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Memorandum

To: Trialists

Fr: Curtis Meinert

Re: Standardize Protocol Items: Recommendations for Interventional Trials (SPIRIT)

Protocol in the SPIRIT statement (www.annals.org 8 Jan 2013) is defined as *a document that provides sufficient detail to enable understanding of the background, rationale, objectives, study population, interventions, methods, statistical analyses, ethical considerations, dissemination plans,people and administration of the trial; replication of key aspects of trial methods and conduct; and appraisal of the trial's scientific and ethical rigor from ethics approval to dissemination of results.*

Protocol, as used in SPIRIT in the context of trials, is actually a collection of documents likely to consist of the following:

- Original prototype protocol prepared by study leaders for use by individual study centers in submissions to their respective IRBs
- Subsequent prototype protocol versions (typically numbered) prepared in relation to revisions of the protocol or in relation to protocol amendments over the course of the trial; used by individual study centers in preparing their respective submissions
- Prototype consent form as contained in original submissions for use by individual centers in preparing consents for local IRB submissions
- Revised prototype consents as needed over the course of the trial in relation to protocol revisions or amendments; for use by individual centers in preparing revised or updated consents for local IRB reviews and approvals
- Data collection forms; originals and revisions thereof over the course of the trial
- Study manual/handbook; original and subsequent revisions (typically numbered)
- Policy and procedures numbered memoranda (PPMs) having force of protocol issued over the course of the trial; including those relating to data collection, paper writing and authoring procedures, and those dealing with data and safety monitoring
- Minutes of investigator meetings

In the case of the Alzheimer's Disease Anti-inflammatory Prevention Trial (http://jhuccs1.us/adapt/; a multicenter randomized trial): five versions of the protocol (Original: 8 Aug 2000; Version 1.4: 19 Nov 2002), three versions of the study handbook, five consent forms, 45 data collection forms involving 89 numbered revisions, 99 PPMs (PPM #1: 31 May 2000; PPM #99: 9 Aug 2007), and 31 steering committee meetings (2000 - 2007).

The SPIRIT writers specify that *"the full protocol* (as defined by content specified in a 33 item checklist) *must be submitted for approval by an institutional review board (IRB) or research ethics committee and that if details for certain items have not yet been finalized, then this should be stated in the protocol and the items updated as they evolve."*

But alas, in multicenter trials done in countries like the U.S. not having central IRBs, there can be as many IRBs as there are centers in a trial. That which is submitted to any given IRB must be submitted to all other IRBs represented in the trial. In multicenter trials that number can be 50 or more.

The goal of the trialist is to minimize the number of IRB submissions because of the effort and money associated with IRB submissions. For example, a 50 center study involving a $750 payment to each IRB for costs of review and a 1.5 day person effort per center associated with the submission, the total effort would be 75 person days and $37,500 for fees paid to IRBs for reviews.

The updating process outlined by SPIRIT would lead to multiple submissions over the course of a trial simply to update IRBs on information considered essential by drafters of the document but not necessary or even desired by IRBs.

The problem with the updating process outlined is threefold: (1) the proposers assume all IRBs have the same information requirements (they do not!); (2) the proposers assume that every IRB wants to know details outlined in the 33 item checklist (they do not; most IRBs have set requirements and formats for what they require); and (3) the proposers assume there is such a thing as "final".

As a trialist I have deleted "final" from my vocabulary. I simply number things. Just numbered versions of a form. Ditto for protocols and handbooks.

Often things, such as represented in item 31b in the checklist (authorship eligibility guidelines), are not worked out until the trial is finished. Even if authorship policy is established during the trial it is likely to change when paper writing starts. Hence, including statements on authorship eligibility in IRB submissions is not something I am inclined to do because of the likelihood of whatever was specified being wrong when papers are actually published.

Item 13 in the checklist requires *"time schedule for enrollment, interventions (including any run-ins and washouts), assessments, and visits for participants"*. The trialists is disposed to hedge on time simply because of uncertainties in predicting time requirements before the trial starts. The more specific one is with respect to time in consents, the more likely the need for revisions and reconsents when the original time schedule proves to be wrong later on.

The drafters of SPIRIT are to be applauded for their work but protocols are simply plans for study. They are no better in conveying the actual details of study than a building plan is in conveying an accurate depiction of a finished building. For the actual details underlying a study one needs the collection of documents listed above.