Chapter 32
Setting up a Clinical Trial Research Office

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Introduction

The success of a clinical trial is dependent on the organizational infrastructure set by the principal investigator. The principal investigator and the executive committee are responsible for the management of a large personnel spread across multiple institutions, multiple committees, a large budget and responsibilities for the safety and privacy of enrolled subjects and the integrity of the data. The following chapter describes how to set that infrastructure in place, a schematic representation of which is presented in Fig. 32.1.

Chair's Office

The chair's office, also known as the clinical coordinating center, should consist of the study chair who is usually the principal investigator (PI) for the whole study, the national nurse coordinator who leads the site coordinators, and an administrative assistant if budgeted. The PI and national nurse coordinator usually are not the site investigator and coordinator for their own site to maintain separation between the clinical coordination and data collection. This responsibility is usually to others within their center. It is advantageous for the PI's center to be enrolled within the study in order for both the PI and the National nurse coordinator to have firsthand experience with all issues related to the study.

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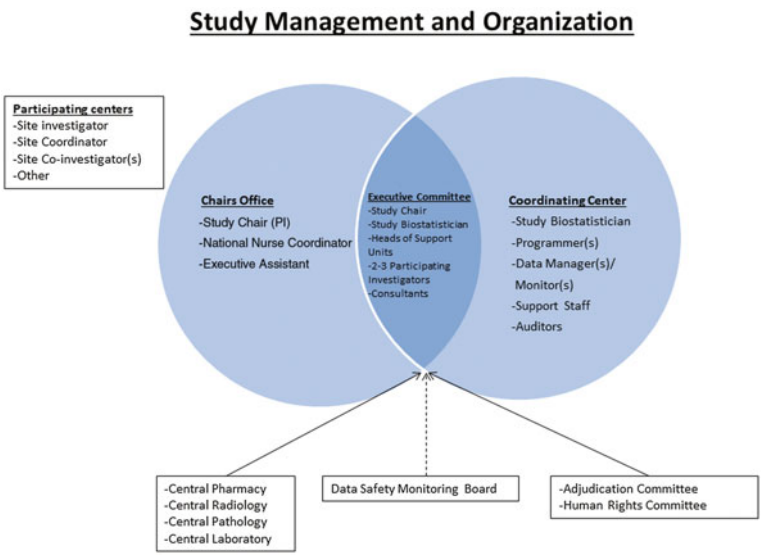

Fig. 32.1 Clinical trial study infrastructure

Once the study is approved and funded, the first order of business is to recruit a National nurse coordinator who will work closely with the PI and the coordinating center on all aspects of the study.

The identification of participating centers and the timeline for recruitment, institutional review board approval (central and local) as well as progress of the study are all delineated within the original proposal. The chair's office will have to make every effort to comply with the timelines.

One of the first activities of the chair's office is to put together a study operations manual, also known as a manual of procedures, for the study as a whole. The operating guidelines manual will describe step by step all activities of the study and the delegation of study tasks and training of each individual within the study. This manual is intended to provide complementary information to that which is found in the study protocol and to provide additional details on specific study procedures. In the event of personnel turnover or in case of a sudden emergency, any study personnel should be able to obtain information about any step or role within the study from the operating guidelines manual.

The chair's office should also set the date for the first investigator's meeting which should coincide with the time that all or most of the participating sites' personnel are in place. The meeting should include at least every site investigator, co-investigator if the budget allows, site coordinators, members of the coordinating center, members of the executive committee including representatives of all support units such as radiology, laboratory, pathology, and consultants as well as members of the adjudicating committees. During the meeting, the PI and coordinating center staff will cover all aspects of the study, step by step, review of the study protocol,

recruitment strategies, retention of participants, data tools, and the operations manual. For specific procedures or surgeries, the details and material are agreed on by the investigators with hands on training through videos, mannequin, or cadavers (as deemed necessary) occurring during that initial meeting. The site coordinators will have their own training session on all aspects of the data entry tools. A review session on good clinical practices for human research should be included during that meeting.

It is during that first meeting that all staff meet each other, understand each other's roles, and the tone, expectations and details of the study are set. All possible questions should be answered. It is not infrequent during this first meeting that questions might not be answered or that a step within the protocol might not be realistic based on consensus by the investigators. These issues can be taken back to the executive committee, who can provide an answer or decide to proceed with a protocol amendment that will require IRB approval. Yearly face-to-face meetings can be held if budgeted and deemed necessary for the proper progress of the study.

The chair's office will then organize monthly conference calls with all site investigators and coordinators to discuss challenges, learn from each other, and respond to questions. These conference calls might be held more or less frequently depending on the difficulties encountered and the progress of the study.

The national nurse coordinator should have a separate conference call with the site coordinators at least monthly to discuss issues related to recruitment, screening strategies, data entry and transmission, participant follow up, and retention.

It is also very beneficial for the chair's office to publish a newsletter at least quarterly that provides information about each site's recruitment, overall study progress, responses to frequently asked questions, and to feature one site each time.

Study Coordinating Center

The study coordinating center, sometimes known as the biostatistical and data coordinating center, is led by the lead biostatistician who interacts frequently and closely with the chair's office. The study coordinating center allocates various staff to the study including a programmer, data manager, other statisticians, and support staff depending on the size of the study [1].

The randomization process and tools for enrolling patients are built by the coordinating center which will then monitor screening at each participating center, recruitment, data quality, protocol compliance, and participant retention. The coordinating center will provide reports as well as any concern to the Chair's office prior to an executive committee meeting. The coordinating center will also prepare various reports including safety and efficacy to be reviewed by the independent data monitoring committee at their regularly scheduled meetings. Data requested by other committees to adjudicate end points or other issues can be provided as long as it does not compromise the integrity of the results and any blinding of the participating staff.

Executive Committee

The executive committee, sometimes known as a steering committee, is led by the study chair with participation of the lead biostatistician, 2–3 principal investigators, the national nurse coordinator, key consultants, and the heads of any supporting unit (radiology, pharmacy, etc…).

The executive committee acts as the management group and decision-making body for the operational aspects of the study. They usually meet on a monthly basis and as needed to review compliance with timelines, recruitment strategies, additional efforts and retention of study participants. Based on feedback during the site investigator conference call, the committee makes decisions about protocol amendments and takes actions on medical centers whose performance is unsatisfactory. The executive committee makes decisions about site visits to review compliance with protocol or observe a procedure or surgery. Depending on the concerns at a specific center, the executive committee might decide to dispatch the study chair, a consultant or site PI, or a multidisciplinary team to review and report on any issue of concern.

The executive committee refers cases to the adjudication committee in case the outcome is not clear or to the human rights committee in case of a safety breech or ethical concern. Those committees report back to the executive committee for action.

Data Safety Monitoring Board

The data safety monitoring board (DSMB) is an independent oversight committee organized by the study sponsor. It is responsible for monitoring the progress of the study. The lead biostatistician provides the DSMB unblinded reports on the efficacy and safety outcomes according to a prespecified plan. The DSMB also considers new scientific information from sources outside the study that may impact whether the study should continue. The DSMB is a recommending body that communicates its recommendations to the study sponsor. If the sponsor accepts the recommendations of the DSMB, the sponsor then communicates that information to the study executive committee. However, the study investigators do not receive any discussions concerning unblinded data. The DSMB is covered in more detail in Chap. 39.

Supporting Units

Different studies might require different services to support various functions of the study. Medications might be dispensed through a central pharmacy if the study drug is experimental or not on the market; for devices and implants, these might be

distributed through central supply on a case by case basis or through limited batches to ensure proper handling, storage, and compliance with expiration dates. Specialized laboratory testing such as special histologic staining for genetic markers and biomarkers might be sent to central laboratories for standardization purposes. This will require training for proper handling of human specimen and safe shipping in accordance with the International Air Transportation Association (IATA) regulations. Radiologic testing can be done locally but might require reading in a central location by dedicated staff for standardization purposes. Representatives from any of those areas should be on the executive committee available to discuss any issue, challenges or progress.

Other Committees

An adjudication committee or ends point committee consisting of various experts in the field under investigation should be in place. It is not uncommon for disagreements to arise when an outcome is determined by clinical interpretation and the necessity for an unbiased opinion to adjudicate that outcome.

Although the IRB provides oversight over all aspects of the study, it is important to have a human rights committee especially with procedural and surgical trials to ensure ethical and safe conduct of all aspects of the protocol without bias, avoiding un-blinding especially when the control consists of a sham operation or procedure. In some instances, a DSMB may include one or more members who are ethicists and patient advocates in lieu of having a separate human rights committee.

A publications committee might be established for large trials with the potential for several sub-studies. However, it is not unusual for the executive committee to also act as the publications committee if a separate one was not established. All requests for publication by any member of the study should be channeled through that committee for approval and release of the data. Before submission, the publications committee reviews any manuscript for accuracy, authorship and proper credit.

Large complex trials may also have additional committees responsible for various aspects of study conduct, such as recruitment and retention, and quality control.

Site Investigator's Research Office

The site investigator's office mirrors the set up in the chair's office. The site PI recruits the site coordinator as well as co-investigators to help with all aspects of the study. The site PI should designate one or multiple co-investigators as his/her delegate when absent from the study site. The co-investigators should be familiar with the protocol and the study operations manual. One or several of them will

attend the investigators' meetings and will be trained in all aspects of the study procedure or surgery. The PI is responsible for maintaining up to date files, consents and IRB approvals, will report protocol deviations at the site and all adverse and serious adverse events to the chair's office within the allowable timeframe and is responsible for securing data safety and protecting personal health information for each patient. The site PI must also provide information that the IRB requires to fulfill its oversight role, such as serious adverse events and documentation on the informed consent process. The site PI will also identify ancillary staff in radiology, laboratory, pathology as well as other specialties needed for the study. Communication with and availability to study subjects is essential at each study site.

Although strategies for recruitment and retention of study subjects are delineated by the chair's office, it is ultimately the responsibility of the site investigator to implement a plan that best fits the culture and environment of a particular site.

It is also critical that study personnel at each site participate in the scheduled conference calls and meetings and remain apprised of all changes and issues pertaining to the study.

Summary

In summary, the organization of the Chair's office, the various committees, the study coordinating center and the ongoing consistent communication from that office and response to various questions, challenges, and issues are critical to the success of that study. The cost of a large prospective randomized trial usually in the millions of dollars, the large number of participating sites, personnel, and most importantly patients place a tremendous responsibility on the study chair's office to make sure that every aspect of the study is attended to in a fair, equitable, and responsible fashion.

Reference

1. Williford WO, Krol WF, Bingham SF, Collins JF, Weiss DG. The multicenter coordinating center statistician: "More than a consultant". Am Stat. 1995;49(2):221–5.