dedicated to research
CRA and/or Coordinator and/or Data Manager	Annual Salary + Benefits (est. @24%) Assume full time (number of working days per year)
Pharmacy/Contract	Annual Salary + Benefits (est. @24%) / percent of time dedicated to research

A key component of a clinical trial is calculating the actual cost of personnel.

Example: Research coordinator

\$50,000 salary plus \$15,000 benefits/260 working days per year = \$250 per day

The formula can be used to calculate the cost of personnel for base cost analysis as well as dividing by time estimated per study for actual per patient budget costs. Annual review of input and output will help identify variances and allow implementation of cost-saving measures.

2.2 Step 2: Assess the protocol

The decision to participate in a particular study should be based on review of factors already described: 1) scientific merit, 2) fit with patient populations, 3) ability to accrue, 4) adequate time and availability of resources, and 5) funds available for the study budget. Careful evaluation of patient populations within the practice and potential patient sources from referrals, assessment of investigator interest in types of studies, and basic ethical and scientific beliefs will help determine areas of interest. Further research into the types of available studies from potential sponsors from references such as www.clinicaltrials.gov can outline current investigative potential. Next, it is important to plan how many studies will be feasible with available site resources at standard study duration.

Phase II studies typically have a shorter enrollment and follow-up period for primary endpoints, but if secondary endpoints include survival, that time should be considered. Phase III studies are usually longer in duration and longer in follow-up. It is important to estimate resource utilization for the entire timeline, including start-up, accrual, follow-up and closure.

While selecting trials with high accrual potential is important, the investigator may choose to participate in a trial with low accrual potential based on other important criteria, such as scientific merit or interest, or otherwise limited therapeutic options for patients. These decisions are individual and should be discussed with potential sponsors as applicable.

2.3 Step 3: Model the cost per patient

The cost per patient should be modeled using the protocol document and reporting requirements of the sponsor, and careful assessment of staff responsibilities and time.

There are costs that are associated with study start-up and maintenance that are generally considered “fixed or one-time costs,” and ongoing study costs that are associated with patient accrual and study management. It is generally agreed, however, that the overall cost to a site of doing a trial is greater when accrual is poor; fixed costs can be offset as accrual increases.⁴⁰ For example, a pharmacy yearly cost that may be fixed at \$1000 will be fully taken from the patient budget if one patient is enrolled, \$500 per patient if two are enrolled, and \$200 per patient if five are enrolled.

One Time Costs

Actual study costs will also vary by the type of trial sponsor (Cooperative Group/CTSU or Pharmaceutical Sponsor), the phase of the study (randomized versus enrollment, Phase II or III), the registration status of the investigative agent or device (safety reporting requirements, IND requirements) and the study oversight requirements (monitoring frequency, number of case report forms).⁴¹

Publicly funded trials offer a flat patient stipend fee but also allow access to a multitude of trials that operate under uniform procedures and standards. Pharmaceutical sponsors can provide, in some cases, reimbursement based on actual workload through budget negotiations. They can often account for geographical differences, institutional costs, and some start-up, and regulatory fees (IRB and review).

⁴⁰ Factors Affecting Workload of Cancer Clinical Trials: Results of a Multicenter Study of the National Cancer Institute of Canada Clinical Trials Group, Kathryn Roche, Nancy Paul, Bobbi Smuck, Marlo Whitehead, Benny Zee, Joseph Pater, Mary-Anne Hiatt, Hugh Walker JCO Jan 15 2002: 545-556

⁴¹ A Guidance Document for Implementing Effective Cancer Clinical Trials, prepared for C-Change by The Lewin Group, June 7, 2005.

One time costs per study can be found either in the protocol document or in communication with the Sponsor or CRO. A representative list is below:

(Please consider those appropriate to your site)

IRB review	Local or central IRB charges
Scientific review	Other institutional review committees
Pharmacy costs	Pharmacy setup and storage of drug
Feasibility review	Review and assessment of the protocol
Consent preparation	Preparing consent template for site approval
Regulatory documents	Collecting and submitting packet to sponsor
Translation services	As needed for site-specific population
Contract review	Site legal review of contract and execution
Preparation costs	Sponsor pre-study visits and initiation visit and staff training
Study-specific requirements	Specific study requirements (internet for data management, special equipment)
Projected IRB reviews	Subsequent IRB submissions for annual reviews, estimated amendments, and Safety Letter submissions for life of study
Regulatory costs	Regulatory document management for number of years study open. Estimate for appropriate staff time (PI, CRA, administration, pharmacy, etc.)
Study closure	Long-term document storage

Per Patient Costs

Per patient cost estimates are derived from review of the protocol document, from the accurate estimation of accrual, and from information from the sponsor. The time needed to screen a patient will depend upon the complexity of the study and eligibility criteria. Patient registration should also be described and the number of steps delineated. Estimate of consent time should come from institutional standards and compliance with regulations. The number and complexity of case report forms (CRFs) should be estimated, including how they will be retrieved and reviewed. Will the data be collected electronically or on written CRFs?

The time spent for monitoring preparation will be influenced by the site's overall structure; i.e., available staff and their costs. Although monitoring is not directly patient-specific, the frequency of monitoring is often determined by accrual.

Sites should include any procedures required by the study that will take time and/or staff to complete, such as tissue or blood sampling. Sites should be sure to address who will be responsible for what task, and determine the FTE as above for average time spent for each activity.⁴² A separate spreadsheet to determine staff time for study procedures may be developed.

⁴² Roche et alia, *op. cit*

Study Execution	Screening	Assume that 1 in 6-10 screened patients will enroll
	Registration	Informed Consent, documentation, enrollment
	Patient visits	Review protocol for frequency of patient visits, requirements at each visit, and time to perform, including treatment
	Follow-up	How long patients will be followed (primary and secondary endpoints), and the frequency and workload expected per protocol requirements
Data Management	CRF completion	Complexity of CRF, number of CRFs, query resolution process, submission of CRFs and any postage or mailing costs not covered by the sponsor
	Monitoring	Monitoring or auditing frequency and expectations of staff. Estimate 4 hours preparation for each visit and 4 hours during each visit day or greater. Site closure visit (estimate one day)
Other Protocol	Other	Laboratory, correlative specimen and processing. Estimate the cost for tests not anticipated to be covered by reimbursement (reimbursable not billable cost)
	Safety	Estimate number of SAEs per patient and time to follow-up per site standards.

2.4 Step 4: Negotiate the study budget

Budgets are not always negotiable. The per-patient stipend for a publicly funded trial will be fixed. However, with standardization of start up processes, CRFs, and auditing procedures, the cost of opening a public study and for the performance of a public study may be lower.

Often industry sponsors will approve payment of one time and pre-trial costs to cover some initial activities as stated above. It is important to also review the contract and budget for investigator and site obligations such as:

- Accrual obligations and timelines
- Data completion and query resolution timelines
- Covered costs and reimbursement, such as scans, laboratory
- Patient compensation, if any, including travel or hotel
- Criteria for payment; i.e., eligible patients, screened patients
- Payment schedules; i.e., how often payments are made and the critical milestones for payments

When possible, sites should ask sponsors to consider factors, such as geography, in determining a per-patient budget. The U. S. Bureau of Labor Statistics or other Internet sites can help identify a multiplier for cost of living.

It is acceptable that a site may ask to negotiate per-patient costs with a non-public sponsor. Properly documented costs are the best defense to a sponsor, a monitor, or an auditor for a site's requested costs.

Indirect cost recovery and profit

Indirect cost recovery compensates a site for rent, administrative telephone costs, and support staff. As a rule, any cost that can be allocated to a trial process or procedure should be included in direct costs to reflect the appropriate nature of the cost and excluded from indirect cost, i.e., overhead. All requested costs must be related to the cost of study performance.

For-profit sites may include a profit percentage for each of its costs. Profit is applied as the site's administration advisors determine. Federal government trials are not eligible for profit. Not-for-profit sites are limited to spending any overage in cost recovery for the purposes of research and education. Site legal advisors should determine billable indirect cost as applicable.

Budget Worksheet Example⁴³

Protocol Type:			
<input type="checkbox"/> Cooperative Group/CTSU <input type="checkbox"/> Pharma Sponsor <input type="checkbox"/> Network/Other			
	Projected Accrual:		Number of patients
Functional Step	Unit Cost	Pass Through	Notes
Personnel Costs			
Fixed (One-Time)			
Protocol feasibility	\$	\$	
IRB submission			
Scientific review			
Regulatory documents			
Consent preparation			
Translation			
Contract approval			
Preparation			
Pharmacy			
Ongoing reviews			
Other:			
Other:			
Other:			
			Subtract any startup costs from sponsor as applicable
SUB-TOTAL	\$	\$	
Patient-Specific			
Study execution			
Data management			
Other protocol			
Other:			
SUB-TOTAL	\$	\$	
Other			
Cost of living			Obtain multiplier
Indirect costs			Institutional overhead
SUB-TOTAL	\$	\$	
TOTAL	\$	\$	Add sub-totals together
PER PATIENT COST	\$	\$	Divide by projected number of patients

Additional examples of personnel and patient budget sheets can be found at http://www.researchpractice.com/r_forms.shtml. Other references are available by conducting on-line searches.

⁴³ There is an easy to use spreadsheet for doing budgets at: http://www.researchroundtable.com/Oct2001/CostCalcIntro.htm

2.5 Step 5: Conduct the study

The sponsor and the site have a mutually beneficial relationship. In general, non-public sponsors are willing to pay fair compensation for work performed efficiently and effectively. A sponsor will expect a site to meet its accrual on a timely basis and to conduct the trial under all applicable regulations. Often payments are linked to data submission and query response. The site should understand the payment process prior to any patient accrual. A site should expect a sponsor to process eligible payments on a timely basis per the study contract or other agreement.

It will be beneficial to document a comparison of actual time and expense versus estimated time and expense once a study is underway. The fixed and one-time costs will be incurred regardless of the number of patients accrued. As stated before, the actual cost to manage a patient may decrease as accrual increases. As a site gains experience with managing patients and data, the actual time to perform some study tasks, such as case report form completion, decreases. Experience with study requirements also leads to fewer errors in compliance and patient management.⁴⁴

Good, honest communication established during budget negotiation and continued through the life of the project will develop a good working relationship between sponsor and site.

2.6 Step 6: Conduct a post-study evaluation

Review each study carefully at completion for actual versus projected costs, as applicable.

- Were fixed costs as projected?
- What was the actual versus projected accrual, and what were the issues surrounding accrual?
- Did patients stay on study?
- Did study staff perform tasks as projected, and what were the outcomes of sponsor audits and monitoring visits?
- What could be done differently or more efficiently?

Spending time on this type of review can help a site: 1) develop more accurate budgets, 2) better allocate resources, 3) evaluate time-management, and 4) project more efficient staffing models for site development.

Clinical trial administrators from other, similar institutions may be willing to share their own best practices. Clinical research support organizations also offer classes and publications that address this issue. These are noted in the reference section or applicable sections of this document.

V. Guidelines for Sites New to Clinical Research

The decision to begin clinical trial participation should include thoughtful consideration to the time, staff, regulatory, ethical requirements, and other resources that are required to effectively manage this endeavor. Some tools to help determine what will be necessary for a practice to succeed are elsewhere referenced in this document in associated links and references.

While participation in cancer research offers patient access to new drugs and therapies, there must be a commitment to the process, as evidenced in the Elements of Success document. The time necessary for patient management on clinical trials differs greatly from standard of care practice. Time must be allowed for patient consent, treatment per protocol, toxicity management, data recording, regulatory oversight, and compliance with Good Clinical Practice guidelines.

The commitment to time and resources, such as staff, training, and financial support will ultimately determine the success of the program. Understanding requirements and setting realistic expectations for a practice for at least the first year will aid in achieving success.

⁴⁴ Roche et alia, *op cit*.

The following steps may help identify starting activities:

Lead Investigator

There should be at least one physician who is committed to research. This person will usually be the principal investigator on studies and should have time, weekly, to dedicate to the implementation of the research program and structure.

Study Staff

Study research staff should have time dedicated just for research. Sponsors will look for sites that have staff with time and training to manage research requirements. As stated elsewhere in this document, some regulatory obligations may be delegated to staff. This person may be a nurse, a CRA, or study coordinator.

Training and Education Needs

All study staff, including investigators, should be trained in Good Clinical Practice on an ongoing basis. Understanding regulatory requirements is essential for compliance and for protection of human subjects. Human subject protection and HIPAA training for clinical trials is very important.

A system should be developed for maintaining general information (regulatory document files), protocol tracking (IRB approval, safety, and patient status), and monitoring patients on study.

Regulatory

Does the site have a local Institutional Review Board (IRB)? It is the responsibility of the PI to know who the IRB is and what institutional guidelines need to be followed. While the Code of Federal Regulations governs IRB activity, an IRB may develop stricter adherence guidelines. If a local IRB is not available, there are many central IRBs that can be contracted to review protocols.

Regulatory files should be separate and maintained so only active and current documents are used. All documentation must be kept for periods defined in each protocol or contract. Identify a way to manage patients and studies so that accurate data on patient populations and active protocols are available.

Other resources

Is there a pharmacy available for mixing and storing investigational drug? If not, who in the practice would be trained to handle drugs in adherence with the protocol? Legal counsel or contract specialists may be required to review potential contracts from clinical trial sponsors. Although most companies indemnify investigators for research, it is a good idea to identify malpractice gaps and ensure that study staff is covered by professional practice guidelines.

Space and equipment

What space is available for staff to conduct research, and for research charts and regulatory documents? Is there adequate long-term storage, and is there space for study sponsor monitors to come and review data?

Dedicated phone line, fax line, copy machine, and computer with high-speed internet service. All study related information must be maintained in a secure area and protect patient privacy.

Patient populations

It is important to know what kinds of studies should be opened first. As discussed in this document, much time is necessary just to open a trial. Thus, it is important to start with studies for which a site knows it can get enrollment. Keep a record of billing codes, check with the tumor registry (especially if trial practice is the only one to use it), keep a log of diagnoses and stage of patients seen, including new patients and patients who return for a period of time. Review study schemas on <http://www.clinicaltrials.gov/> against practice standards. Studies should comply clinically and ethically with usual practice.

Identify internal and external support

Is there a way to “market” the new clinical trial endeavor? Will the hospital or practice support this? How will referring physicians know of studies being opened? Can this information be added to an existing web site? Please note that most IRBs will require review of any advertising outside of listing on required government web sites.

Visit with colleagues who have a clinical trial practice, and if possible have discussions regarding execution, maintenance, pitfalls, and early issues. Successful sites did not get there automatically. If possible, develop a mentorship.

Oncology networks and some academic centers will collaborate with new sites and can assist in training and infrastructure support.

Financial

Once the staff needs are determined, estimate salaries to support research. Individual salary, benefits, and travel should be considered. Equipment (copy, fax, and computer with software) and space should be considered for the practice. An initial financial commitment is required to begin, but it is necessary to determine what is actually “extra” for each site. Determine what it takes to start a study from budget worksheet templates, including IRB, pharmacy, and institutional overhead.

Choosing Trials

Each study should be reviewed against patient populations, scientific merit, and the work of accruing and following patients on study. Review each potential trial using templates referred to in this document or ones developed by the site. Choose only a representative few until it is clear how the entire enterprise is functioning.

Studies should be reviewed for compatibility with sponsors (Pharma or government), budget, and time to execute and manage all trial activities such as safety submissions, time for patients on study, case report forms, and monitoring.

Quality Review

Early on, develop internal procedures to identify responsibilities and steps for study implementation and management. There are many websites and books that offer standard SOP templates that can be adapted. Also, have the investigator map out delegation early in the process so that it is clear to everyone who is doing what.

At pre-defined intervals during the first year, review actual practice against regulations, SOPs, and expectations. Develop contingency plans and risk management plans where necessary.

Task	Resource
<ul style="list-style-type: none"> <input type="checkbox"/> Investigator <input type="checkbox"/> Staff <ul style="list-style-type: none"> <input type="checkbox"/> Research Nurse <input type="checkbox"/> CRA <input type="checkbox"/> Pharmacy <input type="checkbox"/> Study Coordinator <input type="checkbox"/> Other <input type="checkbox"/> GCP, Ethics, Patient Protection, Privacy Training <ul style="list-style-type: none"> <input type="checkbox"/> Staff <input type="checkbox"/> Investigators <input type="checkbox"/> IRB <ul style="list-style-type: none"> <input type="checkbox"/> Local (Name) <input type="checkbox"/> Central <input type="checkbox"/> Regulatory Files <ul style="list-style-type: none"> <input type="checkbox"/> CV <input type="checkbox"/> Labs <input type="checkbox"/> Licenses <input type="checkbox"/> Financial assurance <input type="checkbox"/> Pharmacy/ Investigational Drug space <ul style="list-style-type: none"> <input type="checkbox"/> Locked? <input type="checkbox"/> Refrigeration? <input type="checkbox"/> Back up? <input type="checkbox"/> Training and forms <input type="checkbox"/> Contracts and Legal <input type="checkbox"/> Space and Equipment <ul style="list-style-type: none"> <input type="checkbox"/> Storage <input type="checkbox"/> Office <input type="checkbox"/> Fax and Phone (dedicated) <input type="checkbox"/> Copy <input type="checkbox"/> Charts, protocols and regulatory <input type="checkbox"/> Computer <input type="checkbox"/> Room for monitor review <input type="checkbox"/> Other <input type="checkbox"/> Financial <ul style="list-style-type: none"> <input type="checkbox"/> Salary and benefits <input type="checkbox"/> Travel and training estimate <input type="checkbox"/> Overhead and infrastructure <input type="checkbox"/> Equipment (above) <input type="checkbox"/> Identify existing resources <input type="checkbox"/> Patient Identification <ul style="list-style-type: none"> <input type="checkbox"/> Existing Population <input type="checkbox"/> Compile Results <input type="checkbox"/> Choosing Studies <ul style="list-style-type: none"> <input type="checkbox"/> Tumor types <input type="checkbox"/> Scientific and ethical review <input type="checkbox"/> Cost review <input type="checkbox"/> Agreement with practice <input type="checkbox"/> Time review <input type="checkbox"/> Sponsor/CRO and work <input type="checkbox"/> External support: visit site <input type="checkbox"/> Quality Plan <ul style="list-style-type: none"> <input type="checkbox"/> Delegation of tasks <input type="checkbox"/> Develop procedures <input type="checkbox"/> Develop timeline for review 	<p style="text-align: center; vertical-align: middle;">Input/Output Plan</p>

VI. References

General Resources

NCI Investigator's Handbook.
<http://ctep.cancer.gov/handbook/index.html>

Clinical Trials Cooperative Group Program Guidelines <http://ctep.cancer.gov/resources/trialguide.html>

NCI clinical trial documents
This site specifically focuses on information specifically related to conducting clinical trials.
<http://www.cancer.gov/clinicaltrials/conducting>

NCI/CTEP resources
<http://ctep.cancer.gov>

Clinical Trial Network: Contains information from Duke University for network sites, funded under NIH grant. Not Oncology specific, but a good resource that includes downloadable forms and checklists.
<https://www.ctnbestpractices.org/>

Coalition of Cancer Cooperative Groups
www.cancertrialshelp.org

Oncology Information

General Sites

ASCO American Society of Clinical Oncology
<http://www.asco.org/portal/site/ASCO/>

Oncology Nursing Society
<http://www.ons.org/>

ECOG Eastern Cooperative Oncology Group
<http://www.ecog.org/>

RTOG Radiation Therapy Oncology Group
<http://www.rtog.org/>

SWOG Southwestern Oncology Group
<http://www.swog.org/>

NCCTG North Central Cancer Treatment Group
<http://ncctg.mayo.edu/>

NSABP National Surgical Adjuvant Breast and Bowel Project
<http://www.nsabp.pitt.edu/>

HOG Hoosier Oncology Group
http://hog.walther.org/hog_index.html

ACOSOG American College of Surgeons Oncology Group
<https://www.acosog.org/>

Disease Information

Oncology Tools Home Page

This FDA page has detailed information on Approved Oncology Drugs, Disease Summaries, Regulatory Tools, Oncology Reference Tools, Patient Liaison Program, FDA Centers and Divisions, as well as Additional Resources.
<http://www.fda.gov/cder/cancer/index.htm>

FDA Disease Summaries

This detailed page lists referenced websites concerning specific diseases and includes references provided by NCI.
<http://www.accessdata.fda.gov/scripts/cder/onctools/disum.cfm>

NCCN National Comprehensive Cancer Network

This website provides treatment guidelines, info for patients, online learning, as well as listings of clinical trials, guideline updates, and NCCN Drugs and Biologics Compendium.
<http://www.nccn.org/>

ASCO Practice Guidelines (American Society of Clinical Oncology)

This website provides information about Practice Guidelines, Education and Training, Legislative Issues, and News.
<http://www.asco.org/guidelines>

Cancer Statistics (American Cancer Society) Occurrence, Death and Survival Rates, Promoting factors

http://www.cancer.org/docroot/STT/stt_0.asp

Cancer Statistics (NCI) Consolidated list of SEER data, publications and links

<http://www.nci.nih.gov/statistics/finding>

Cancer Statistics (WHO) World Wide Cancer Epidemiology Information

<http://www.who.int/research/en/>

Costs

NCI Study Link on Cancer Care Costs

<http://healthservices.cancer.gov/areas/economics/clinical.html>

State Clinical Trial Laws

National Conference of State Legislatures

<http://www.ncsl.org/programs/health/clinicaltrials.htm>

States Requiring Health Care Coverage for Trials

This site details which states require, or have regulations about, insurance coverage for the cost of clinical trials.
<http://www.cancer.gov/clinicaltrials/learning/laws-about-clinical-trial-costs>

Study Tools Information

Oncology Tools all in One (CTCAE, Performance Status Scales, Dose Calculators)

<http://www.fda.gov/cder/cancer/oncrefto.htm>

PDQ Physician Data Query

<http://www.nci.nih.gov/cancertopics/pdq>

RECIST (Response Evaluation Criteria in Solid Tumors) Measurement Criteria

(Published in JNCI [Therese, P. Journal of the National Cancer Institute, Vol. 92, No. 3, 205-217 February 2, 2000].

This is the NCI link to that article)

<http://ctep.cancer.gov/guidelines/recist.html>

Common Terminology Criteria for Adverse Events (CTCAE v3.0)

The most current version of toxicity reporting scale is Version 3. Protocol documents contain the version used.

<http://ctep.cancer.gov/reporting/ctc.html>

Clinical Trial Listings

Clinical Trials Listing site required by FDA and ICJME (International Committee of Medical Journal Editors)

<http://clinicaltrials.gov/>

PDQ (Physician Data Query) listing is a voluntary listing for government supported and other trials.

<http://www.nci.nih.gov/cancertopics/pdq>

TrialCheck Sponsored by the Coalition of Cancer Cooperative Groups lists all studies on PDQ and others: site for professionals and patients

<http://www.trialcheck.org/Services/>

Oncolink is a University of Pennsylvania sponsored site.

<http://www.oncolink.org/treatment/treatment.cfm?c=3>

Thompson Centerwatch lists trials across disease types and therapeutic areas. This is a paid site and is not all inclusive.

<http://www.centerwatch.com/>

Listing of Government Supported Studies and Study Results

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

Searchable database for Pharma-sponsored drugs in development

http://www.phrma.org/medicines_in_development/

Regulatory

Code of Federal Regulations

<http://www.gpoaccess.gov/cfr/index.html>

GCP FDA Regulations (relating to clinical trials/investigators)

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

ICH GCP E6

This site contains a 58-page document covering all aspects of clinical trials.

<http://www.fda.gov/cder/guidance/959fnl.pdf>

FDA Guidance Documents (FDA current interpretation of CFR)

<http://www.fda.gov/Cder/guidance/>

Information on Drug Development and IND for Drugs and Biologics

CDER Center for Drug Evaluation and Research

http://www.fda.gov/cder/regulatory/applications/ind_page_1.htm

CBER Center for Biologics Evaluation and Research

<http://www.fda.gov/cber/sitemap.htm>

FDA/ PHS/ ORI Disqualification and Administrative Action Lists

http://www.fda.gov/ora/compliance_ref/bimo/dis_res_assur.htm

http://www.fda.gov/ora/compliance_ref/debar/

<http://silk.nih.gov/public/cbz1bje.@www.orilist.html>

IND Information

http://www.fda.gov/cder/regulatory/applications/ind_page_1.htm

Human Subject Protection

NIH Link OHSR Office of Human Subjects Research

This site contains a .pdf file of the Gray Booklet, a valuable short reference.

<http://www.nihtraining.com/ohsr/site/guidelines/guidelines.html>

Office for Human Research Protections (OHRP)

<http://www.hhs.gov/ohrp/>

Office of Research Integrity (investigator misconduct)

<http://ori.dhhs.gov/>

HIPAA in Clinical Trials

This Health & Human Services site has a set of decision-making tools about whether HIPAA (Health Insurance Portability and Accountability Act) applies to an entity.

<http://www.cms.hhs.gov/apps/hipaa2decisionsupport/default.asp>

This NIH site contains detailed information about HIPAA and research.

http://privacyruleandresearch.nih.gov/clin_research.asp

Training and Education for Investigators/Staff**Books**

Go to any online bookstore and type in search criteria for clinical trial training materials, SOP development for Investigators and Sites, FDA guidelines (printed and bound), etc.

Human Subject Protection

<http://www.nihtraining.com/ohsr/site/guidelines/guidelines.html>

GCP

Centerwatch

<http://www.centerwatch.com/>

MRM Medical Research Management, Inc.

This site details both on-line and on-site courses offered for clinical research personnel by Medical Research Management, Inc.

<http://www.cra-training.com/>

Barnett International

This is a private company with varied training and development seminars.

<http://www.barnettinternational.com/bi-about.cfm>

Certification Site for Research Personnel

NCI Certification Training

This site has a variety of booklets and publications.

<http://www.cancer.gov/clinicaltrials/learning/clinical-trials-education-series>

This website contains the NCI basic workbook which includes exercises and answers for self-paced study.

<http://www.cancer.gov/clinicaltrials/resources/basicworkbook/>

This site has more web-based course listings.
<http://www.cancer.gov/clinicaltrials/learning/page3>

This website for Association of Clinical Research Professionals lists all of their available seminars and programs.
<http://www.acrpnet.org/certification/index.html>

SOCRA (Society of Clinical Research Associates)
This is one of several sites offering certification for Clinical Research Associates.
<http://www.socra.org/>

ACRP (Association for Clinical Research Professionals)
<http://www.acrpnet.org/>

SRA (Society of Research Associates) International
<http://www.srainternational.org/sra03/template/tntbEDUd.cfm?id=864>

This page lists certifications for Clinical Research Associates (CRAs), Clinical Research Coordinators (CRCs), and Clinical Trial Investigators (CTIs).
<http://www.acrpnet.org/certification/index.html>

Patient Education Services

Clinical Trial Information

This page enables patients to look for appropriate trials.
<http://www.cancer.gov/clinicaltrials>

This page provides links to the Basic Workbook, a resource that can be used by clinical personnel as well as patients.
<http://www.cancer.gov/clinicaltrials/resources/basicworkbook/>

This page from the Coalition of Cancer Cooperative Groups has a Patient Toolkit which provides information about trials, support groups, publications and other relevant topics.
<http://www.cancertrialshelp.org/patientsCaregivers/toolkit.jsp>

Patient Disease Information

NCI

These two pages provide links to numerous relevant topics of interest to patients: <http://www.cancer.gov/>
<http://www.nci.nih.gov/cancertopics/>

ASCO (American Society of Clinical Oncology)
This is the People Living with Cancer page and is specifically designed for patients.
<http://www.plwc.org/>

ACOR Association of Cancer Online Resources
This is a collection of online communities designed to provide timely and accurate information in a supporting environment for patients.
<http://www.acor.org/>

Advocacy

This site lists all of the advocacy organizations in an easy to use table.
<http://ncilistens.cancer.gov/moderator.asp?action=groups&view=in&gap=10>

This site is sponsored by the Association of Community Cancer Centers and lists resources by cancer-type.
http://www.accc-cancer.org/ONCRES/oncres_advocacy.asp

Another listing of patient support resources.
<http://www.cancerindex.org/clinks6a.htm>

Downloadable Forms

Research Roundtable

This site has an easy to use spreadsheet for budgeting.
<mailto:http://www.researchroundtable.com/Oct2001/CostCalcIntro.htm>

World Oncology Network (Library, Billing Services, Free Journals)
http://www.worldoncology.net/medical_library.htm

Business Information and Downloads

This page includes downloadable FDA forms.
http://www.fda.gov/cder/about/smallbiz/clinical_investigator.htm

Clinical Trial Agreements

This webpage contains an article about clinical trial agreements; it does not have a sample.
<http://content.nejm.org/cgi/content/short/352/21/2202>

ACCC (Association of Community Cancer Centers)

This site links to public policy web pages, education opportunities, publications, and meetings.

VII. Notes



Collaborating to Conquer Cancer

1776 I Street, NW, Suite 900
Washington, D.C. 20006
800.830.1827 202.756.1600
202.756.1512 FAX
www.c-changetogether.org

Coalition *of*

CANCER COOPERATIVE GROUPS

1818 Market Street, Suite 1100
Philadelphia, PA 19103
877.520.4457
215.789.3655 FAX
www.cancertrialshelp.org