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: Curtis Meinert

Re: Coordinating center IRB approvals

A few weeks back I got the e-mail below from a colleague at another medical school in the U.S.

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> We are trying to start an observational study here at XXX. The data coordinating center (DCC) will be at XXX. We have one clinical site that we will start with that will also be at XXX. There is a third group, also at XXX, that will collect and store specimens in an existing biobank. We anticipate over the years that other clinical sites will be added. All data will be sent to the DCC from participating clinical sites and all bio-specimens will be sent to the biobank.
>
> We currently have 3 separate IRB applications in for consideration by the XXX IRB:
>
> 1) The DCC (headed by W)
> 2) Clinical site (headed by Y)
> 3) Biobank (headed by Z)
>
> Our IRB wants us to merge 1 and 2, with either W or Y as the IRB PI of record.
>
> Your thoughts?

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It was not long ago when coordinating centers were exempt from IRB review. But no more.

The reality is that the activities of coordinating centers have always been a little mysterious to IRBs. People in coordinating centers do not have contact with study participants and do not collect data. To be sure, they receive and process data from people studied, but the activities are perceived more as services than as research.

The option for IRB approvals of coordinating centers is to "piggyback" their approvals or have their own approvals.

A piggyback approval is one in which coverage is provided by another approval, e.g., by the IRB application submitted by the director of a clinical center located at the same institution as the coordinating center.

Piggyback approvals are expedient in investigator-initiated proposals when there is not sufficient time for the coordinating center to seek its own approval before submission of the funding proposal. For example, the activities of the coordinating center here for what was to become the Citalopram for Agitation in Alzheimer's Disease (CitAD) Trial were originally covered in the IRB approval granted the study PI, also here. The applications were separated after funding.

Piggyback approvals for coordinating centers should be converted to independent submissions and approvals if any of the following apply:

1. The study has two or more clinical centers
2. The coordinating center is to be an autonomous independent center in the study structure
3. The coordinating center is responsible for treatment effects monitoring
4. The coordinating center is responsible for ensuring compliance to reporting procedures for adverse events
5. The study is a randomized trial
6. The study involves an IND or IDE, whether or not randomized

Arguments against merging approvals are outlined below. The focus is on non-centralized IRB systems as in the U.S. and various other regions of the world. The arguments may not apply with centralized IRB systems elsewhere in the world.

1. *The duties and activities of coordinating centers are different than those for clinical centers and, hence, not appropriately merged into a single IRB application*
   Comment: Coordinating centers have responsibilities for ensuring compliance to the study protocol, for ensuring adverse events reported by clinics are reported to other investigators, for treatment effects monitoring, performance monitoring, plus creation and maintenance of systems for receiving, processing, and analyzing data. Clinical centers have responsibility for treatment and data collection of people enrolled at study clinics. Merging applications of disparate centers, like a study clinic and coordinating center, is ill-advised.

2. *The protections afforded study participants are increased with separate approvals for clinical centers and coordinating centers*
   Comment: Subjugating activities and duties of coordinating centers to those of a clinical center will make it more difficult and cumbersome for the coordinating center to perform its duties.

3. *The route to an IRB in non-centralized structures should be direct from the center director to the IRB*
   Comment: Merging the coordinating center approval into that of a clinical center means that communications to and from the IRB flow through the director of the clinical center. (Note: Most IRBs will not accept communications relating to an approval by anyone except the IRB investigator of record.)

4. *Confidential communications from the director of the coordinating center to the IRB of record are precluded if the director reports via another person*
   Comment: This means that anything unmasked to the IRB is unmasked to the IRB investigator of record (see note for item 3).

5. *Reports from the coordinating center to the IRB holding its approval are subject to delay, modification, or interdiction when via another person*
   Comment: Since communication to and from the IRB have to be via the holder of the IRB approval, direct communications to and from the IRB via the director of the coordinating center is precluded with piggyback approvals. The ability to report directly is important if the report relates to the performance of the clinical center holding the piggyback approval or to that of another clinical center.

6. *Communications to and from the IRB of record for the coordinating center are subject to "lapses" and "gaps" when they do not flow directly from the coordinating center director to the IRB and from the IRB to the director*
   Comment: The IRB communications log is of fundamental importance if something bad or untoward happens. "Gaps" in the log can be serious if the FDA comes calling in an IND or IDE trial. Maintaining two logs, one for the clinic and the other for the coordinating center, when both the clinic and coordinating center are covered by one approval, is difficult and error prone.

7. *The relationship of the coordinating center in non-centralized IRB structures to its IRB should be at parity with that of clinical centers to their respective IRBs*
   Comment: Coordinating centers must be perceived as impartial in multicenter studies. That perception is more difficult to maintain if the relationship of the coordinating center is different for the clinical center at its institution than for other clinical centers in the study.

8. *Combining approvals via piggybacking exposes both the clinical center and coordinating center to shutdown with a lapse of approval or shutdown of the IRB*
   Comment: The IRB of the Johns Hopkins School of Medicine was shutdown 19 July 2001 in the wake of a tragic death in a research study. The shutdown resulted in halt of all research under the purview of the IRB. Coordinating centers under that IRB were likewise shutdown. Our coordinating center approvals were not affected because they were via the Johns Hopkins School of Public Health IRB, not affected by the shutdown.

Results of the "survey"

The e-mail below was sent to whom I have distributed writings posted to trialsmeinertsway.com.

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3 July 2012

This e-mail is directed to trialists who are or have headed a data coordinating center in a multicenter trial or observational study.

For the current or last center headed, did you have your own IRB approval, i.e., an approval independent of all other IRB approvals for the study?

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Eighteen people replied. Seventeen answered "yes". I have no way of knowing how many, if any, approvals where originally piggybacked at locations where piggybacking was possible. That possibility existed for several of the respondents.