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Memorandum

To: Trialists

Fr: Curtis Meinert

Re: So you want to run a trial, do you?

Suppose you are the director of the coordinating center in a multicenter trial and that, either by understanding or default, you are responsible for running the trial. Your duties are akin to those of a general contractor responsible for building a skyscraper. You are responsible for making sure legal and ethical requirements for the trial are met, for ensuring compliance to the study protocol, and for ensuring the integrity of the study data. Your major duties and responsibilities are as listed below.

Funding initiative

Permission to submit funding application (applicable to NIH investigator-initiated funding with a budget of ≥$500,000 in direct costs for any given year of requested funding; http://grants.nih.gov/grants/guide/notice-files/not-od-02-004.html.)
Comment: The request is usually submitted by the study chair or director of the coordinating center.

IRB training and certification Technically, the regulation is applicable only to research funded by the NIH or other US governmental agencies, but most research institutions impose the requirements of the regulation regardless of source of funding. The regulation specifies *" ... that institutions and their designated IRBs establish training and oversight mechanisms (appropriate to the nature and volume of their research) to ensure that investigators maintain continuing knowledge of, and comply with, the following:*

Relevant ethical principles;
Relevant federal regulations;
Written IRB procedures;
OHRP guidance;
Other applicable guidance;
State and local laws; and
Institutional policies for the protection of human subjects.

Furthermore, OHRP recommends that investigators complete appropriate institutional educational training before conducting human subjects research."
(http://www.hhs.gov/ohrp/education/training/introduction.html)
Comment: The institution housing the coordinating center must provide evidence that key personnel in the center have received such training. If the application also contains funding for clinics, the institution housing the coordinating center must also provide evidence that key clinic personnel have received such training.

HIPAA training and certification The requirement for training is applicable only to "covered entities" as defined in the Act, but most research institutions impose the training requirement without regard to applicability.
Comment: The institution housing the coordinating center must provide evidence that key people in the center have received HIPAA training; likewise for clinic personnel if the application contains funding for study clinics.

Inclusion of women and minorities (NIH funding)
"The inclusion of women and members of minority groups and their subpopulations must be addressed in developing a research design or contract proposal appropriate to the scientific objectives of the study/contract. The research plan/proposal should describe the composition of the proposed study population in terms of sex/gender and racial/ethnic group, and provide a rationale for selection of such subjects. Such a plan/proposal should contain a description of the proposed outreach programs for recruiting women and minorities as participants."
(http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm)

Data sharing (NIH funding)
"Starting with the October 1, 2003 receipt date, investigators submitting an NIH application seeking $500,000 or more in direct costs in any single year are expected to include a plan for data sharing or state why data sharing is not possible. As indicated above, all investigator-initiated applications with direct costs greater than $500,000 in any single year will be expected to address data sharing in their application. Applicants are encouraged to discuss their data sharing plan with their program contact at the time they negotiate an agreement with the Institute/Center (IC) staff to accept assignment of their application." (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html)

Data and safety monitoring (NIH funding)
"Applications that include clinical trials must include a general description of the data and safety monitoring plan. The description of the data and safety monitoring plan in competing applications will be reviewed by the SRG. A general description of a monitoring plan establishes the overall framework for data and safety monitoring. It must describe the entity that will be responsible for monitoring how adverse events will be reported to the IRB and the NIH and, when appropriate, how the NIH Guidelines and FDA regulations for INDs and IDEs will be satisfied."

"A detailed monitoring plan must be included as part of the research protocol, be submitted to the local IRB, and be reviewed and approved by the NIH awarding IC prior to the accrual of human subjects. The awarding IC may specify the reporting requirements for adverse events, which are in addition to the annual report to the IRB. The clinical trial monitoring function is above and beyond that traditionally provided by IRBs; however, the IRB must be cognizant of the procedures used by clinical trial monitoring entities and the monitor must provide periodic reports to investigators for transmittal to the local IRB."

"NIH specifically requires the establishment of DSMBs for multi-site clinical trials involving interventions that entail potential risk to the participants, and generally for Phase III clinical trials. Although Phase I and Phase II clinical trials also may use DSMBs, smaller clinical trials may not require this oversight format, and alternative monitoring plans may be appropriate."
(http://grants1.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm)

Conflict of interest disclosure The requirement is that institutions *"maintain an appropriate written, enforced policy on conflict of interest that complies with this subpart and inform each Investigator of that policy, the Investigator's reporting responsibilities, and of these regulations. If the Institution carries out the PHS-funded research through subgrantees, contractors, or collaborators, the Institution must take reasonable steps to ensure that Investigators working for such entities comply with this subpart, either by requiring those Investigators to comply with the Institution's policy or by requiring the entities to provide assurances to the Institution that will enable the Institution to comply with this subpart."*
Comment: The institution housing the coordinating center must provide assurance that it is in compliance with the regulation. If the application contains funding for clinics the institutions housing the coordinating center must also provide assurance that all institutions housing clinic are in compliance with the regulation.

IRB documents, submissions, processes, and procedures In the US and other parts of the world not having central IRBs, there are as many IRBs as there are clinics and resource centers in a trial. This means that there has to be a central control structure for directing interactions with IRBs. Establishing and maintaining that structure is usually the responsibility of the coordinating center. **Note**: Increasingly, funding agencies for multicenter trials require a central IRB layered on top of the existing IRB system. This requirement basically imposes another level of complexity on an already complex IRB process because IRBs are autonomous entities and, hence, not bound by any other IRB, even if "central".

Study protocol A document submitted to IRBs specifying eligibility requirements, treatments being tested, method of assigning treatment to persons, and details of consent/assent and of data collection and followup. **Note**: The definition of protocol as used in SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) is much broader extending to the various key documents of a trial including the study handbook/manual and Policy and Procedure Memoranda.
Comment: Usually prepared by the coordinating center in conjunction with study investigators for distribution to clinics for use in submissions to their IRBs.

Prototype consent/assent statement: A statement intended to serve as a model for use by participating clinics when preparing for submission to their respective IRBs.
Comment: Typically prepared by the coordinating center in conjunction with other study investigators.

Review of IRB approved consent/assent statements IRBs have their own requirements for consent and assent statements. They are not bound by prototypes provided by the coordinating center. Hence, a prudent practice is to review IRB-approved statements consents and assents to make certain the statements contain essential information and that they do not make promises that cannot be met.
Comment: Such reviews typically fall to the coordinating center. For the review to be useful the coordinating center must have authority to forestall enrollment of a clinic if statements are not adequate.

Orchestration of IRB submissions With multiple IRBs, some person or body has to be in charge of directing IRB submissions.
Comment: The logical choice is the coordinating center. Typically, clinics are forestalled from submitting to their respective IRBs until directed to do so by the coordinating center.

Monitoring to avoid lapsed approvals IRB approvals are for defined periods of time, typically one year, but sometimes less depending on IRBs. Lapsed approvals require a shutdown of activity at the site with the lapsed approval and lockout of data flow from the site to the coordinating center.
Comment: Monitoring is typically assumed by coordinating centers; done by maintaining a file of renewal dates for clinics and notifying clinics of pending lapses.

Reporting adverse events to IRBs The rule in multicenter trials is that adverse events reported to any IRB must be reported to all IRBs in the trial. Indeed, the requirement can extend to events in other trials if they are done under a common IND or IDE.
"Effective July 1 [1999], all multi-site trials with data safety monitoring boards are expected to forward summary reports of adverse events to each IRB involved in the study. This action in no way reduces the responsibilities of individual IRBs to address such reports coming to them from the site over which they have responsibility. NIH program staff will ensure that this language appears in new solicitations for clinical trials and is broadly disseminated to current principal investigators with appropriate follow-up."
"Guidance on Reporting Adverse Events to Institutional Review Boards for NIH-Supported Multicenter Clinical Trials"; 11 June 1999.
Comment: The duty to satisfy the requirement falls to the study sponsor or the coordinating center; the coordinating center if the IND or IDE is held by an investigator in the trial.

IRB notification of meetings of the Data and Safety Monitoring Committee (DSMC) IRBs are to be informed of meetings of the DSMC and of the result of the meeting. This means that someone has to inform clinic directors of meetings and that they in turn inform their respective IRBs. The only communications IRBs will accept are from the investigator named in an IRB submission. Hence the transmission to center directors and by them to their respective IRBs.
Comment: The duty falls to the coordinating center.

Management of protocol amendments Technically, any change to a protocol is an amendment, but the term is best reserved for changes submitted to IRBs for review and approval – generally, any change that can be reasonably argued as having the potential of changing the risk-benefit ratio for persons studied, having potential of influencing a person's decision as to whether to enroll or to remain in a study, or that increases the nuisance of being studied; including any change to the treatment protocol, study procedures, schedule of study visits, or period of followup and any change considered to require changes to existing consent forms or requiring reconsent.
Comment: As a rule, the coordinating center is responsible for orchestrating submissions to IRBs for protocol amendments. An issue that has be determined in multicenter trials is when the change is implemented. Is the change implemented on a per-clinic basis as approved by individual IRBs or is the change held until all clinics have cleared IRBs?

Certificate of confidentiality A certificate, issued by federal agencies, having the purpose of protecting study records and data from subpoena in criminal, civil, administrative, or legislative hearings at the federal, state, or local level; certificate must be renewed if the time period of study extends beyond that indicated in the original request. The protection is void to the extent waived in writing by study subjects. The protection does not preclude access to study records by the FDA. The protection provided is not time limited. Certificates are granted only on request and then only when the applicant makes a case as to need (usually stated in terms of the likely negative impact on the degree of cooperation

absent the protection provided with a certificate). Typically, issue is limited to research involving the collection of data on persons which, if revealed, could be embarrassing or in some way injurious to such persons. Use generally limited to studies involving study of aberrant or illegal behaviors or involving collection of information having to do with personal life styles.
Comment: If obtained, usually obtained by the coordinating center.

Execution

Creation and maintenance of study data collection forms The first orders of business in any trial is the creation of data collection forms for enrollment and followup. After creation they have to be maintained to reflect changes in data collection procedures over the course of the trial.
Comment: The coordinating center is responsible for the job. The pressure to produce forms is considerable because clinics cannot start enrollment until forms have been produced and cleared for use.

Creation and maintenance of key study documents Key study documents include the study protocol, prototype consent and assent statements, study forms, study handbook/manual, and policies and procedures memoranda (PPMs), the latter issued as needed to communicate study policy, changes in study procedures, and protocol changes to study personnel.
Comment: Responsibility for all of the above documents falls to the coordinating center.

Patient enrollment
Comment: The coordinating center is responsible for enrollment procedures and for checks to make certain persons meet eligibility requirements. Checks include being certain that persons have consented for study, that necessary baseline data have been collected, and that eligibility is confirmed before randomization.

Randomization
Comment: The coordinating center is responsible for construction of the randomization scheme, for ensuring assignments are concealed until issue, and masked if treatments are masked.

Data intake The usual approach to data intake is via clinics keying data as collected and harvested by the coordinating center.
Comment: The system cannot be developed before data collection forms are developed and cleared for use. Enrollment cannot start until the electronic system for receiving data has been developed and tested.

Performance monitoring There has to an ongoing process to monitor adherence to the study protocol and compliance to data collection procedures. Indeed, it is foolish to undertake a trial without such monitoring. Typically, the monitoring includes preparation of reports at periodic intervals over the course of the trial for distribution to and review by study investigators. The reports detail performance on a clinic basis in regard to enrollment, missed visits, dropouts, and protocol deviations.
Comment: The coordinating center is responsible for the monitoring. The coordinating center director, in conjunction with other study leaders and sponsors, are responsible for taking necessary actions in dealing with performance issues.

Interim data analyses Virtually all randomized trials require systems for interim analyses and for modifying or stopping the trial if effects are large enough to merit action.
Comment: The coordinating center is responsible for those analyses and for preparation of monitoring reports submitted to and reviewed by duly constituted DSMCs.

Analyses for paper writing
Comment: The coordinating center is a partner in the writing process with responsibility for the analyses needed for paper writing, and responsibility for ensuring the accuracy of analyses.

Data custodian
Comment: The coordinating center is responsible for safeguarding data generated in the trial. Typically, access is limited to persons in the coordinating center until the trial is finished.

Record custodian
Comment: Somebody in the trial has to be the keeper of study documents, including minutes of meetings, performance monitoring reports, treatment effects monitoring reports, study protocols, study handbooks, and study forms. The duty typically defaults to the coordinating center.

Site visiting The usual practice is to visit clinics at periodic intervals and/or as needed for cause to monitor adherence to the study protocol and data collection procedures over the course of the trial.
Comment: The visiting is done by people from the coordinating center alone or in conjunction with others. The crème de la crème job for the junkyard dogs of coordinating centers!

Drug acquisition, labeling, and distribution Placebo-controlled trials require drug and placebo that are packaged, labelled, and supplied to clinics masked.
Comment: Typically, the coordinating center is responsible for acquisition of the study drug and placebo and for ensuring labeling and packaging so as to be indistinguishable.

Investigational New Drug; Investigational Device Exemption Drugs and medical devices not approved for marketing cannot be tested in trials without an IND or IDE. The IND or IDE is held by the study sponsor or an investigator in the trial.
Comment: The usual option when held by someone in the study is for it to be held by the study chair or director of the coordinating center.

Other duties, responsibilities, and guidelines

Registration Registration of the trial in ClinicalTrials.gov or like registry is required before the start of enrollment in order to be considered for publication.
Comment: Registration and updates of the registration, originally a responsibility of sponsors, is now the responsibility of study investigators; usually a responsibility of the coordinating center.

FDA amendment A provision of the FDA Amendments Act of 2007 (section 801; http://www.gpo.gov/fdsys/pkg/PLAW-110publ85/pdf/PLAW-110publ85.pdf) requires that sponsors/investigators summarize results on ClinicalTrials.gov for drug and device trials within one year of the date of completion; defined as *"the date that the final subject was*

examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the prespecified protocol or was terminated". Results are to be summarized in tabular format, without discussion or conclusion. Sponsors/investigators may be granted extensions of the deadline if able to provide reasons for extension and dates when results will be provided. Sponsors/investigators failing to comply for applicable clinical trials are subject to substantial fines.
Comment: Responsibility for the summary, when assumed by study investigators, usually falls to the coordinating center.

CONSORT The Consolidated Standards of Reporting Clinical Trials are guidelines adopted by various medical journals. Journals subscribing to the reporting standard require contributors to include a chart containing specified counts.
http://www.consort-statement.org/index.aspx?o=1096.
Comment: Responsibility for the chart and required counts falls to the coordinating center.

Standard Protocol Items: Recommendations for Interventional Trials SPIRIT was published early in 2013 in the *Annals of Internal Medicine*. It provides a checklist of items to be included in protocols.
Comment: The checklist is useful but blurs the lines between information included in protocols submitted to IRBs and information contained in other study documents.

Data security standards The electronic transmission of medical data has to meet standards for ensuring privacy.
Comment: The coordinating center is responsible for knowing those standards and for ensuring they are met.

Policy guru There is a menu of policies needed for conduct of trials. The committee structure and conditions for membership has to be defined, as does the relationship of committees, one to another. Policy has to established on the organization and operation of the DSMC, on publications and presentations, and on authorship of publications and presentations.
Comment: The first step in establishing policy is drafting policy. Typically, because coordinating centers cannot operate effectively in the absence of organization and policy, it is the coordinating center that takes a lead in drafting policies.

Study website Increasingly, multicenter trials have password protected websites for posting essential study documents and PPMs for study investigators. They may also have an open website for posting the study protocol, prototype consent and assent statements, study forms, and study publications.
Comment: Usually, the site is created and maintained by the coordinating center.

Preparation of investigator dataset The expectation, when the trial is finished, is that investigators will be provided a finished dataset.
Comment: The coordinating center is responsible for preparing the dataset and accompanying data dictionary and for distribution of the dataset to study investigators.

Data sharing agreement
Comment: Typically, the coordinating center is responsible for fashioning data use agreement, if there is data sharing beyond the investigator group.