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Memorandum

To: Trialists

Fr: Curtis Meinert

Re: In search of the Yellow Brick Road for coordinating centers

My e-mail of 7 November to a number of coordinating center directors, study heads, and sponsors posed five questions.

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 where 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 blackout depending on 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?

I had my own answers to the questions, but I am a hard ass so I wrote to see if it needs annealing.

I got responses from twelve people; three from study chairs, six from directors of coordinating centers, and three from representatives of NIH sponsoring agencies. Summaries of responses are below.

Operation under results blackouts?

Blackouts are universal among respondents. All twelve indicated operations under results blackouts.

When is the blackout lifted, how is it lifted, and are the rules different depending on sponsor?

Excerpts of answers reproduced below.

Generally, well in advance of publication of main results so that clinicians can prepare for informing patients and provide comments on main results paper.

With industry supported trials, usually the investigators find out about the results when they see a press release. After the press release they are notified in writing of the overview of the results by the sponsor. The sponsor generally has a study group meeting after that to share the results. The NIH trials are somewhat more varied, but follow a general theme. For most of them the investigators are treated as "authors" and are involved in the manuscript preparation. This means that they (usually all PIs) see the data prior to its release. They generally sign confidentiality agreements at the time they see the data restricting release until the time of the embargoed press release. As a rule, no data are publicly released until the manuscript is published. Embargoed material is released to the press about a week ahead of time to allow for thoughtful preparation on their part. Investigators are encouraged to participate by talking to the press at the time of the press release (linked to manuscript release, which these days is usually an expedited e publish).

Blackout lifted after the DMC recommends publication of findings, typically when they also recommend halting accrual, and results are presented to clinical personnel.

Only when the last participant contact has been completed and data entry finished.

Generally via an investigator unmasking meeting usually/ideally in conjunction with review of a draft manuscript.

At the end of the trial, typically at a meeting of the group (either planned or scheduled for that purpose) before publication.

Concern with data release also centers around when patients should be informed of results. One wishes for this to occur before release of the data by the press and is timed close to date of publication. Journals are publishing manuscripts on-line first and later in print. The turn around time to inform all who need to know before wide public release of data has been crunched significantly.

In industry trials, the timing of release depends in part on whether the company is privately or publicly held. In publicly held companies, the investigators learn through the press release. In privately held companies, they may be told at a meeting prior to a press release. The difference is due to the SEC and the possibility of insider trading.

It varies. Some pharma trials never present the final results to the investigators. Sometimes, for landmark studies, they do so with great ceremony in a big event that just precedes the public disclosure of the trial to the scientific community at a meeting.

Who does the analyses for primary publications?

Coordinating center staff

For NIH trials, the Coordinating Center for the trial is responsible for the data analysis. For industry it is varied. Some do all analyses "in-house" while others have an analytic group that independently does analyses, especially for the DSMC, during the course of the study and occasionally at the conclusion. However, in general it seems the sponsor takes over the analyses at the end of the study as they prepare for an NDA or manuscript/presentation.

Depends. Usually coordinating center staff.

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Coordinating center

Analyses (i.e. data crunching) is certainly the coordinating center; however interpretation of the data as well as the analytic plan will have input from a number of sources: study investigators (study chair, resource center input) and for NIH trials from the DSMC.

For NIH trials, the Coordinating Center for the trial is responsible for the data analysis for primary study publications.

In some cases, statisticians within the same coordinating center can be responsible for the interim analysis - unmasked and then when the DSMC recommends unmasking, the statisticians involved with the running of the trial at that same CC do the analysis for the primary publication.

Interpretation of the data as well as the analytic plan (ie, Statistical Analysis Plan created before data are unmasked) will have input from a number of sources in addition to the coordinating center statisticians: Sponsor, study investigators (study chair, resource center input) and from the DSMC.

For industry trials in cardiology, the Steering Committee operates much like the Steering Committee in NIH sponsored trials – writing the paper, interpreting the data, etc. The Steering Committee is usually a combo of academics and Sponsor representatives. My experience in other fields is much more varied; often the Sponsor writes the paper (or, some medical writer ghost writes it) and academic folks become authors.

For pharma studies where I am a site investigator, the company statisticians perform the analysis. For investigator initiated studies, the analyses are done locally.

Are study investigators provided with a datasets and, if so, when?

After publication of main results (and important secondary papers), the dataset is available to people who request it. Few if any requests for the data itself – investigators work through the Coordinating Center for analysis, sometime such analyses are done unfunded.

I have never been involved with an industry study that provides the investigators with a dataset. Investigators are often asked to be involved in the preparation of a manuscript, but then, in my experience, they are given the tables that the company wants them to see (and perhaps they will do other tables if requested or even in some cases work directly with the statistical group doing data analysis). Investigators in the NIH trials are often ex-officio on the DSMC so they see evolving data sets and at study completion are actively involved with the Coordinating Center in carefully culling results from the full data set. The writing team is involved at this level, but usually only this small group has direct access to the full data set. Generally the NIH studies release to full data set for public review after publication. In theory, the new FDA regulations will require data from all registered clinical trials to be released after the conclusion of the trial.

No datasets have been provided to investigators before the study (trial) ended. (It has been difficult enough after the trial ended.)

Depends on the project. The [xxx] requires a data use agreement even from investigators and we provide either the 'deidentified' dataset that has certain values scrubbed, or a custom-created dataset generated for the particular proposal. We do not distribute 'identified' data to the investigators.

and whether study investigators get a finished study dataset when the trial is done? No -- slide set, yes, but not a dataset.

No. Data Sharing is now an NIH mandate and investigators, including the Study Chair, would have access to the same datasets as the general public. As you are aware, NIH does not provide funding for the CC to tailor data sets for individual use.

Yes if requested (rare), typically after publication.

Again, in my experience, the practice in cardiology differs from other fields. In many of the large-scale Phase 3 trials in cardiology sponsored by industry, the industry gives the database to the principal investigator to perform further analyses. A lot of cardiologists I know will not participate in trials unless there is a promise of a release of the database to the PI. I know that there are intense negotiations concerning access and intellectual property in these transfers.

In the [xxx], the study dataset is distributed as a limited use dataset or as a particular analytic dataset to investigators who request it with a data use agreement. This is not done until the mainline manuscript is completed, but we do not necessarily have a rule about this.