JOHNS HOPKINS
UNIVERSITY

Center for Clinical Trials

Department of Biostatistics
Department of Epidemiology
Department of International Health

Department of Medicine
Department of Ophthalmology
Oncology Center

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Memorandum

To: Trialists

Fr: Curt Meinert

Re: IRBs, coordinating centers, and multicenter trials

I wrote previously on guidelines for maintaining study protocols in trials (trialsmeinertsway.com). It is useful to review that document when reading this one.

Definitions

eligibility override *n* - 1. A decision to enroll a person into a trial even though not all enrollment criteria are met. 2. A violation of the study protocol by enrollment of a person not meeting eligibility criteria as specified in the IRB approved protocol.

numbered policy and procedure memorandum *n* - A policy and procedure memorandum issued to update the study protocol, provide clarification or interpretation of the protocol, clarify the meaning of items on data collection forms, instruct in regard to methods and procedures to be followed in data collection, or instruct centers in regard to communications with local institutional review boards; numbered to underscore importance and to facilitate reference, filing, and tracking.

policy and procedure memorandum (PPM) *n* - A memorandum distributed to centers in a trial detailing policy or procedure for the trial and issued from the coordinating center, office of the chair, or sponsor.

protocol *n* - [MF *prothocole*, fr ML *protocollum*, fr LGk *prōtokollon* first sheet of a papyrus roll bearing date of manufacture, fr Gk *prōt-* prot- + *kollon* to glue together, fr *kolla* glue; akin to MD *helen* to glue] 1. Specifications, rules, and procedures for performing some activity or function. 2. study protocol 3. data collection schedule 4. treatment plan ***Usage note***: Subject to varying use. Often used as a synonym for treatment, as in "on protocol".

protocol amendment *n* - 1. A proposed change to an approved protocol. 2. A protocol change that has been implemented. 3. A proposed protocol change submitted to an IRB; such a proposed change approved by an IRB. ***Usage note***: Subject to varying use. Technically, any change to an approved protocol is an amendment. 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, or having potential to influence a person's decision as to whether to enroll or to remain in a study. In trials, including changes to the treatment protocol, study procedures, schedule of study visits, or period of followup; especially any change considered to require changes to existing consent forms or to require reconsent. Avoid

in relation to trivial changes due to spelling errors or minor wording changes on data collection forms.

protocol override *n* - A decision, after due consideration, to proceed with some act or procedure contrary to requirements of the protocol, e.g., as with a protocol exemption or randomization override. ***Usage note***: Any override is a protocol violation; avoid overrides; revise protocol via protocol amendments.

Guidelines

The guidelines that fellow are written assuming the coordinating center is the custodian of the study protocol and, hence, having responsibilities for ensuring compliance to the protocol, responsibilities for answering question from clinic personnel regarding matters of protocol, and umpiring the protocol. The responsibilities may be shared with the sponsor or study chair but with the assumption that the coordinating center serves as the nexus of communication to clinics regarding issues of protocol.

Guideline 1: Obtain and maintain IRB approval for the coordinating center independent of all other IRB approvals

Comment: Arrangements in which IRB coverage of the coordinating center is via the IRB of the study chair or another center is inconsistent with autonomy needed for proper operation of the coordinating center.

If coverage for the coordinating center is provided by the study chair's IRB when the project is funded, steps should be taken to obtain its own coverage. People from the coordinating center listed on the chair's IRB approval should be delisted from that approval once the center has its own approval.

Guideline 2: List the IRBs represented in the trial

Comment: The number of IRBs will equal the number of centers in the trial (clinical centers plus resource centers), if every center has its own IRB, eg, as may be the case in trials with centers in academic institutions. The number will be less than the number of centers when centers have the same IRB, eg, as in trials with centers served by the same commercial IRB.

Guideline 3: Determine the model used for IRB submissions

Comment: If the IRB of the coordinating center is regarded as the parent IRB, then clinics must hold their submissions until the coordinating center IRB has approved the protocol. If the standing of the coordinating center IRB is at parity with all other IRBs, then submissions to IRBs by clinics is simultaneous with the submission of the coordinating center. The downside of simultaneous submission is that clinics may have to resubmit if the coordinating center's IRB requires changes to the protocol. The downside of the parent model is that it delays clinic submissions.

Guideline 4: Establish policy as to minimum IRB approvals needed to start enrollment

Comment: Investigators have to decide whether to start on a per clinic basis or to hold start until all clinics have cleared IRBs. The usual approach is to allow start on a per clinic basis once the coordinating center has its IRB approval.

Guideline 5: Maintain a list of IRB approvals and of expiration dates

Guideline 6: Monitor the list (Guideline 5) for near lapses; notify clinics of impending lapses; require clinics to cease data collection when lapsed; lock out data flow from clinics with lapsed approvals

Guideline 7: Establish the coordinating center as the loci of communication regarding matters of IRB submissions and on issues of protocol
Comment: Avoid multiple loci (eg, the office of the study chair and the coordinating center). Multiple loci lead to breakdowns in communications.

Guideline 8: Specify protocol changes that require IRB approvals before implementation
Comment: Regard changes that have the potential of increasing risk to persons studied or that add to the burden of being studied as changes requiring IRB approval before implementation. Regard changes to the eligibility criteria, additions to the data collection schedule, addition of tests or procedures, collection of body tissues (new or additional), changes to the treatment or dosage schedule, or addition of sensitive questions to data collection as changes requiring IRB approval. Cosmetic changes to data forms do not rise to the level requiring IRB approval.

Guideline 9: Differentiate protocol changes that can be implemented without IRB approval from those that may not be implemented until approved
Comment: Broadly, changes deemed necessary to reduce risk to persons (even if they require additional tests or procedures) are made without IRB approvals. The practice in such cases is to inform IRBs of the changes and reasons for implementing them. The rule of thumb is that if waiting for IRB reviews has the effect of increasing risks to persons being studied, the changes are implemented with notice to IRBs following the changes.

Guideline 10: Consider any change expanding eligibility criteria as a change requiring IRB approval before implementing the change

Guideline 11: Proscribe eligibility overrides
Comment: Eligibility overrides are protocol violations and should be reported to IRBs. If investigators desire to override eligibility criteria, they should amend the protocol and refrain from enrolling under the revised criteria until the amendment is approved by IRBs.

Guideline 12: Funnel communications from the coordinating center that are to be directed to IRBs through study center directors; no direct communications with IRBs save for the center's own IRB

Guideline 13: Produce prototype consents (and assents when used) for use by clinics in their submissions; produce in conjunction with clinician investigators

Guideline 14: Produce consents intended to inform study participants of prospect of transmission of names, addresses, and other personal identifying information to the study coordinating center
Comment: See posting to trialsmeinertsway.com on collection of names.

Guideline 15: Require study centers to maintain files of IRB correspondence and approvals; inspect for completeness during site visits

Guideline 16: Collect approved consents; review to ensure that they contain essential information and that they do not contain promises or commitments that cannot be met

Guideline 17: Collect IRB approvals of study clinics at the coordinating center
Comment: The task of collecting such approvals is no small task in trials involving dozens of clinics. If possible, limit collection to initial approvals. Extension of collections to renewals and approvals of amendments markedly increases the effort.

Guideline 18: Establish and maintain formal written modes of communications for instructing study centers on issues of protocol; use numbered procedure and policy memoranda (PPMs)
Comment: The obvious advantage to formality is in the audit trail provided; useful when summarizing protocol changes in study publications.

Guideline 19: Distribute safety reports to all study clinics; the clinic where the event is observed reports to its IRB and sends report to coordinating center; coordinating center sends report to all other study clinics for transmission to their respective IRBs
Comment: If the trial is done under an investigational new drug application (INDA), any safety report, even if observed in some other trial under the same INDA, is reportable to all IRBs of record for trials under the INDA.

Guideline 20: Instruct centers to keep IRB approvals active after close of the trial
Comment: Active approvals are needed so long as paper writing goes on.