JOHNS HOPKINS
BLOOMBERG
SCHOOL of PUBLIC HEALTH

Department of Epidemiology
Johns Hopkins Bloomberg School of Public Health
615 N. Wolfe Street
Baltimore, Maryland 21205

Thursday, 24 March 2011

Memorandum

To: Center staff and faculty (via pdf attached to an e-mail distribution)

Fr: Curt Meinert

Re: A trialist's view of enrollment overrides

An enrollment override is permission granted by a study official to allow a clinic to proceed with enrollment even though the person is not eligible for enrollment.

The predominant reasons for exclusions from enrollment are to:

1. Exclude persons in which use of a study treatment is contraindicated because of some condition, eg, exclusion of persons with an allergy to aspirin in a trial involving aspirin as one of the study treatments

and

2. Increase the precision of the trial by excluding persons not likely to benefit from treatment or who are on treatments that may have effects similar to the study treatment, thereby confounding the treatment effect, eg, exclusion of persons on anti-convulsant treatments in a depression treatment trial because anti-convulsants have anti-depression effects

Most enrollment overrides are in relation to the 2nd reason for exclusions. However, regardless of the reasons, all enrollment overrides are protocol violations and have to be treated and reported as such.

The occurrence of enrollment overrides is symptomatic of communication problems in the trial. The usual route to overrides is when the study sponsor or study chair issues protocol dispensations absent input or communications with the coordinating center. The disconnect means that the coordinating center is in the dark regarding the fact of overrides and that it never learns of them or learns of them after-the-fact.

The problem with enrollment overrides is where they lead. The only way to get a randomization with online data systems is for clinic personnel to falsify data. If they enter the correct enrollment data the system will block the randomization because the person does not meet eligibility requirements. The falsification is scientific misconduct.

The basic rule with regard to enrollment overrides is that they should be banned. To achieve the ban investigators have to be schooled against overrides during the training period prior to the start of the trial. That training should be followed by issuance of a Policy and Procedures Memoranda (PPM), by the coordinating center indicating zero-tolerance for overrides and what will be done if they occur.

The coordinating center should maintain a list of enrollment overrides for inclusion in treatment effects monitoring reports and in primary study publications and documentation of how and when reported to local IRBs.

Urges during the trial to override the protocol should be dealt with by amending the study protocol to change the inclusion criteria. Obviously, that means that enrollment of the person at issue cannot proceed until the protocol is amended and approved by the IRBs of the coordinating center and enrolling clinics. Usually, the end result is that the person triggering the amendment will not be eligible or willing to enroll by the time the amendment is finally approved.

Clinical investigators, anxious to enroll, are not likely to embrace the time delay and the work they have to do to submit protocol amendments to their respective IRBs. But the good thing about the requirement is that it puts a brake on the rush to modify. The reality is that most protocol modifications for enrollment eligibility have little impact on enrollment rates.

The view of study protocols depends on perspective. IRBs tend to view them as blueprints. Clinical investigators see them as guides, and coordinating centers see them as something between these two views.

Clinical investigators are not likely to be sympathetic with the coordinating center's view of protocol overrides. But in multicenter trials everybody is tarred with the same brush if things go wrong. In any case, typically, coordinating centers are seen as the "keeper" of protocols by IRBs. If there are overrides coordinating centers will be held accountable. The excuse that the centers were not parties to the overrides will not cut it.

The probability of enrollment without notification of the coordinating center is rife in settings where issues of eligibility for enrollment are turfed to the study chair or study sponsor absent a communication structure including the coordinating center. In such structures, when the coordinating center learns of overrides, it is incumbent on it to take decisive action to shut the practice down forthwith.

The likelihood of communication disconnects is real in structures where clinics communicate directly with the study chair or sponsor on issues of protocol. The preferred structure is a single communications node centered in the coordinating center with all issues regarding data collection and the study protocol coming to the center. Questions beyond the medical competence of people in the coordinating center are referred to an appropriate study investigator with communications fed back to the clinic from the coordinating center with copy to the medical expert providing input. Establishing that structure will be difficult after a trial is underway. Hence, if problems are to be avoided, the structure has to be established prior to the start of enrollment with buy-in by study leaders.

Practices of coordinating centers that contribute to breakdowns in communications include:

1. Deferral to the study chair on issues of eligibility for enrollment
2. A flat internal communication structure with all communications going to everyone in the center without indication who is required to respond
3. Absence of a formal review and sign-off process on PPMs or key study documents

4. Anonymous sign-off on replies to clinics, eg, "The Coordinating Center"

Turfing issues of enrollment to the study chair or sponsor creates an independent communication structure in which the coordinating center is out of the loop.

The trouble with flat communication structures in which everybody receives questions and draft documents to review is that there is no way to know who considered the question or reviewed the documents in question. There should be a defined hierarchal communication structure.

Likewise, people in clinics need to know who is responding to them. "The Coordinating Center" or similar sign-offs without the name of the person producing the reply leaves clinics in a quandary as to who to contact if they have questions. Anonymous sign-offs instill as much faith in the receiver as those "Dear Customer" letters we all receive.