Guidelines on maintaining study protocols in trials

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 5. The research plan submitted to study investigators by a sponsor, study chair, or coordinating center in a multicenter trial for submission to their respective IRBs. 6. A research plan involving human beings, as approved by an investigator's IRB.

study protocol *n* - 1. study plan 2. General rules and procedures for carrying out a study. 3. data collection protocol [trials] 4. A written document specifying eligibility requirements, treatments being tested, method of assigning treatment to treatment units, and details of data collection and followup; also trial protocol. 5. treatment protocol ***Usage note***: May refer to unwritten document when used loosely. Assumed to refer to a written document in formal usage; in the context of trials, a written document that is submitted to IRBs for approval and followed by investigators in conduct of the trial.

Protocols are not blueprints. The writing lacks crispiness and precision and is sprinkled with qualifiers. Protocols in trials are purposely written to allow room for clinical judgment, especially in regard to treatment administration and when to stop a treatment because of side effects or patient complaints.

The qualifiers and escape clauses make monitoring for compliance difficult. Indeed, what is compliance when compliance allows room for variation based on clinical judgment? An act that is seen as a protocol violation from one perspective is seen as sound clinical judgment from another.

The problem in any trial is adherence to the study protocol, even if done by a single person. Problems multiply when the trial involves multiple people and again when the trial involves multiple study sites and still again when it involves multiple sites in different countries.

The assumption is that study subjects are enrolled, treated, and followed according to the same protocol. But without efforts to ensure that, the assumption is just wishful thinking.

The guidelines are written assuming the data center/coordinating center is the keeper of the protocol. IRBs for data and coordinating centers vary as to what they expect. Here the IRB expects the coordinating centers for multicenter trials to ensure compliance to the protocol and to report protocol violations to it. Ensuring compliance requires that clinics follow the study protocol and refrain from amending it except when instructed to do so by the coordinating center. Amendments on ad hoc clinic bases places the coordinating center at risk of violating its approval as keeper of the protocol.

The extent to which the guidelines below can be followed depends on when they are implemented. They are written assuming that they are implemented at the start of the trial, but groups are not usually that disciplined or organized. Hence, often that means groups come to them a little at a time as problems arise.

Guideline 1: Make certain study investigators accept the data center/coordinating center as the keeper of the protocol.
Comment: It is hopeless to maintain adherence to a study protocol absent that recognition and nobody in charge of keeping the protocol.

Guideline 2: Produce a written document before the start of enrollment that outlines policies and procedures for maintaining adherence to the study protocol, including details regarding performance monitoring; statement should include actions to be taken if protocol violations occur; policy should be reviewed and approved by study leadership; review and modify as necessary over the course of the trial.
Comment: The time to establish policy is before there are issues to deal with.

Guidelines on maintaining study protocols in trials

Guideline 3: Devote time at kickoff research group meetings to instruct study personnel on the need for a common protocol, on the processes for maintaining a common protocol, and on ways commonality is defeated; repeat periodically over the course of the trial.
Comment: Discussion of ways the protocol is violated are useful because the majority of deviations and violations are innocent, without intent to evade the protocol.

Guideline 4: Arrange for in-person meetings of the investigator group over the course of the trial; frequency at least yearly.
Comment: By far, the most effective means of ensuring familiarity with the study protocol and adherence to it is via face-to-face interaction.

Guideline 5: The data center/coordinating center to have its own IRB approval, independent of all other IRB approvals.
Comment: If the data center/coordinating center is the custodian of the protocol it should have its own IRB approval. Arrangements in which the data center/coordinating center is covered by another approval, eg, the head of the study, is inconsistent with the independence required for the keeper of the protocol.

Guideline 6: Outline the process to be followed in submitting the protocol and revisions to it to IRBs.
Comment: The options depend on whether the IRB of the data center/coordinating center is regarded as the parent IRB. If so, then the process is for clinics to hold submission to their IRBs until the data center/coordinating center's IRB has approved the protocol. If not then the submissions are simultaneous. The downside of simultaneous submissions is that clinics may have to resubmit if the data center/coordinating center's IRB requires changes in the protocol.

Guideline 7: Establish rules as to when a protocol is official; promulgate the rules via numbered memos to the research group.
Comment: Absent such rules there is no way to manage the protocol or to be certain as to the protocol version in effect at a clinic. Clearly, if the data center/coordinating center is the custodian of the protocol, there is no start until the IRB of the data center/coordinating center has approved the protocol. In regard to when to start enrollment in multicenter trials, investigators have to decide whether to start on a per clinic basis as they get their approvals, or to hold enrollment until all clinics have cleared IRBs. The usual approach is to allow start on a per clinic basis once the coordinating center has IRB approval.

Guideline 8: Identify different versions of the protocol by number and date of issue.
Comment: Numbering and dating is important when resolving questions as to the protocol in force at any point in time.

Guideline 9: Specify protocol deviations rising to the level of protocol violations; outline reporting procedures for violations to IRBs.
Comment: Broadly, a protocol violation is an act or action counter to the protocol that has potential of being adverse to study subjects or that adds to the burden, risk, or nuisance of being studied. The violation may be wilful, the result of a mistake, or due to a misinterpretation of the study protocol. Deviations, as distinct from violations, are of no direct consequence to persons being studied. The impact is on study data, eg, as with a clinic failing to complete a missed visit form for a person not seen for a scheduled visit.

Guideline 10: Specify changes to the protocol that rise to the level of amendments and method of IRB reviews and approvals before implementation.

Comment: Regard changes that have the potential of increasing risks to persons studied or that increase the nuisance or risk of being studied as changes requiring IRB approval. Regard changes to the eligibility criteria, additions to the data collection schedule, addition of tests or procedures, collection of body tissues (new or additional), change to the treatment or dosage schedule, or addition of sensitive items to data collection as amendments requiring IRB approval. Cosmetic changes to data forms do not rise to the level of amendments requiring IRB approval.

Guideline 11: Specify changes to the treatment protocol that are made without IRB approval.
Comment: Limited to changes that reduce risks or the burdens or nuisances of being studied, eg, stopping a treatment because of harm or a test procedure because of the risk of ill-effects. The normal course with regard to such changes is to implement them and then inform IRBs of the change.

Guideline 12: Specify when amendments become effective.
Comment: A key operational issue in multicenter trials is whether to allow clinics to start operating under the amended protocol once it and the coordinating center receives IRB approval, or to wait until all clinics have IRB approval. The obvious downside of implementing on a clinic-by-clinic basis is that it is more difficult for the coordinating center to manage than waiting until all clinics have cleared IRBs.

Guideline 13: Have clinical investigators sign statements indicating their intention to comply with the protocol and to refrain from initiating amendments to the protocol, except as instructed by the data center/coordinating center.
Comment: The process is useful in underscoring the commitment to a common protocol and in forestalling rouge actions.

Guideline 14: Establish a single channel of communication from clinics to the data center/coordinating on issues of protocol.
Comment: Multiple channels, eg, to the study chair or to the data center/coordinating center foster confusion as to who the keeper of the protocol is.

Guideline 15: Establish and maintain a policy of no eligibility overrides.
Comment: An eligibility override is a decision to enroll a person even though enrollment criteria are not met. Eligibility overrides are protocol violations and should be treated and reported as such. If there is a desire to override eligibility criteria, investigators should amend the protocol by submission to IRBs and refrain from enrolling under the revised criteria until IRB approved.

Guideline 16: Maintain a list of protocol violations by time and by clinic; include the list in reports to the treatments effects monitoring committee (data and safety monitoring committee) and to the research group.

Guideline 17: Conduct clinic site visits over the course of the trial; in multicenter trials comprise the visit team to include at least one remember from a clinic other than the one being visited; comprise to include another clinic director in the case of "for cause" visits.
Comment: Site visiting is an important component of ensuring compliance to the study protocol. The frequency is a function of funding. The ideal is to have a round of site visits prior to the start of enrollment (or soon thereafter) and then periodically thereafter.

Guideline 18: Site visits should include checks to ensure that clinics are using IRB, date stamped, approved consents.

Guidelines on maintaining study protocols in trials

Guideline 19: Reports of site visits to be distributed to the study leadership and sponsor.

Guideline 20: Produce prototype consent forms (and assent forms when necessary) for use by clinics in preparing consents submitted to their IRBs.
Comment: The prototypes should be produced by the data center/coordinating center in conjunction with the study chair and clinical investigators.

Guideline 21: Collect approved consents from clinics; review to make certain they contain the information contained in prototypes and that the information presented is accurate and true and that they not contain promises that cannot be met.