

Keys to Building a Successful Research Site



UNDERSTANDING THE REGULATORY ENVIRONMENT

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TRAINING YOUR STUDY COORDINATOR

RECRUITING AND RETAINING SUBJECTS

MANAGING THE STUDY BUDGET

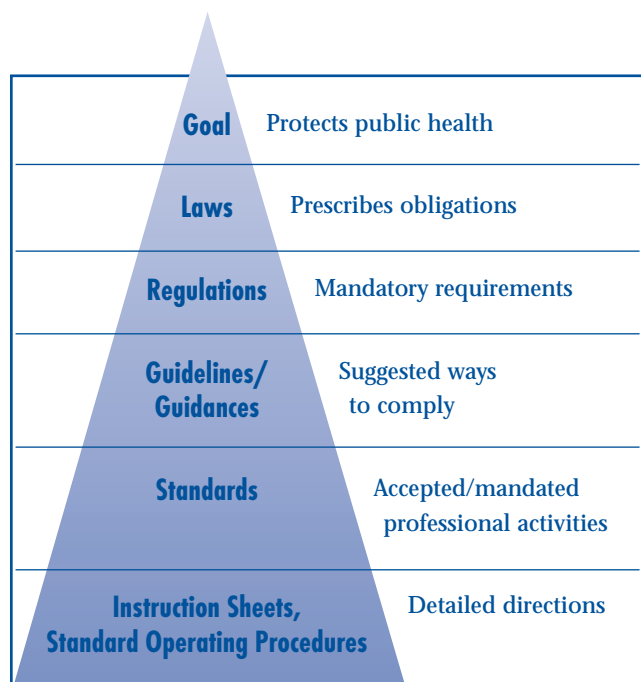
STUDY FEASIBILITY/PROTOCOL ASSESSMENT

SETTING UP YOUR FACILITY

MARKETING YOUR SITE

Understanding the Regulatory Environment

GOOD CLINICAL PRACTICE (GCP)



Good Clinical Practices (GCP) describes the obligations of the sponsor, monitors, investigators and Institutional Review Boards (IRB) in protecting human subjects, both in the laws governing clinical research and the ideals of research ethics and “good science”. Although many of its precepts are not legally binding (e.g., guidelines and information sheets issued by FDA), GCP is widely accepted and expected in clinical research. Failure to meet GCP standards may result in sanctions and penalties.

Laws. All the government-approved rules of conduct that are in force over a certain territory (e.g., the “laws” of the US). An example would be HIPAA (Health Insurance Portability and Accountability Act).

<http://www.hhs.gov/ocr/hipaa/>

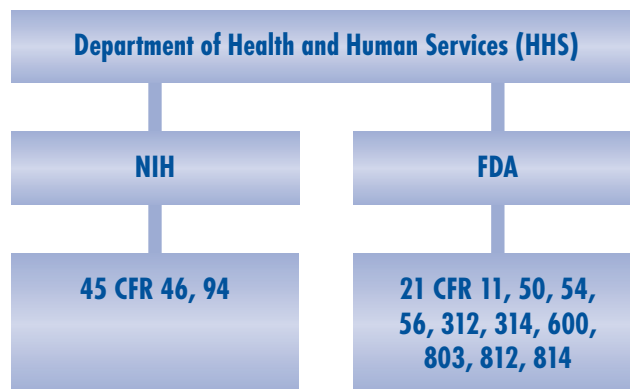
Regulations (or rules). Promulgated by administrative agencies like FDA, using authority delegated to them by Congress. Often, regulations implement a statute or set procedures to allow an agency to exercise the authority delegated to it by Congress. New regulations are codified in the collection of all current regulations, called the Code of Federal Regulations (CFR). Although they are not laws, regulations have the force of law, since they are adopted under authority granted by statutes and often include penalties for violations.

Guidance/Guidelines. Provide assistance by explaining how a regulated industry may comply with those statutory and regulatory requirements. Guidance documents for industry do not establish legally-enforceable rights or responsibilities and are not legally binding.

Standards. Accepted or mandated obligations, behaviors, and ethical imperatives for one’s profession, such as a code of ethics, standards of care, etc.

Instruction Sheets and Standard Operating Procedures (SOPs). Detailed instructions. FDA requires that IRBs have SOPs, but does not require sponsors or investigative sites to have them.

FEDERAL REGULATION OF CLINICAL RESEARCH



Much of the biomedical and behavioral research conducted in the United States is governed by the Department of Health and Human Services (HHS) or the Food and Drug Administration (FDA).

HHS. Oversees federally-funded studies (e.g., NIH grants) and is governed by the Federal Policy for the Protection of Human Subjects (also known as the “Common Rule,” codified at subpart A of Title 45 CFR Part 46). The main elements of the Common Rule include requirements for assuring compliance by research institutions, requirements for researchers obtaining and documenting informed consent, and requirements for IRB membership, function, operations, review of research, and record keeping.

In addition to the Common Rule, HHS has adopted three (3) subparts which provide additional protection for vulnerable populations. These include:

- Pregnant Women, Human Fetuses and Neonates (Subpart B, 45 CFR 46.200, et al.)
- Prisoners (Subpart C, 45 CFR 46.301)
- Children (Subpart D, 45 CFR 46.401)

FDA. Regulates all drugs, biologics, and devices used for diagnosis, treatment, and prevention of disease in humans and animals. Investigational products under FDA jurisdiction are highly regulated and are subject to several parts of Title 21 CFR:

- Part 11 (Electronic records; electronic signatures)
- Part 50 (Protection of Human Subjects).

- Part 54 (Financial Disclosure)
- Part 56 (Institutional Review Boards)
- Part 312 (Investigational New Drug Application (IND))
- Part 314 (Applications for FDA approval to market a new drug)
- Part 600 (Biological Products)
- Part 812 (Investigational Device Exemptions)
- Part 814 (Premarket approval of medical devices).

NOTE: If you are conducting a study with an FDA-regulated product, you must follow FDA regulations. If you are conducting a federally-funded study, you must follow 45 CFR 46. If you are conducting a federally-funded study *with* an FDA-regulated product...you must follow both sets of regulations.

The Common Rule was adopted in 1991 following a decade in which different government agencies had different requirements. Each agency defines its own jurisdiction. Many regulate only their funded research; others regulate products or activities. FDA has concurred with the Common Rule, but did not adopt the Policy in its entirety. FDA regulations and the provisions of the Common Rule are similar, although some significant differences exist. Most government agencies require funded institutions to submit an agreement assuring that all appropriate rules and regulations will be followed. Others, like FDA, inspect and audit institutions to determine compliance. All agencies require the use of an IRB.

STATE AND LOCAL LAWS

State and local laws and regulations supercede federal regulations as long as they are more restrictive and do not put the subject at increased risk. An investigator must be familiar with state and local regulations that may directly affect research, such as legal age of consent, legal guardianship requirements, and informed consent requirements.

INTERNATIONAL REGULATORY ENVIRONMENT

International Conference on Harmonisation (ICH) Guidelines (<http://www.ich.org/>). In recent years, regulatory authorities and industry associations have promoted international harmonization of regulatory requirements. One of the goals of the ICH is to identify and reduce differences in technical requirements for drug development within regulatory agencies among three regions: the European Union, Japan, and the United States. In the Federal Register of May 9, 1997, FDA adopted the ICH's "Good Clinical Practice: Consolidated Guideline," representing the agency's current thinking on good clinical practices. FDA chose to adopt the ICH GCP guidelines without making them regulation under the assumption that everything in the ICH GCP guidelines is already contained in current regulations.

REGULATORY WEB SITES

Canadian Standards Council
 CanReg, Inc
 Center for Biologic Research and Evaluation (CBER)
 Center for Devices and Radiological Health (CDRH)
 Center for Drug Evaluation and Research (CDER)
 Code of Federal Regulations
 Declaration of Helsinki (1987 version—recognized by FDA)
 Declaration of Helsinki (2000 version)
 Department of Health and Human Services (HHS)
 EMEA—European Agency for the Evaluation of Medicinal products
 EUDRANET—European Union Council Directives and Regulations
 FDA—Food and Drug Administration—Main
 FDA—Information Sheets
 Federal Register Online
 Health Canada Home Web Site
 ICH—Int'l Conference on Harmonization
 ICH Guidelines
 ISO - International Standards Organization
 NIH Online
 OHRP (Office for Human Research Protection)
 The Belmont Report

ADDRESS

<http://www.scc.ca>
<http://canreg.ca>
<http://www.fda.gov/cber>
<http://www.fda.gov/cdrh>
<http://www.fda.gov/cder>
<http://www.access.gpo.gov/nara/cfr/index.html>
<http://www.fda.gov/cder/guidance/ftud.htm>
<http://www.wma.net/e/policy/b3.html>
<http://www.os.dhhs.gov>
<http://www.emea.eu.int>
<http://www.europa.eu.int/eur-lex/en/search.html>
<http://www.fda.gov>
<http://www.fda.gov/oc/ohrt/irbs/default.htm>
<http://www.gpoaccess.gov/fr/index.html>
<http://www.hc-sc.gc.ca/english/index.html>
<http://www.ich.org>
<http://www.ifpma.org/ich5.html>
<http://www.iso.ch/iso/en/ISOOnline.openerpage>
<http://www.nih.gov>
<http://ohrp.osophs.dhhs.gov/>
<http://ohsr.od.nih.gov/mpa/belmont.php3>

Meeting Principal Investigator Obligations

The principal investigator (PI) must submit a signed and dated Form FDA 1572 (Statement of Investigator) to the sponsor before a sponsor is permitted to allow an investigator to participate in an FDA-regulated study. In signing the 1572, the investigator agrees to "... ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulation" (21 CFR 312.60). After the investigator has signed the 1572, the sponsor forwards it to FDA. This two-page document requests information specific to the investigative site and requires documentation of the qualifications of the investigator. The 1572 states the investigator's commitments and is considered a contract between FDA and the investigator.

NOTE: For example, only studies conducted under an IND require a 1572. Observational and postmarketing studies do not require a 1572.

INVESTIGATIONAL DEVICE REGULATIONS

Regulations differ somewhat for device studies. For example, an investigator completes an Investigator Agreement instead of a 1572. Regulations 21 CFR 50, 54, and 56 still apply, but in addition, 21 CFR 803, 812 and 814 govern investigational device studies. Specifically, investigator obligations can be found in 21 CFR 812.

1572 COMMITMENTS

- I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.
- I agree to personally conduct or supervise the described investigation(s).
- I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.
- I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.
- I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.
- I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

- I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.
- I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.
- I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

INVESTIGATOR REGULATIONS

Study Conduct. 21 CFR 312.53(c)

The investigator will *personally* conduct or supervise the investigations.

HELPFUL HINT: This responsibility CANNOT be delegated.

Human Subject Protection. 21 CFR 312.60

The investigator is responsible for protecting the rights, safety, and welfare of subjects under the investigator's care.

Investigator's Brochure (IB). 21 CFR 312.53(f), ICH 4.1.2

The investigator will read the IB and understand the potential risks and side effects of the drug.

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

- Administer the drug only to subjects under the investigator's personal supervision or under the supervision of a subinvestigator responsible to the investigator
- Give investigational drug only to those authorized to receive it
- Maintain adequate records of the disposition of the investigational drug, including dates, quantity, and use by subjects
- Return unused supplies of the drug to the sponsor, or otherwise provide for their disposition under § 312.59

HELPFUL HINTS: Ensure the person dispensing or administering drug has been properly trained to do so and is in compliance with any local or state laws (e.g., RN must have a doctor's order to dispense or administer drugs).

If alternative disposition is used, obtain written permission from sponsor.

Controlled Substances. 21 CFR 312.69

Store in securely locked, substantially constructed enclosure. Take adequate precautions to prevent theft or diversion into illegal channels of distribution.

Subject Medical Records and Other Source Documents. 21 CFR 312.62 (b), 21 CFR 312.68

Prepare and maintain adequate and accurate case histories that record *all* observations and other pertinent data required by the sponsor. Make the records available for inspection to any properly authorized officer of FDA (21 CFR Part 312.68).

HELPFUL HINT: FDA prefers to see the original source of documentation (i.e., where pen was first put to paper).

Record Retention. 21 CFR 312.62(c)

Maintain records (study files) for the study for 2 years after study discontinuation, drug approval or drug disapproval.

HELPFUL HINT: Some studies conducted under ICH Guidelines may require storage as long as 15 years. ICH 4.9.5.

Investigator Reports. 21 CFR 312.64, 21 CFR 54, ICH 4.10, 4.11, 4.13

Submit reports to sponsor at times required by regulations and the sponsor:

- Progress reports
- Safety reports: adverse events (AE) and serious adverse events (SAE)
- Final Report at study end
- Financial Disclosure

HELPFUL HINT: Financial Disclosure applies to the investigator and all those listed on the 1572. It also applies to spouses and dependent children of those disclosing.

Adverse Experiences. 21 CFR 312.64(b), ICH 4.11

Report adverse events (AEs) to the sponsor in accordance with 21 CFR Part 312.64.

Follow sponsor requirements for expedited reporting of serious AEs (SAE). Sponsor will define SAE criteria and timeframes for reporting in protocol.

IRB. 21 CFR 56, 21 CFR 312.66, ICH 4.4

- Assure that the IRB is in compliance with 21 CFR Part 56
- Obtain IRB initial and continuing review and approval of the study

- Promptly report all changes in the research activity and unexpected risks to subjects or others to IRB
- Do not make any changes in the research without IRB approval, except when necessary to eliminate a hazard to a subject

HELPFUL HINT: Follow IRB requirements for reporting.

Protocol Compliance. 21 CFR 312.66, ICH 4.5

Changes to the protocol to be made only after receiving sponsor and IRB approval except to eliminate hazard to human subjects.

HELPFUL HINT: If departure from protocol does occur, the nature of the departure and actions taken to prevent reoccurrence must be documented in study files.

Informed Consent and IRB Requirements. 21 CFR 50, 21 CFR 56, ICH 4.8

- Obtain consent in compliance with 21 CFR 50 and 56
- Obtain IRB approval of the informed consent prior to implementing the consent process with any subject
- Obtain informed consent before enrolling subject in study
- Provide subject with sufficient time to make decision about participating in study
- Ensure subject understands language in the consent form and the consent contains all the required elements
- Consent should not contain any language that is exculpatory or waives or appears to waive any of the subject's rights

Investigative Staff. 21 CFR 312.53(g), ICH 4.1.5

Ensure that staff are qualified, capable and trained to perform their study-related responsibilities. Keep personnel informed of study-related information and changes.

HELPFUL HINTS: Develop study-specific delegation list

Maintain records documenting how staff members were trained to perform their duties (e.g., on-site training by team member, through their licensing, etc.)

Maintain records on protocol-specific training

Investigator Disqualification. 21 CFR 312.70

Investigator may be disqualified for repeated or deliberate failure to comply with regulations or submitting false information to the sponsor.

Training Your Study Coordinator

The primary responsibility of the study coordinator (SC) or clinical research coordinator (CRC) is to ensure the smooth progress of the study from start-up to close-out through the day-to-day coordination of study operations. Although the Principal Investigator (PI) delegates many duties to the SC (and these delegated duties should be documented), the PI remains responsible, legally and ethically, and accountable for study operations and outcomes. The SC must comply with all the regulations that apply to the PI, and ensure the PI is informed and up-to-date on study subject and study-related issues.

The role and general responsibilities of the SC will depend on the allocation of responsibilities at the investigative site and the types of studies the site will be conducting. For example, some facilities may allocate budget preparation and negotiation to another individual or department. There are no specified educational requirements for study coordinators, although many have a clinical background and/or nursing degree. The PI must be realistic about what expectations are placed on the SC, and hire the right person to fulfill those expectations. The more the SC is qualified to do (e.g., phlebotomy, blood pressures, ECGs, etc.), the less he or she will be dependent on the investigator.

COMMON STUDY COORDINATOR TASKS

Administrative

- Marketing the site/securing studies
- Assessing the protocol
- Training study staff
- Preparing and negotiating study budgets
- Preparing and submitting documents to the IRB
- Interacting with sponsor (CRO), IRB, office staff, niche providers, other department personnel
- Tracking study budget, payments
- Maintaining regulatory files
- Documenting communication and study progress
- Documenting subject study visits
- Resolving queries on study data

- Transcribing source information to CRFs
- Coordinating, preparing for, and participating in monitoring visits, audits, and inspections
- Ordering study supplies and drug as needed

Subjects

- Recruiting subjects
- Developing and coordinating advertising
- Screening subjects for eligibility
- Discussing study and conducting consent process
- Scheduling study assessments and visits
- Ensuring all visits, tests and procedures are completed in required time intervals
- Interviewing and evaluating subjects at appropriate intervals
- Reviewing laboratory and clinical information for signs of adverse events
- Identifying, documenting, reporting and following up on adverse events
- Maintaining drug accountability
- Dispensing investigational product per protocol and under PI supervision
- Obtaining, preparing, and shipping biological specimens
- Coordinating study subject reimbursement

HIRING THE RIGHT STUDY COORDINATOR

The ideal SC is one who has clinical research experience, is able to conduct the procedures the site will be performing most frequently, and possesses the qualities listed below. When hiring an SC, write a job description identifying the minimum qualifications necessary and the activities the SC will be expected to perform. Also consider any licensure restrictions and state and local laws (e.g., is a Licensed Practical Nurse allowed to draw blood).

Desirable Qualities in a Study Coordinator

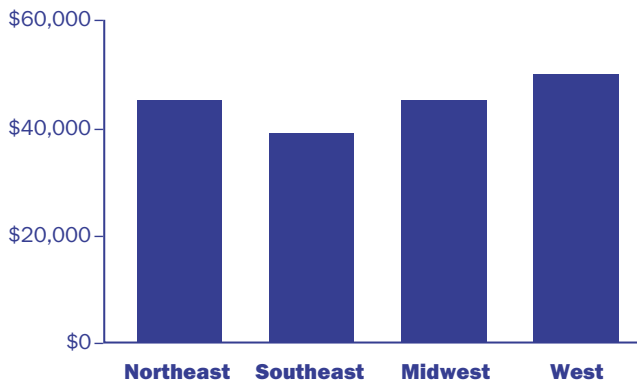
- Scientific/medical background

- Strong communication skills
- Excellent organizational skills
- Good interpersonal skills with patients
- Creativity and resourcefulness
- Ability to work independently
- Clinical research experience
- Good problem solving skills
- Strong conflict resolution/negotiation skills
- Ability to work flexible hours
- Good computer skills

Study Coordinator Salary

The SC's salary should consider salary ranges in the site's locale for study coordinators or other competitive positions (e.g., if hiring a nurse, what are the salary ranges of nurses in area hospitals, private practices, etc.). Other considerations in determining salary include degree of responsibility and independence, experience in clinical research, and available benefits package (Are the benefits competitive? If not, consider increasing the salary offer).

Average Study Coordinator Salary by Region (\$39,000–49,000)



MAINTAINING YOUR STUDY COORDINATOR'S JOB SATISFACTION

- Provide training and educational opportunities (for instance, if you hire an SC without clinical research experience, ensure he/she attends classes)
- Provide adequate work space and equipment
- Be accessible
- State your expectations regarding quality of work and human subject protection
- Discuss studies with your coordinator before accepting
- Stay actively and visibly involved in studies
- Listen to your coordinator—respect his/her issues and concerns
- Share the wealth: offer incentives and bonuses

CAUTION

With a competent and capable study coordinator, the PI will be able to delegate responsibilities with confidence. However, there are some study-related responsibilities that cannot be delegated:

- Overall responsibility and accountability for the study
- The Form FDA 1572: Only the PI can sign
- Determining relatedness (causality) of an adverse event to the investigational product
- Medical decisions, diagnoses, assessments and physical exams. These can only be done by a qualified medical doctor, unless otherwise stipulated by state law. For instance, some state licensing laws will allow a nurse practitioner or a physician's assistant to conduct physical exams. Although the law may allow it, some sponsors will want only a qualified physician to conduct physical exams.

REFERENCE BOOKS

Guide to Clinical Trials Bert Spilker
Guide to Good Clinical Practice Thompson Publishing Company
CFR/ICH Guidelines Reference Handbooks Barnett International
The CRC's Guide to Clinical Research CenterWatch
Lessons from a Horse Named Jim Margaret Liu, Kate Davis

Recruiting and Retaining Subjects

SUBJECT RECRUITMENT

The investigative site is responsible for recruiting and enrolling study subjects who meet the protocol's criteria for inclusion and exclusion. Remember that this recruitment process is considered part of the informed consent process. The following are some reasons sites do not meet enrollment goals:

- Ineffective recruiting from available resources
- Ineffective forecasting of number of subjects during the planning stages of the study
- Diversion of potential subjects to competing studies
- Improper understanding of the enrollment criteria
- Overly restrictive enrollment criteria
- Higher percentage of dropouts or more concurrent illness than anticipated

When approached about conducting a study, carefully assess whether your site can meet the enrollment goals in the time frame stipulated for the study. Sponsors would prefer that the investigator turn down a study rather than inflate their ability to meet enrollment goals.

Questions to Ask Before Accepting a Study

- What is the subject population? Do you have patients in your practice? If seasonal, is the enrollment period within the peak time?
- What is the enrollment timeline? If it is extremely tight, will you be able to enroll the number needed in the time frame required?
- Is the sponsor developing a central recruitment effort (central calling center, centralized materials, logos, etc.)? If, yes, what does that mean for the investigative site? If there is a centralized call center and two sites in the same area, how will the leads be distributed?
- Will the sponsor provide a budget for advertising materials? If yes, how much?

Establishing a plan for recruiting subjects is vital to meeting enrollment goals. The recruiting plan will vary based on the

subject population to be enrolled, how the site will access those subjects, and the time frame for enrolling. During the process of selecting investigators, many sponsors will visit the potential site to assess the facilities and discuss the study with the investigator. Have a basic recruiting strategy outlined to discuss with the sponsor.

SUBJECT RECRUITMENT SOURCES

Patients in the Practice

One of the more common places to find subjects is within the physician's own private practice. If the subject is interested, the informed consent must be signed before beginning procedures related to qualification requirements. If your site intends to expand its research capabilities, consider developing an authorization form asking the patient for their permission to enter their name in a research database at the site and permission to contact them if a research study becomes available (this is especially important when dealing with subjects recruited through advertising). Maintaining such a patient database can be a valuable asset in recruiting patients.

Subjects Referred from Other Physicians

Tapping into the medical community is another means of recruiting subjects for studies. Some physicians may be reluctant to refer their private patients to another private practice for participation in a clinical study. To overcome the more common concerns, a site may make the following assurances to physicians who have patients to refer.

- Participants who are referred and qualify will still be followed by the referring MD.
- The investigator will send information on study subjects' responses to the investigational product to the referring physicians—after the completion of the study, if the study is blinded.

Open communication with referring physicians contributes to a good working relationship and opportunities for future referrals.

Develop a template for letters to physicians who have referred their patients to the investigative site, informing them of the final enrollment numbers and thanking them for their assistance. If a referred patient is not enrolled as a subject, include the reason for exclusion, especially if the physical examination at screening revealed a medical problem.

Other Sources

You can find subjects through referrals from nonmedical sources. You can target advocacy groups for the particular disease state you are working with—such as the Arthritis Foundation, Lupus Foundation, Diabetes Association, or local senior centers. Mass research-oriented mailings for health care professionals and the community can educate the public while raising awareness of your research efforts.

Advertising

FDA considers direct advertising (i.e., advertising intended to be seen or heard by prospective subjects) to be part of the informed consent process as well as the subject-selection process. Therefore, IRB review and approval is required to ensure that the information is not misleading and that the ad is not coercive.

If sponsor or CRO anticipates difficulty in enrolling subjects, they may develop advertising materials for sites to use or implement a broad advertising campaign to enhance enrollment.

A site may also advertise for study subjects in its own community. All advertising, whether developed by the sponsor or the site, must have written IRB approval.

In general, FDA believes that advertising to recruit research subjects should be limited to the information prospective subjects need to determine their eligibility and interest. Advertisements may include the following information, when appropriately worded. However, this information is not required.

- The name and address of the clinical investigator or research facility
- The condition under study and the purpose of the research
- A summary of the eligibility criteria

- A brief list of the benefits of participation—such as a no-cost physical examination
- The time or other commitment required of the subjects
- The location of the research and the person or office to contact for more information

SUBJECT RETENTION

Once recruited, subjects may withdraw from a study for several reasons. Some major obstacles to retention can be:

- The study is long or there are numerous tests and procedures
- No improvement in the subject's disease state
- Lack of customer service, including uninterested staff, long waits to be seen with no explanation or apology, difficulty in contacting research staff, or no contact between visits
- Lack of physician involvement or contact. In clinical research, the subject provides a service to the study. The physician should accord the subject the appropriate respect for that service.

Overcoming These Obstacles

- Stay in contact with subjects at least monthly, if the study is long-term. (Make reminder telephone calls the day before a scheduled visit.)
- At each visit, briefly review the informed consent form and ask if subjects have any additional concerns or questions.
- Say thank you, but also thank them in other ways such as sending birthday cards.
- Ensure that staff maintain patient confidentiality and are friendly, enthusiastic and professional in all patient encounters.
- Pay attention to your subject population's special needs. For example, in a study of the elderly, transportation may be an issue. Can the site pay for transportation such as taxis or pickup vans?

Managing the Study Budget

Whether you are developing your own budget or the sponsor presents you with one, the budget should cover all study-related costs and overhead. If a budget presented by a sponsor is inadequate, you will need sufficient evidence to support your request for additional funds. In addition to identifying costs at your facility, it may be helpful to survey other medical facilities in the area to identify their standard charges. The more ammunition you have in support of reasonable and customary costs in your area, the better your chance of obtaining additional funding.

THE CONTRACT OR AGREEMENT

Besides budget considerations, there are other variables in the study agreement (contract) that could affect the financial viability of a study:

- Will the sponsor cover IRB and advertisement costs?
- Will screen failures be paid? If so, how much and when?
- Will the site receive prorated payment for subjects who are terminated, drop out, or are lost to follow-up? If so, how much and when?
- When will study payments occur? What will trigger the payments (e.g., patient enrollment, completed CRFs)? How does the payment cash flow affect your site?

Ask for (you may not always get it, but it doesn't hurt to ask):

- Up-front payment (e.g., 10%) to defray the cost of start-up work such as preparing regulatory documents, attending investigator meetings, site initiation training, enrollment efforts, etc.

- Payment based on procedures performed
- Monthly payments
- Cancellation fee; either a percentage of budget or a fixed fee

DEVELOPING THE BUDGET

- Identify fixed costs for procedures and tests (e.g., x-ray, CBC). Do not include costs of standard-of-care treatments that will be reimbursed by insurance carriers.
- Figure overhead costs of 15%–25% (more if working within an academic center).

- Define fixed vs. hourly charges for study staff time (e.g., MD charge for physical exam is \$200/exam vs. \$200/hour). Hourly rate = annual salary ÷ 2080. For every hour spent with a subject, estimate 1.5 hours of paper work.
- Identify your projected profit margin (applies to for-profit facilities only) and roll the % into line items. For example, if projected profit margin is 10%, and the charge for a physical exam is \$200:
 $\$200.00 \times 10\% = \20.00
 $\$20.00 + \$200.00 = \$220.00$, the cost of procedure with profit margin included.

SAMPLE SPREADSHEETS

Sample Spreadsheet I—Subject Charges

Item	# Required During the Study	Cost/Item	Total Cost
Colonoscopy	2	\$850	\$1700
Parking passes	8	\$5	\$40
Urinalysis	2	\$15	\$30
Pregnancy test	1	\$4	\$4
Total cost/subject			\$1774

Sample Spreadsheet II—Study Personnel Time (Enrollment Goal = 15 Subjects)

Staff	Task	Estimated Time (hours or fractions of hours)	Frequency of Task	Total Hours	Hourly Cost	Total Cost
Study Coordinator	Review protocol	2.5	1	2.5	\$23	\$57.50
	Conduct informed consent	1.0/subject	15	15	\$23	\$345
PI	Review protocol	2.0	1	2.0	\$100	\$200
	Physical exam	1.0/subject	15	15	\$200	\$3000

BUDGET CONSIDERATIONS

Consider the following when developing a budget. Study budget line items will vary depending on the nature of the study and the location where subjects will be seen (e.g., private practice vs. academic center).

Location of Subject Visits (hospital, clinic, MD office)

- Outpatient clinic room charges
- Inpatient room rates (what does the room rate include—medications, supplies, equipment, etc.?)
- Niche providers (e.g., free-standing radiology facility)

Overhead

Consider the many costs that make up overhead, including rent, phone/fax bills, utilities, copies, storage facilities, and support staff salaries. Time spent in negotiations, at investigator meetings, transcribing, and talking to subjects can also be considered as overhead, or included in separate line items with SC and PI time.

Who Will Be Seeing the Subject?

Account for the time of all study personnel involved in the study:

- **Study coordinator/clinical research coordinator (SC/CRC):**
See the enclosed document “Training Your Study Coordinator” for a complete discussion of the SC’s many duties.
- **Administrative:**
 - Study accounts receivable and payable
 - Processing subject reimbursements
 - Reconciling sponsor payments with milestone requirements
- **Technical/professional staff:**
 - Services provided by other groups (blood draws, procedures)
 - Computer programming for devices or special study equipment
- **Investigator and subinvestigators:**
See the enclosed document “Meeting Principal Investigator Obligations” for a complete discussion of the PI’s duties.

Subject-related Costs

Consider all hospital charges associated with procedures, including the technical charges associated with specific clinical procedures (e.g., ECG, CXR), as well as supplies, equipment, and medications. There may also be additional professional fees associated with specific clinical procedures:

- **Study-specific procedures:**
 - Initial history and physical exam
 - Subsequent physical exams and symptom evaluation
 - Vital signs
 - Tests or procedures done by study staff (e.g., ECG, X-rays)
 - Incidentals such as subject meals, parking, or travel
 - Research subject reimbursements or stipends
 - Administrative costs—fax, telephone, office supplies

- **Laboratory services:**
 - Phlebotomy fees
 - Lab supplies (e.g., vacutainers, needles, dry ice)
 - Processing or shipping to outside lab
 - In-house lab processing and analysis
 - Biological specimen storage
 - CLIA waiver/license application
- **Pathology services** may charge fees for preparing and reading slides
- **Pharmacies** may charge initiation fees, per-patient dispensing fees, or randomization and blinding/unblinding fees.
- Having procedures done outside of practice (such as Radiology) may incur fees for conducting procedures and reading procedure results.

Up-front Charges

- IRB fees
- Pre-study and Investigator meetings can create costs in terms of PI/SC preparation and time, travel costs (meals, hotels, airfare, etc.), and study-specific procedure training (if required)
- Study-specific equipment (e.g., glucometer, EKG machine)

One-time Charges

- Potential AE-related charges. If insurance does not cover treatment associated with AEs, will sponsor pay? Estimate the likelihood and incidence of AEs associated with the use of the investigational product.
- Subject-specific one-time charges (e.g., pregnancy test, CXR if not done within last year.)
- Records storage: Where and how long?
- Required FAA certification for shipping of biological products

What Can go Wrong

An inaccurate budget can spell financial disaster. Some common flaws in study budgets include underestimating the time commitment for the SC, failing to include overhead, failing to secure payment for screen failures, lack of money for subject recruitment, and unforeseen protocol revisions changing the amount of work to be done. Be prepared!

Study Feasibility/Protocol Assessment

An important part of an investigator's responsibility is to perform a thorough and thoughtful review of any protocol offered for consideration. Pharmaceutical companies know the required quality systems and regulatory expectations that surround the conduct of a clinical trial. What they need from their investigators is expert scientific and medical input, including a rigorous critique of their study goals and objectives, as outlined in their protocol design. The protocol should be assessed from four perspectives: scientific, regulatory, ethical and feasibility.

Key points to determine before you conduct your review:

- Is this a draft protocol or the final version?
- What are the study objectives?
- What phase study is this study?
- Is this a single or multicenter study?
- What is the total number of subjects to be enrolled?
- What is the total number of subjects per site to be enrolled?
- How many study visits are required?
- What procedures are to be performed at each study visit?
- What is the length of the study?
- What are the inclusion and exclusion criteria?

SCIENTIFIC CONSIDERATIONS

- Does the study's design support its objectives?
- Are the objectives and expected outcomes clearly expressed?
- Are the data to be collected appropriate for determining the product's safety and efficacy?
- Are the inclusion and exclusion criteria realistic for the disease under investigation?

REGULATORY CONSIDERATIONS

A protocol is required by regulations to contain the following information (21 CFR 312.23 (a) (6) (iii)):

- A statement of the objectives and purpose of the study
- The name and address and a statement of the qualifications (such as a curriculum vitae) of each investigator, and the name of each subinvestigator (e.g.,

research fellow, resident) working under the supervision of the investigator, the name and address of the research facilities to be used, and the name and address of each reviewing IRB

- The criteria for patient selection and for exclusion of patients and an estimate of the number of patients to be studied
- A description of the design of the study, including the type of control group to be used, if any, and a description of methods to be used to minimize bias on the part of subjects, investigators, and analysts
- The method for determining the dose(s) to be administered, the planned maximum dosage, and the duration of individual patient exposure to the drug
- A description of the observations and measurements to be made to fulfill the objectives of the study
- A description of clinical procedures, laboratory tests, or other measures to be taken to monitor the effects of the drug in human subjects and to minimize risk.

NOTE: The specific elements and details of the protocol are dependent on the phase of the study.

ETHICAL CONSIDERATIONS

- Are the risks to the subject minimized?
- Are the risks reasonable in relationship to the knowledge or benefits to be gained?
- Is subject selection equitable?
- Are there errors or inconsistencies in the protocol that affect the site's ability to recruit subjects ethically?

FEASIBILITY CONSIDERATIONS

Assessing the feasibility of conducting a clinical study involves comparing the investigator's present schedule, professional obligations, facilities, and staff with the study's requirements for enrollment and the overall quality of the protocol's design. If specific aspects of the protocol present problems for the site, the investigator should discuss them with the sponsor's representative. In some cases, a sponsor may be willing to make adjustments to accommodate the concerns of a particular site; this is more likely in a study with only a small number of sites.

Consider the following questions while assessing your site's suitability for a particular investigation.

- Does your site have the resources to meet all the requirements of the protocol—study population, staff, facilities, equipment, supplies, and time?
- Is the site able to enroll subjects and treat them according to the protocol?
- Is there a potential workload that is not specified—e.g., the time needed for reporting and following up on adverse events?
- If the site is using a local IRB, can the IRB provide approval within the time frame necessary for initiating enrollment?
- Will enrollment compete with other studies?
- Are inclusion and exclusion criteria reasonable? How will they affect enrollment?
- Does the study have any special or unusual requirements—e.g., visits to subjects' homes?
- Will compliance to the study be difficult for the subjects?
- Do requirements for drug or device storage pose a problem?
- Is your space adequate?
- Does your site have the necessary equipment? If not, will the sponsor provide it? Does the site have the right brand of equipment? Can you borrow equipment from other departments?
- Will other departments (e.g., pharmacy, laboratory, x-ray) be able to meet the requirements of the protocol for conducting procedures and tests? Are laboratory tests required at times when the laboratory is closed?
- Will study procedures be required at inconvenient times (during shift changes, on weekends, evenings)? Will shift requirements result in overtime costs?
- Will demands placed on key personnel be excessive?
- How will staff be trained? Will there be sponsor training for the staff to administer procedures and tests? Will there be hiring and training of new staff, or training of staff members in a situation where multiple studies are in startup—all requiring additional training and commitment of time?
- Is the staff qualified to conduct all the tasks and procedures required for the study? Can more than one per-

son do the tasks required if reassignment becomes necessary?

- How will potential staff turnover, vacations, and leaves of absence affect the conduct of the study?
- Does the investigator have enough time for the study? Although US federal regulations do not mandate how much time a principal investigator must devote to a study employing other physicians, FDA expects to see evidence of appropriate oversight.
- Is the staff motivated to participate in the study?

HELPFUL HINTS

- Have other staff (especially study coordinator) review the protocol. Ask for their feedback—listen!
- Know your patients: If you have a patient database, search by ICD-9 diagnosis code. How many patients with each diagnosis, how many patients with each diagnosis of interest, how many patients with diagnosis are seen/month, how many are research-naive?

SUGGESTED FORMULA FOR DETERMINING POTENTIAL NUMBER OF SUBJECTS

- 1 Divide the number of patients in your database by 2 to estimate the number of patients that might qualify to screen.
- 2 Divide that number by 2 to estimate the number of patients that might consent to be in the study.
- 3 Apply the estimated screen failure rate to this number to determine the number of patients you could plausibly randomize in this trial.

Be careful! This formula depends on the protocol. For example, if patients with asthma have to have a required number of Albuterol puffs/day, what percentage of patients in your practice meet that criterion? If it is 20%, apply this to the formula first.

Sponsors assessing your readiness to participate in research will conduct on-site qualifying visits to determine if your facility meets study requirements. A dedicated research area within your practice is ideal; if this is not feasible at first, ensure that the space you are using is not only functional for research purposes, but would meet the basic requirements for most clinical trials.

GENERAL ENVIRONMENT

You only get one chance to make a first impression. The areas where subjects will be seen and research office activities will take place should be clean and well-organized. The waiting area for study subjects should be comfortable and well-lit.

SECURE DRUG/INVESTIGATIONAL PRODUCT (IP) ROOM.

This applies to any area where IP will be stored, i.e., doctor's office, pharmacy, etc.

Secure means limited access and out of the general flow of patients and staff. Although federal regulations do not require it, most sponsors will require these rooms or cabinets be locked. If your study includes a controlled drug, the storage area must be locked.

Refrigerator, freezer and shelving to store products. Consider locking cabinets to increase security and minimize dust and clutter. Refrigerators should be clearly labeled for food, specimens, or study drug.

Thermometers. Protocols will state the temperature range for investigational drug storage. Demonstrate your compliance with this requirement by providing daily documentation of the temperature of the area where drug is stored (e.g., the room, refrigerator, etc.).

Backup plan for loss of electricity. Consider how you would maintain storage requirements if you lost electricity, including the loss of air conditioning if you live in a hot/humid climate.

EXAM ROOMS

Exam rooms should comply with local, and state requirements, if any, and OSHA requirements. <http://www.osha.gov>

OTHER STORAGE AREAS

There should be dedicated space to house other study-related materials:

- Laboratory kits. If a central lab will be used for a study, all supplies necessary to obtain biological specimens will be provided to the site.
- Medical records and subject case report form books (also called casebooks or CRFs). These are usually the standard 3-ring binder size but can be rather thick.
- Filing cabinet(s) for storage of study-specific regulatory files or binders and other study-related documentation
- Post-study storage of materials (if your space is limited, you will need to identify climate-controlled off-site storage space)

WORK SPACE FOR STUDY COORDINATOR AND MONITOR

The study coordinator will need dedicated office space to meet with potential and enrolled subjects and to conduct the operational aspects of the study (i.e., budget development, regulatory document completion, transcription, etc.).

Many studies will require frequent on-site visits by the sponsor's or the CRO's monitor. The ideal space for a monitor is in a quiet location where confidentiality of other studies is not compromised, and will provide enough desk space to accommodate both an open medical record and an open case book. In addition, easy access to a telephone, copier and fax machine are beneficial.

COMPUTER AREA WITH DATA PORTS

Some studies will involve capturing subject data electronically. This may require accommodating sponsor-specific hardware and software. A site conducting several studies involving electronic data may have to accommodate several computers or laptops.

Site computers with subject/patient data should be secure and password-protected.

LABORATORY

Clinical Laboratory Improvement Amendments (CLIA) Certification. If your site has its own laboratory, sponsors will require documentation of a CAP or CLIA Certificate or a Certificate of Waiver. <http://www.cms.hhs.gov/clia/>

Dangerous Goods Training Requirements. Any entity that is preparing dangerous goods for shipping (e.g., infectious specimens, dry ice) must complete required training. <http://www.saftpak.com/>

EQUIPMENT

Document that your equipment has been maintained/calibrated according to manufacturer's specifications.

Initially, getting the business can be a challenge! But consistently meeting enrollment goals and providing quality work and data will contribute to your reputation in the industry and turn that initial business into repeat business.

1. Network with colleagues who are already conducting research. Can you function as a subinvestigator (or co-investigator on NIH studies) with your colleague? Ask your colleague to refer you to the sponsor or CRO.

2. Be prepared to market your site. Identify your strengths as a site: access to subject population, naïve subject population, facilities, staffing, etc.

- **Develop a site profile.** What makes your site unique? Include staff and specialties. Create a comprehensive list of physical facilities and storage areas. List any trial experience, particularly emphasizing enrollment goals met, especially those met ahead of schedule.
- **Create site CVs.** Standardize format, margins, spacing, and font for a professional, uniform look. Eliminate any irrelevant information. Many sponsors will request an updated research experience section with a “revised” date on each page, and require a signature and date on the CV.

3. Develop marketing materials for distribution.

- **Generate a standard cover letter.** Keep the tone formal and businesslike, and limit the letter to one page. Incorporate a mention of a mutual colleague and enclose references. State follow-up action you will take. Provide a name, address, phone numbers, and e-mail for site contact.

- **Develop a logo** if you don’t already have one. Use this logo on your cover letter as well as in the design of business/rolodex cards.

4. Increase your site’s visibility

- **List your site** at one of the internet site listing services such as www.centerwatch.com or www.clinicalinvestigators.com. Note that this can be expensive.
- **Profile your site** at an internet site-profiling service such as www.fast-track.com, www.invantage.com, www.acurian.com
- Become involved in your community. Attend health fairs and set up a display for your facility; you can even conduct screening at these events. Conduct or participate in seminars pertinent to your areas of research. Give something back to the community: become a source of information (handouts, etc.) on subjects related to your areas of research—this helps attract the volunteers you’ll need.

5. Mine other sources for leads:

- Talk with sales representatives
- Make cold calls to sponsors/CROs
- Set up exhibit booths at conferences (and visit sponsor and CRO booths at conferences)
- Read advertisements in industry publications
- Attend professional meetings
- Attend research meetings, conferences, and symposia

6. Use available resources:

- *CenterWatch* (*TrialWatch*, free with *CenterWatch* subscription, is a useful source for leads)
<http://www.centerwatch.com>
- FDA websites
<http://www.fda.gov>
- NIH websites
<http://www.nih.gov>
- *Clinical Trials Advisor*
<http://clinicaltrialsadvisor.com>
- *Clinical Researcher*
<http://www.clinical-researcher.com>
- *Drug Information Association (DIA) Journal*
<http://diahome.org>
- *Research Practitioner*
<http://www.researchpractice.com>

7. Develop your business. Improve your space and acquire appropriate equipment. Create systematic methods to track patients. If you do not have access to a local IRB, identify a central IRB.

Growing your business requires developing a trained, dedicated staff with a knowledge of GCP. You may need—

- A clinical research coordinator
- A regulatory document specialist
- Research assistants
- Administrative assistants
- A research manager
- A marketing manager\patient recruitment specialist
- An accountant

HEALTH PORTAL	ADDRESSES
WebMD	http://webmd.com
CenterWatch	http://www.centerwatch.com
Clinical Trials	http://clinicaltrials.gov
Veritas	http://www.veritasmedicine.com
Acurian	http://www.acurian.com
Medscape	http://www.medscape.com
Health Finder	http://www.healthfinder.gov

Duke Clinical Research Institute

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IR@DCRI.DUKE.EDU**

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**COMPLETE THE INVESTIGATOR INFORMATION SHEET AT
WWW.DCRI.DUKE.EDU/INVESTIGATOR**