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28 June 2012

**Memorandum**

To: Trialists

Fr: Curtis Meinert

Re: Multiple enrollments in trials

Suppose a trial with two clinics and 100 people enrolled at each clinic. How many people in the trial? If you answered 200 you assumed no overlap of enrollees at the two clinics. Your answer is wrong if some people represented in one clinic are the same as represented in the other clinic.

The multiple enrollments discussed herein are:
Duplicate enrollments,
Repeat enrollments,
Transfer enrollments,
Coenrollments,
and
Reenrollments.

**Duplicate enrollment**

**Definition**

Errant enrollment of a person into a study in which already enrolled

**Comments**

Duplicate enrollments are mistakes and should not occur, but do, as detailed in the story of the Duplicate LSOCA Patient (posted to trialsmeinertsway.com; Guidelines, Rules, Suggestions and Reminders).

The likelihood of a person seeking entry into a study already in at another study clinic will depend on the proximity of study sites, whether persons are paid for study, and whether the person knows the study is the same as the one already in.

Duplicate enrollments are unlikely in masked drug trials but may not be in unmasked trials where persons can safely receive more than one study treatment, e.g., in trials involving life-style changes in which persons are paid and study clinics are close enough to allow persons to enroll at two study clinics.

**Prevention**

There is no reliable way of preventing duplicate enrollments. The chance of duplicates might be reduced by inclusion of questions on entry forms to determine whether the person is already enrolled, but the utility of such screening is nil to the extent to which persons will not answer

truthfully and to the extent to which persons do not recognize that the study being entered is the same as the one already in.

Coordinating centers receiving personal identifying information can check a person's name, address, and social security number against those for persons already enrolled, but names and addresses change and persons are not required to report their social security number.

Even without personal identifiers, coordinating centers can check for probabilistic matches using birthdates and demographic characteristics, but probably with only limited utility.

**Repeat enrollment**

**Definition**

Enrollment of a person on two or more occasions in the same trial

**Comments**

Repeat enrollments are legitimate when part of the study design, e.g., in short-term treatment trials where persons are allowed to reenter if they experience recurrences of the condition being treated during the trial.

The malignant version of reentries is due to "gaming" the assignment system, i.e., getting extra flips of the randomization coin in efforts to get the "right" treatment.

There is nothing stopping a person, unhappy with the assigned treatment, from dropping out and trying again at another clinic if clinics are close enough to make that possible. The chance of "gaming" by study subjects is likely nil in masked trials but may not be in unmasked trials of life-limiting conditions.

Study personnel can also "game" the system where it is possible to get more than one assignment for a study subject. That is possible with self-administered envelope schemes for unmasked trials and even with centralized administration of assignments if it is possible to get more than one assignment for persons being considered for enrollment. Gaming is precluded where assignments are not issued until the person being considered has been determined to be eligible, has consented to being randomized, and the person is counted as enrolled when the assignment is issued.

**Management and prevention**

If repeat enrollments are allowed, the coordinating center will have procedures for linking records of persons reentering and will not confuse reentries with new enrollments.

Detection of the nefarious form of reentries can be difficult. The best protection is probably informed consents in which persons considered for enrollment understand reasons for randomizing and have an understanding of what happens to the trial if the assignment scheme is subverted.

One can include screening questions to identify illegitimate reentries, but probably without much benefit because "gamers" are not likely to admit to reentering. The coordinating center can run checks using personal identifies (when available) and/or demographic data to identify suspicious entries but also with limited return.

Coordinating centers can prevent study personnel from gaming assignments by fail safe systems to ensure assignments are not issued until a person has been screened eligible and has consented to randomization.

**Transfer enrollment**

**Definition**

Enrollment of a person transferring from one study clinic to another study clinic during the trial or followup study

**Comments**

The need for transfer enrollments increases with the length of followup and number of study clinics. Systems for transfers are important in reducing dropouts.

**Management**

Data systems for long-term trials should be designed to accommodate transfers. Without a system for transfers, persons who move from the area where enrolled become dropouts. LSOCA, over its life to present, has about 90 transfers. The Galveston clinic, decimated by Hurricane Ike in 2008 and closed in 2009, alone accounted for 20+ transfers to the Houston study clinic.

**Coenrollment**

**Definition**

Enrollment of a person enrolled in another study

**Comments**

Most enrollment procedures in trials are designed to exclude people enrolled in other studies if treatments or procedures in the study conflict with those in the trial.

The push for coenrollment came to the fore with the AIDS epidemic. AIDS activists objected to being excluded from trials because of enrollment in other trials or studies.

By and large, trialists are indifferent to coenrollment so long as the activities and procedures are not in conflict with those in the trial. Coenrollments are of concern to meta-analysts to the extent to which the same persons are represented in the different trials pooled for analysis.

**Reenrollment**

**Definition**

Enrollment of a person exited from a trial into a related trial; enrollment of a person exited from a trial into a related followup study

**Comments**

Reenrollments happen after a trial is finished or stopped. The Coronary Drug Project (CDP) Aspirin Study involved reenrollment of people in the CDP exiting from treatment groups stopped in the CDP. The Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT) Followup Study involved reenrollment of people from ADAPT some years after its end.

Reenrollments happen downstream of the trial and, hence, are not of consequence in the trial. The difficulty with reenrollments arise in the follow-on trial or followup study in linking records from the trial, in counting persons eligible for study in the follow-on trial or followup study, and in reconciling data collecting during the trial with those collected in the follow-on trial or followup study.

**Closing observation**

Trialists are preoccupied with enrollment as well they should be. The issues and problems of counting due to multiple enrollments are not usually on their radar screens when data forms and data systems are designed.

There is no doubt that we could have reduced our collective effort and frustration in dealing with transfers in LSOCA if we had designed data forms and data systems for transfers at the outset. Likewise, the notion that someone would enroll in LSOCA at different clinics did not occur to us until confronted by a duplicate enrollment years into LSOCA.

Trialists should be proactive in considering and dealing with the possibility of multiple entries when systems are designed rather than when encountered during the trial.