CHAPTER 13

Clinical Research in an Allergy Practice

Cheryl K. Bernstein, RN, BSN, CCRC
David I. Bernstein, MD
Iftikhar Hussain, MD, CPI

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INTRODUCTION

A clinical research center can be a successful part of a clinical allergy practice provided that necessary infrastructure is in place. This chapter will identify the basic business model, infrastructure requirements and key personnel necessary to establish a successful center.

THE SPONSOR AND SITE SELECTION

A pharmaceutical company may contact a clinical research site directly, or through a contract research organization (CRO), to determine whether the site center is qualified and interested in participating in a clinical trial. The first contact may be in the form of a simple question: "Is your center interested in participating in this clinical trial?" The sponsor will describe very briefly in a synopsis the study and patient population needed. If the research site is interested in learning more about the trial, both parties will be required to sign a Confidentially Disclosure Agreement (CDA). This contract allows the sponsor and clinical research center personnel to openly discuss the study, while protecting the confidentiality of proprietary information.

The next step is for the site to complete a site feasibility survey. Sites are selected based on the site survey responses combined with information collected from the onsite visit evaluation. The site should complete the site survey accurately, using proper grammar and spelling. The survey inquires about accessible patient populations, subject enrollment and recruitment strategies, experience and expertise of site personnel, available equipment, and layout of the facility. Candid and accurate completion of the form is essential. The sponsor/CRO is looking for realistic patient recruitment estimates and the center's ability to successfully recruit, randomize and complete the clinical trial. If a site has limited experience with recruitment of the patient population being studied or has insufficient staff and equipment, it is better to decline the clinical study rather than accept and fail to meet recruitment goals. Once a site commits to recruiting a specific number of subjects, that number is used as a benchmark by the sponsor to assess overall performance, and may help determine if the site is considered for future clinical trials by the sponsor. Preferred sites for future studies are those that have met or exceeded subject recruitment, enrollment and randomization goals; sponsors also

prefer those sites with subjects who are protocol compliant and adherent, and have experienced a relatively low frequency of screen failures.

After reviewing information from the site feasibility survey, the sponsor may plan a site evaluation visit (SEV). It is essential that the principal investigator (PI) be available on site to meet with the sponsor/CRO to discuss the clinical trial. A knowledgeable and experienced clinical research coordinator (CRC) is also important. Ideally, the CRC who meets with the site visitor is a senior research staff member who is knowledgeable in institutional review board (IRB) procedures and experienced in conducting clinical research trials. During the tour, the CRC should discuss how the subjects will be consented/assented, assessed and managed. The center personnel must be able to demonstrate their knowledge of guidelines of Good Clinical Practice/International Committee on Harmonization (GCP/ICH). Recruitment strategy should be discussed during the site tour, and the PI must show he/she is actively involved in providing direct oversight and supervision of existing clinical trials. The sponsor/CRO needs to know that the research center will complete the clinical trial with qualified subjects and will follow and adhere to GCP/ICH guidelines and Food and Drug Administration (FDA) requirements.

Site selection is globally competitive. According to Center Watch, only about 33% of the clinical trials sponsored by pharmaceutical companies are conducted in the United States. Respiratory and allergic rhinitis trials are conducted in sites including Canada, Russia, Hungary, Poland and South America. The U.S. FDA rules and regulations apply to countries outside the United States.

Good Clinical Practice (GCP) is defined as "a standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected" (Guide for Good Clinical Practice, E 6 [R1]). GCP is concerned with the protection of human subjects and protects the rights and safety of the subjects involved in clinical trial investigations. GCP also is concerned with the protection of future patients who may receive the approved product based on study results in the marketing application.

ICH and technical requirements for registration of pharmaceuticals for human use (ICH guidelines) are unique in bringing together the regulatory authorities and pharmaceutical industries of Europe, Japan and the United States to discuss scientific and technical aspects of drug registration. Since its inception in 1990, ICH has evolved through its ICH Global Cooperation Group to respond to the increasingly global face of drug development. Thus, the benefits of international harmonization for better global health can be realized worldwide. ICH's mission is to achieve greater harmonization to ensure that safe, effective and high-quality medicines are developed and registered in the most resource-efficient manner. Please refer to the U.S. FDA website for more information, www.fda.gov/RegulatoryInformation/Guidances/ucm122049.htm.

In order to participate in a clinical trial, the investigator and all study personnel directly involved with the clinical trial must pass the required GCP and protocol-specific training provided by the

pharmaceutical company. The site staff also can become certified in clinical research by several professional organizations specializing in certification and testing. The Association of Clinical Research Professionals (ACRP) and Society of Clinical Research Associates (or SoCRA) are well-respected organizations that provide information and training. The ACRP provides programs and certification in the United States and overseas. Certification is not mandatory but is helpful for demonstrating the overall professional competency of site personnel at the center during the site selection process. It is important that the research staff receive training and certification in the following areas before conducting research activities.

Protecting Human Subject Research Participants certification course: It is free from the NIH website. http://phrp.nihtraining.com/users/login.php

GCP training certification course: It is available free from the NIAID website. https://gcplearningcenter.niaid.nih.gov/Pages/default.aspx

Dangerous Goods Training and certification course: This course is required to ship biological specimens and meet IATA requirements. It is also available free from the Mayo Clinic website. www.mayomedicallaboratories.com/education/online/dangerousgoods/

BASIC BUSINESS MODEL

Intelligent design of the facility and infrastructure of a new research center, and careful hiring of research staff, will likely determine success and level of profitability. Some centers hire staff for specific roles, and each staff member completes a specific job responsibility and task. For example, some centers have patient recruiters, phlebotomists, pulmonary function technicians, CRCs and secretarial staff who complete the case report forms. This model may work for large centers but is expensive to operate. An organizational model, which seems to be more cost-effective for conducting asthma, allergy and respiratory trials, follows the critical care nursing model of "primary care." Research coordinators are trained to perform all aspects of the clinical research trial including recruiting subjects, conducting the study visits and procedures, drawing blood, pulmonary function testing, and completing source documents and case report forms. The coordinator responsible for the trial also attends the investigator meeting and the initiation visit. If the protocol is complicated, with many procedures and time-sensitive tests, a team approach is advised. Several coordinators assist the primary coordinator to complete the visits as per protocol. In the "primary care" research center, all staff members are trained as CRCs and should be prepared to fill in for an absent primary coordinator. Each staff member may have additional responsibilities and roles, but ultimately each is responsible for successful completion of their assigned clinical trials.

THE RESEARCH CENTER INFRASTRUCTURE

Clinical research requires designated space for study supplies, investigational drugs, documents, research staff, monitors, auditors and clinical research subjects. The following is a list of minimum requirements:

1) Locked and secure drug storage, with limited access to only study personnel.

2) Exam and treatment rooms for clinical research subjects.
3) Adequate workspace for clinical research staff.
4) General office equipment (printer, fax, paper shredder, dedicated modem lines/high speed Internet, wireless access for sponsor/CRO and guest).
5) Adequate office space including shelf space to store case report form records, case books and documents. Secure area for long-term storage of study documents.
6) Internet access for research staff plus monitors and computers.
7) Private workspace for CRAs (clinical research associates who are responsible for monitoring and reviewing the source documents and records of the study subjects). The CRA works for the pharmaceutical company or CRO and is the main contact for the research staff during the clinical trial. The CRA audits all the records and reports findings following the monitoring visit.
8) Office space for meetings, sponsor and FDA audits.
9) Quiet and private area for patients to read and sign the informed consent form (ICF). Review the FDA's publication, "A Guide to Informed Consent—Information Sheet," 21 CRF 50.20; 21 CRF 50.25 and 21CRF 50.27. The signing of the ICF/assent form is a process outlined in the FDA Code of Federal Regulations. It is important to document that the subject signed and dated the ICF before any study-related procedures were done. The subject should always receive a copy of the signed and dated ICF form.
10) Equipment that includes accurate and well-maintained spirometry equipment; laboratory processing equipment; possibly a refrigerated centrifuge; barometer, thermometers and humidity gauges; -30˚ to -80˚C freezer (-80˚C freezer needed for most pharmacokinetic study participation); and ECG machine and special equipment required by some protocols, which may be supplied by the sponsor.
11) Emergency equipment and medication, with staff CPR certification and training in basic life support.
12) Required logs. Maintenance of logs includes: study drug room temperature logs for storage closets, refrigerators and freezers; daily spirometry and yearly calibration spirometry syringe validation; laboratory equipment and blood pressure device calibration, maintenance, and so forth.
13) Comfortable waiting room for patients and family for extended study office visits, which includes a TV, computers, rest areas, and eating area for meals.
14) Basic documents updated yearly, to include: standard operating procedures (SOPs) that include job descriptions for the research staff; Clinical Laboratory Improvement Amendments, or CLIAs; staff training documents including department meetings; IATA certification, prior FDA audits, electronic signature letter to FDA, HIPAA-covered/non-covered entity, and certification; CV updated and signed; protocol document training; and licensure for all research staff including the PI, CRCs and sub-investigators.

15) Posting of a profile on Center Watch and on your own company website can be helpful, because patients and potential sponsors/CROs may contact your center based on your information.

THE CLINICAL RESEARCH TEAM

Principal Investigator (PI)

An effective clinical research team begins with an involved and knowledgeable PI who has expertise in the diseases and medical specialty to be studied. The PI is generally an MD or DO and is responsible for all the clinical research activity, patient care, decision making and staff; and must demonstrate direct oversight throughout the clinical trial. The PI reviews, assesses and signs laboratory records, pulmonary function tests, ECG readings and all test and procedures ordered during the clinical trial. The PI determines subject eligibility for screening and randomization according to the inclusion/exclusion criteria. He or she assesses all adverse events and serious adverse events, and provides appropriate medical decisions and care. The PI reviews all subject source documents and signs off on the case report forms at the end of the clinical trial. He or she is required to be available during the monitoring visits and should read and sign the monitoring reports provided by the monitor during the frequent review visits. Basically, the PI is responsible for everything involved with a clinical trial, and must demonstrate complete oversight and active participation during it.

Sub-investigator

Sub-investigators can be physicians, nurse practitioners or physician assistants who are licensed to make medical decisions and medical assessments throughout the clinical trial when the PI is not available. The PI, however, must review the source records and then sign and date all assessments and evaluations completed by sub-investigators.

Clinical Research Coordinators (CRC)

The CRC is a registered nurse, licensed practical nurse, respiratory therapist, medical assistant or other health care professional who is detail-oriented, accurate, self-directed and self-motivated, and has strong interpersonal and medical assessment skills including a desire to be an excellent CRC. The CRC also can be the PI and the sub-investigator. The CRC is responsible for understanding, becoming knowledgeable in and adhering to the clinical trial protocol. The CRC actively participates in recruiting qualified subjects (patients) for the trial according to the inclusion/exclusion criteria, and conducts the test and procedures according to the specific protocol training. The CRC is usually the first-line contact for the CRA/monitor who is visiting the site and reviewing the source documents, subject diaries, case report form books (usually electronic) and patients' clinic charts for accuracy and subject study eligibility. The CRC carries out all protocol and study requirements such as, but not limited to, subject recruitment, study drug dispensing, drug accountability, record keeping, development and completion of source clinical trial documents, patient scheduling, patient education and specific study training (electronic diaries, taking study medication, electronic diary completion), blood drawing and study-related procedures and tests.

The CRC and PI are responsible for following and adhering to the protocol, and following GCP guidelines and requirements.

The CRC also can prepare adverse event reports to the IRB. Some centers have regulatory personnel who are responsible for the IRB submissions and ongoing reports. Our center, Bernstein Clinical Research Center, LLC has an experienced CRC who completes the initial IRB submissions for all clinical trials, and then shifts the responsibility for collection of IRB reporting information to the CRC assigned primary responsibility for the trial. The PI reviews and signs all IRB reports and submissions, and is responsible for the accuracy and completeness of the report.

The organization and job description of the CRC are crucial for the center's success. Mentoring and training new CRCs is extremely important, and is key for successfully completing the clinical trials. Certified CRCs with strong leadership mentoring skills are promoted at Bernstein Clinical Research Center as supervisors, and are responsible for the development and training of new staff. The new CRC is trained and mentored by an experienced coordinator on recruiting, screening, randomizing and performance of study procedures according to the study protocol.

The certified CRC demonstrating excellence as a supervisor is promoted to our next level, which involves management responsibilities that include new study inquiries, site tours, completion of the feasibility survey and the confidentiality agreement, IRB submissions, and tracking of budget payments and invoices.

STANDARD OPERATING PROCEDURE (SOP)

Standard Operating Procedures are detailed instructions to achieve uniformity of performance of a specific function. Sponsors/CRO and the FDA will request to review the SOPs during the initial site visits and audits. The SOPs need to include the roles and responsibilities of the entire research staff including the PI, all procedures and test performed, departmental procedures, the Informed Consent Form Process, IRB submissions, management of anaphylaxis and emergencies, and all aspects of conducting clinical trials incorporating the principals of ICH and GCP guidelines. During an audit, the SOPs will be used to verify the research center's conduct of the clinical trial procedures according to the ICH/GCP guidelines and the specific protocol.

CONTRACT AND BUDGET NEGOTIATION

The proposed contract/budget is sent to centers selected to participate in the clinical trial. By that time, site personnel already have signed the confidentiality agreement and completed the Site Feasibility Questionnaire, so that the protocol can be reviewed with the representative from the company or CRO during the site visit and tour.

Contract

When the PI and site personnel receive the contract and budget proposal, it is important to read all sections and parts of the contract. The language can be confusing even for experienced site personnel, so it is recommended that an attorney experienced in clinical research contract law review the document.

After the initial review is completed, the attorney may find some areas of concern and recommend language modification. The new language should be submitted to the company and a new revised contract will be sent to the research center. After the contract has been negotiated and completed, an attorney should review the contract again before the final contract is signed and dated.

All aspects of the contract are important, but some areas are particularly important and require special attention. The first paragraph of the contract lists the **parties** involved, and should include only the clinical research site and physical address and not the PI's name, which incurs personal liability. The sponsor/CRO's name and physical address also are included as the Party.

The site's medical malpractice carrier should be notified that the site is planning on participating in clinical research. The insurance carrier most likely will request to review protocols before providing insurance. The dollar amount of insurance liability provided by the carrier should be at least the amount stated in the contract. The liability insurance also is based on protocol adherence and GCP. The attorney representing the site will assist in negotiating proper language for protocol adherence. Sometimes the contract states "strict" or "complete" adherence to the protocol. It is important to negotiate the removal of the word "strict" or "complete," because minor protocol deviations/violations often occur (i.e., subject visits that occur outside the designated protocol schedule). Additional insurance for liability, **errors** and **omissions** can be added for more comprehensive liability coverage.

Identification of proper indemnification language is extremely important/crucial for the financial success of the research center. It is extremely important that the PI **does not** sign a contract with reciprocal indemnification or cross indemnification even if the clinical trial appears to be simple and easy to complete. An example of reciprocal indemnification language is: "*The Site shall indemnify, defend and hold harmless Sponsor and its Affiliates and their respective employees, agents, officers, directors, contractors, licensees, successors, assigns and representatives.*" Your malpractice insurance carrier may negate your insurance coverage if you agree to reciprocal indemnification in the research contract.

The following is an example of indemnification language used in the clinical contract:

Sponsor *agrees to indemnify, defend and hold harmless the Site, its employees, trustees, directors, officers, sub-investigators, representatives or agents and Investigator (the "Site Indemnitees") against any third-party liability, loss, damage or expense (including reasonable attorneys' fees and expenses of litigation) incurred by the Site Indemnitees to the extent resulting from any third-party claims, suits, actions, demands or judgments made or instituted against Site and/or Investigator that are brought by or on behalf of Study Subjects for bodily injury or death of Study Subjects solely due to the administration or use of Study Drug during and in connection with conducting the Study in accordance with the Protocol, provided such activities were conducted in compliance with this Agreement and the Protocol…*

Contract: Payment Terms

The terms of payment timelines are outlined in the contract. Each center needs to meet certain milestones to receive payment for "completed subjects." Each contract varies from sponsor to sponsor, and the terms can be negotiated if the payment schedule is not acceptable. The payment schedule may be 30, 45, 60 or quarterly days following the payment milestones. Sometimes the payment is tied to completed and monitored subject visits by the CRA. The contract will require that the electronic case report form be completed for each subject 24-72 hours following the visit, and will outline query resolution and database milestones in the agreement. The study coordinator should be aware of the terms regarding subject visit payment so that the participating center meets all requirements to ensure prompt payment. Reimbursement of required purchased supplies needed for the clinical trial also will be outlined in the contract. Accurate, frequent and prompt invoicing as directed by the sponsor/CRO is crucial for cash flow.

Budget

The budget is part of the contract and needs to be reviewed carefully before accepting the proposal from the sponsor or CRO. All budgets are negotiable. The sponsor/CRO will ask each participating center if the budget is acceptable and will request quick acceptance. The entire protocol must be studied to determine whether the budget for the completed per-subject payment is financially beneficial and review the database to determine recruitment feasibility needed in the trial. If the protocol is complicated, the clinical research site may need to advertise to reach the projected recruitment/randomization target. Recruiting adherent and compliant subjects that meet the inclusion/exclusion criteria will determine if the research center will be profitable. Failure to recruit qualified subjects and adhere to the protocol may result in financial loss for the center. The site also can negotiate advertising for subject recruitment, database review, start-up fees and storage document fees after the trial has completed. The sponsor usually has a 10% hold on the final payment until the database is locked and all queries are answered and completed. The site can negotiate with the sponsor if the contact requires more than a 10% hold for the final payment.

It is helpful to prepare a spreadsheet using the protocol schedule of event table. Each procedure and test is added to the spreadsheet with a calculated visit cost, including the subject (patient) stipend, coordinator fee, investigator fee and overhead, calculated in the total per patient payment. Unscheduled and early study termination visits also are calculated and compared to the sponsor/CRO budget offer. The sponsor/CRO will include the number of screen failures allowed for that trial, payment for screen failure/randomized ratio, terms of payments and the amount of financial compensation for each screen failure. The administration fees for IRB submission, documents, advertising for subject participation, medical record chart and database review and storage of the study records and documents also are itemized and listed in the budget proposal. The terms for payment and the timelines are outlined. It is important to review all equipment you may need during the trial and include it in the contract to receive pre-authorization from the sponsors/CRO. Sometimes equipment such as spirometry

is provided for the duration of the trial by the sponsor and requires the clinical site to purchase the equipment when the trial has completed. The site needs to carefully review the contract for hidden cost and fees. Another potential area of hidden cost to the site might be insufficient reimbursement for medications, procedures and test required by the protocol but not supplied by the sponsor. With careful review of the contract, reimbursement terms can be amended prior to signing the final contract.

Table 13 is an example of the spreadsheet schedule of events to determine if the budget proposal is financially acceptable. If not, a new budget proposal

TABLE 13. CLINICAL TRIAL USING THE STUDY PROTOCOL SCHEDULE OF EVENTS

PROCEDURES AND VISIT	VISIT 1	VISIT 2	VISIT 3	VISIT 4	VISIT 5 Final and early study termination	TOTAL
Inclusion/exclusion	X	X				$0.00
Medical/disease history	X					$0.00
Randomization		X				$0.00
Physical exam	X	X	X	X	X	$0.00
Vital signs	X	X	$ for # vitals	XXXX	XXXX	$0.00
Spirometry	X	X	$ for # efforts	XXXX	XXXX	$0.00
Reversibility (FEV1)	X	X				$0.00
Laboratory/blood draws	X	X	$ for # draws	XXXX	XXXX	$0.00
Electrocardiogram	X		$ for # ECGs	XXX	XXX	$0.00
Diary						
(electronic diary dispensing/collecting and subject training and review)	X	X	X	X	X	$0.00
Concomitant medication	X	X	X	X	X	$0.00
Medication dispensing and accountability	X	X	X	X	X	$0.00
Adverse event and serious adverse event assessment	X	X	X	X	X	$0.00
eNO measurement	X	X	X	X	X	$0.00
Quality of life surveys	X	X	X	X	X	$0.00
PK blood samples		X	$ for each draw	XXX	XXX	$0.00
Physician fee	X	X	X	X	X	$0.00
Coordinator fee	X	X	X	X	X	$0.00
Subtotal	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00
Overhead	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00
Stipend (patient) for time and travel	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00
PATIENT VISIT TOTAL	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00

can be submitted to the sponsor/CRO for review and consideration. A site can call the sponsor's budget representative to inquire as to the highest approvable budget payment per subject. The sponsor/CRO bases the budget offer according to industry standard metrics. Often, the site and sponsor compromise on the final dollar amount. A budget should not be accepted, however, if the site is unable to project a financial profit. Even with a fair budget, financial success in a clinical trial depends on the research center's ability to reach the contracted numbers of randomized subjects.

SUMMARY

Clinical research can be professionally and financially rewarding. Success depends on a center's ability to enroll/randomize subjects, adhere to FDA regulations and ICH/GCP requirements, and have a research team that is dedicated and committed to high quality clinical research.

RESOURCES

Association of Clinical Research Professionals. www.acrpnet.org

Center for Drug Evaluation & Research. www.fda.gov/CDER.

Center Watch Publications. www.centerwatch.com.

FDA homepage. www.fda.gov.

FDA information sheets. www.fda.gov/oc/ohrt/irbs.

Editor at *Good Clinical Practices Monthly Bulletin*. Phone (202) 739-9765.

Information for Health Professionals. www.fda.gov/oc/oha.

International Council on Harmonization. www.fda.gov.

IRB Advisor. (800) 688-2421 or www.ahcpub.com/online.html.

National Human Research Protections. www.dhhs.gov.

Office of Health Affairs. www.fda.gov/oc/oha.