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

(Tue) 6 December 2011

Memorandum

To: Trialists

Fr: Curtis Meinert

Re: My Yellow Brick Road for blackouts, shielding, firewalls, and access to study results in multicenter trials

Definitions

blackout: A proscription on the flow of interim treatment results outside the trial until finished or stopped.

contract research organization: A research organization funded, in part or totality, via contract; an organization in the business of contracting with firms developing drugs, biologics, or devices to perform trials or to prepare materials (such as for a New Drug Application) on their behalf.

coordinating center: A free standing center in the structure of a multicenter study that is responsible for receiving, editing, processing, analyzing, and storing study data and for coordination of activities required for execution of the study.

data center - A center in a study structure that is responsible for receiving, editing, processing, analyzing, and storing study data; may be synonymous with coordinating center if the data center is free standing and has a key role in supervision of the study.

early stop - Instance of a trial being stopped prior to its scheduled end because of data suggesting benefit or harm associated with one of the study treatments.

firewall: A construct within an organizational structure designed to keep specified people from having access to certain types or classes of information, e.g., such a construct in a coordinating center of a multicenter trial designed to keep the director of the center from seeing interim treatment results.

interim treatment result: 1. A result indicative of a treatment effect as seen during a trial. 2. Such a result leading to modification of the treatment protocol; such a result causing the treatment effects monitoring committee to recommend that investigators stop the trial or modify the treatment protocol.

primary result: A result of direct relevance to the primary or secondary objective of a study. In clinical trials, a result based on the design variable or the primary outcome measure.

shielding: The act and process of keeping clinic personnel from seeing interim treatment results.

Introduction

This memo has its origins in my e-mail of 7 November 2011 posing a series of questions, as repeated below (responses distributed 18 November 2011).

Question 1: Do the multicenter trials in which you have been or are involved operate under the blackout mode of operation (i.e., a mode in which clinic personnel do not see interim treatment results)?

Question 2: If trials are operated under blackouts when are the blackouts lifted and how are they lifted?

Question 3: Do you have different rules regarding blackouts depending upon whether the trial involves proprietary products or depending on sponsor?

Question 4: Who does the analyses for primary study publications?

Question 5: Are study investigators provided with a dataset similar to the one in the coordinating center when the trial is finished? If yes, is this done before results are published?

The questions arise from a study just completed with plans for a face-to-face investigator meeting in mid April for presentation of results of the study. Presently, work in the coordinating center is concentrated on preparing finished datasets and data dictionaries. The study chair has been pressing for a "preliminary" dataset so the chair and a collaborator (not from the coordinating center) can "shape" a results paper and start work on analysis for it. The study was a trial of proprietary products.

My "rules" for trials are:

Rule 1: Blackout mode of operation; blackout maintained until results published
Rule 2: Clinic personnel shielded from interim treatment results; shielding maintained to end of trial or until lifted in relation to an early stop
Rule 3: Primary results presented at face-to-face meeting of study investigators; presentation by coordinating center with proviso that study investigators not disclose or discuss results outside the investigator group until published or released by study leaders
Rule 4: No coordinating center firewalls
Rule 5: Publication of primary results regardless of nature or direction of results; no presentation prior to publication
Rule 6: Analyses for primary publications done by coordinating center
Rule 7: Study datasets not distributed to investigators until after primary publication(s)

Discussion

This discussion is predicated on the assumptions that:

1. Trials are under the stewardship of study investigators
2. Trials have treatment effects monitoring committees/data and safety monitoring committees that reports directly to study leaders or simultaneously to sponsors and study leaders
3. Study investigators have unfettered rights to publication
4. Trials have free standing coordinating centers that are independent of sponsors and other centers in trials

The implication of assumption 1 is that the sponsor, whether public or private, cedes control of the study to study investigators once protocols are approved.

The implication of assumption 2 is that responsibility for looks at interim treatment results rests with a body constituted specifically for that purpose.

The implication of assumption 3 is that sponsors have nothing to say about publication of study results. Sponsors may have rights of review but not rights of approval.

The purpose of assumption 4 is to distinguish between structures with free-standing, independent, coordinating centers versus structures in which coordination functions are vested in sponsors or delegated by sponsors to contract research organizations as their agents.

Rule 1: **Blackout**

The reason for proscribing access to interim results outside the investigatorship is because "You can't roller skate in a buffalo herd" (Roger Miller). It is tough enough to do a trial without having interim results bantered about in the press during the trial.

The blackout does not extend to factual information describing the trial or its design, such as contained in registrations sites or on public portions of study websites.

Rule 2: **Shielding**

Shielding has its origins in desires to minimize risks of treatment-related biases. Shielding is distinct from masking. Masking relates to treatment assignment. Shielding relates to treatment results. Hence, even if treatments are not masked, investigators can be shielded from interim treatment results in studies in which the study database is locked away in the coordinating center.

A side benefit of shielding is that it minimizes the risk of leaking interim results. Leaks can lead to a host of problems, including insider trading in trials involving proprietary products.

Rule 3: **Lifting the shield**

My protocol for lifting the shield is born of the belief that those who do a study should be first to see results, that everyone in the investigator group should see them at the same time, that results should be presented in a face-to-face investigator meeting, that results should be summarized and presented by personnel from the coordinating center, and that investigators should be asked not to present or talk about study results until published or until released to the public by study leaders.

Even if the elements of rule 3 are accepted when study policy is established, there may well be "work-arounds" when it is time to lift the shield. One "work-around" will be to forego the time and cost of face-to-face meetings in favor of webinars or other remote means.

Save a nickel, spend a dime.

If people labor to collect data they deserve to be brought together to see and hear them presented and to question what they mean. In any case, such discussions are useful preludes to paper writing.

Rule 4: **Coordinating center firewalls**

My opposition to firewalls in coordinating centers is that they reduce the ability of coordinating centers to perform their functions. The reason for firewalls is because of desires to reduce the risks of biases in the center, but firewalls reduce competency and competency in the center is of higher order import than theoretical worries regarding biases.

Rule 5: **Publication of primary results**
This rule, even if engraved in stone when trials are organized, is at risk of violation when finished or stopped. Even if a group is committed to publish, its members will be tempted to present before publishing.

The problem with presentations before publishing is that they distract from effort required for publication, slow the publication process, and can create problem, as evident from the University Group Diabetes Program by presenting its primary results before publication.

Rule 6: **Analyses by the coordinating center**
Why have a coordinating center if responsibility for analyses are done elsewhere? Its people will know the data better than anyone else in the study and the center should have more experience and expertise analyzing data than any other center in the trial.

Rule 7: **Datasets to study investigators**
Part of what gave rise to my e-mail 7 November was the request of the study chair for a preliminary dataset to allow the chair to start work on a results publication. I have objected to the request for three reasons.

First, because it violates Rule 3 and Rule 6.

Second, as custodian of study data, the coordinating center is placed in an uncomfortable position if it supplies data to one investigator without making the same offer to all other investigators.

Third, when it comes to primary results, there is no such thing as "preliminary". Providing anyone with a preliminary dataset merely invites problems with reconciling counts in finished publications and forces the coordinating center to divert resources to maintain and update interim datasets.

Comments
The rules above are the product of the school of hard knocks. For me they are givens -- that is, until you realize every trial is a tabula rasa experience. You do not have to do more than two trials to discover that it matters little to the next group what your war stories are because every new group thinks the problems you enumerate will not befall them.

Hope springs eternal!

Usually, by dent of persistence, I manage to get groups to buy into the rules when they organize but they get forgotten and eroded as the trial goes on.

One of the things that keeps me going in trials is the opportunity each new trial presents for making new mistakes. I am still making them! The frustration is making the same old ones.

Deviate from the Yellow Brick Road and the likelihood is that you are making the same old ones.

All of this gives me pause as a teacher. There is nothing to teach people who know what I am talking about and nothing they will learn if they do not know what I am talking about.

Alas. An empty set?

Woe is me!