



## Center for Clinical Trials

Department of Biostatistics  
Department of Epidemiology  
Department of International Health

Department of Medicine  
Department of Ophthalmology  
Oncology Center

(Tuesday 7:51am) 17 April 2001

### Memorandum

To: Center for Clinical Trials faculty and staff

Fr: Curt Meinert

Re: A primer on how to produce "good" treatment effects monitoring reports

### Definitions

**treatment effects monitoring** *v* - **Monitoring** done to assess the effects of treatments used in a trial as measured by designated **treatment comparisons** and for the purpose of deciding whether the trial should continue unaltered. Typically, a process starting early in the course of the trial and continuing to its planned end or until a decision is made to stop it as a result of the monitoring. The monitoring may be done in **masked** or **unmasked** fashion and may be done by a single individual or a formally constituted **treatment effects monitoring committee**. In **multicenter trials**, usually performed by such a committee using **treatment effects monitoring reports** prepared by the **data center**, **data coordinating center**, or **coordinating center**. *syn* (not recommended): **data monitoring**, **safety monitoring**, **data and safety monitoring** *Usage note:* Harm, in the context of trials, can arise from use of a bad treatment or failure to use a good one. *Safety* in **safety monitoring** or **data and safety monitoring** suggests that the monitoring is concerned primarily with preventing harm arising from use of a bad treatment. The terms are largely silent on the aspect of harm arising from failure to use a good treatment. **Treatment effects monitoring** provides a better description of the process involved by keying on the focus of the monitoring (**treatment effects**) and avoids the one-sided emphasis by neutrality. The term **data monitoring**, while also neutral, is not informative. Technically, any ongoing process involving periodic assessments of **data** of any kind constitutes a form of data monitoring.

**treatment effects monitoring committee (TEMC)** *n* - [**trials**] A standing **committee** in the structure of **single** or **multicenter trials** responsible for the periodic review of accumulated **data** for evidence of **adverse** or **beneficial treatment effects** during the trial and for making recommendations for modification of a **study treatment**, including termination, when appropriate. One of the **key committees** in the organizational structure of a multicenter trial. Usually constituted such that voting privileges are restricted to members not directly involved in the execution of the trial and not associated with participating **centers** or **sponsors** of the trial. Others, such as **officers of the study** or other **key study investigators**, if included as members, serve without vote. Voting members are appointed by the **sponsor** (defn ?) or **research group**, often with the advice and consent of the other party. The committee reports to the appointing authority and usually to the other party via the appointing authority or directly. *syn* (not recommended): **data monitoring committee**, **data and safety monitoring**

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**committee**, ethical committee, **ethics committee**, **safety monitoring committee** rt: **advisory-review and treatment effects monitoring committee**, **external treatment effects monitoring committee**, **internal treatment effects monitoring committee** *Usage note: Data monitoring committee*, though commonly used, is not recommended because the most common usages of **data monitoring** occur in relation to **data collection** and **quality assurance**. **Safety monitoring committee** is not recommended because of the implication that the monitoring relates only to **safety** and not to **efficacy**. Perhaps, the most common name is **data and safety monitoring committee** but it suffers from all the drawbacks listed above; hence is not recommended. The preferred descriptor is *treatment effects monitoring*; preferred because of its currency in suggesting what is done and because of its neutrality with regard to safety versus efficacy. The committee may have a compound name when the treatment monitoring function is vested in a committee having other broad responsibilities, eg, **advisory-review and treatment effects monitoring committee**.

**treatment effects monitoring report** *n* - A report, prepared during the course of a trial that uses accumulated data and provides a comparison of the various **treatment groups** represented in the trial for the **outcomes** of interest. It is used by those reviewing it as a vehicle for deciding whether the trial should continue unaltered. Typically prepared by the **coordinating center**, **data coordinating center**, or **data center** and reviewed by the **treatment effects monitoring committee** in the case of **multicenter trials**.

### Introduction

If your only experience with TEMCs is with half-baked materials distributed loose leaf in dribbles you can think that dribbling is the norm. If you work in a Center where the Director expects even your last will and testament be page numbered, you can think page numbering is the norm. If you have never seen a bad TEM report you will never know when good is good. That said, I feel obliged, to do my part in making certain that all those who read this know what it takes to produce a bad report so they can produce good ones.

By now, I have sat on dozens of TEMCs as an outside "independent" member. That role has provided me with glimpses into the inner workings of coordinating centers in "feeds" to TEMCs. Suffice it to say that not all "feeds" are elegant.

The motivating force behind this essay is my most recent experience as a member of an industry-sponsored trial. It has been a particularly enriching experience.

### The habits of TEMC members

Before getting to **How tos**, it is useful to summarize habits of TEMC members.

1. The review of the report is likely to take place on planes to the meeting.

#### Comment

Virtually, all members are just in time (JIT) reviewers. After all, why prepare too soon? You are likely to forget half of what you learned before the meeting, and if you should die before the meeting you will have wasted valuable time!

2. The typical member "stack files".

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**Comment**

The purpose is to avoid wasting time in dribbles by reading the stack enroute to the meeting. There is no doubt that the strategy saves time except when the most recent missive is a cancellation notice and you are reading the notice as the plane pushes back from the gate!

3. The "typical" member is likely to arrive within minutes of the start of a meeting and leave before it is finished.

**Comment**

This behavior is a consequence of the JIT nature of reviewers. Why waste time getting to a meeting early and why waste more time by staying to the end? Experienced members know that meetings do not start on time and that they always end early, usually with the first departure for the airport.

4. The person with the shortest distance to travel arrives last and late.

**Comment**

This behavior is important to remember if that person runs the meeting.

5. Even the most informed member of the TEMC is likely to be hazy on details of the trial.

**Comment**

The haze can be as thick as pea soup if a person misses a meeting or two. For most members, missing a meeting is the operational equivalent of a stroke.

**How tos**

**How to 1:** Ensure that the person presenting the report has nothing to do with generating it.

**Comment**

This **How to** is important in ensuring "Alfred E Newman" objectivity in the presentation.

**How to 2:** Make certain that there is no one at the meeting involved in generating the report.

**Comment**

The absence of all such persons eliminates the possibility of their being able to bias deliberations by tonal inflections or facial expressions.

**How to 3:** Impose structure at the data center to keep personnel in the dark as to treatment assignment and to keep them from talking to one another when generating the report.

**Comment**

The structure has the advantage of enforced objectivity and helps ensure that not even people in the data center know what is going on in the trial.

This approach, no doubt, leads to reports with inconsistencies, but even the inconsistencies serve a useful purpose. Reviewers generally delight in finding inconsistencies. Usually, the more they find the better they feel.

**How to 4:** Mask the report.

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**Comment**

Among all the **How tos**, perhaps, this one is the most important. The mask ensures that members will spend most of their time trying to break the mask and arguing as to whether it should be lifted.

**How to 5:** Use MDCs (minimal distinguishable character) like X and Y or O and Q for masking.

**Comment**

To realize the full advantage of this **How to** use in combination with **How to 6**.

**How to 6:** Vary the column position of results from table to table.

**Comment**

Variation is likely to be a natural consequence of **How to 3**.

The variation has the advantage of keeping members from over-preparing enroute to the meeting. They are likely to be discouraged from doing so because of uncertainty as to whether the result in any given table is for X vs Y or for Y vs X. The simple fact is that the 8 candle power overhead lights on planes are simply not adequate to allow for differentiation of MDCs (especially when the shades are drawn to accommodate the hypothetical few intent on watching the "movie").

Over-prepared members are easily bored and bored members are prone to sleep, daydreaming, time-sharing (usually by working on a manuscript or grant application) or to be disruptive during the meeting.

**How to 7:** Code results differently from report to report; use MDC codes.

**Comment**

The advantage is that the recoding ensures a tabula rasa approach to monitoring. The recoding erases memory and carryover from previous reports. Hence, every meeting is a new adventure!

The recoding has the added advantage of making code busting more of a challenge (see **How to 4**).

**How to 8:** Maintain the masking even for adverse events.

**Comment**

After all, when it comes to trials, is it not the goal to ensure absolute blind objectivity, even at the expense of competency?

**How to 9:** Collect reports at the end of the meeting.

**Comment**

Collection avoids worries of "leaks" and ensures a "fresh" start for the next review. It also helps to eliminate the "nit picking" likely to occur when members are able to consult previous reports.

**How to 10:** Do not provide a design synopsis.

**Comment**

This recommendation is second only to **How to 4** in keeping members on their toes. The lack of such information tends to increase attentiveness during the meetings. Most members will be reluctant to ask questions concerning basic aspects of design for fear of revealing their ignorance. Hence, they will be more prone to listen attentive in efforts to divine sufficient information to understand the results.

The assumption should be that members are intimately familiar with the protocol and that it is an insult to their prowess as reviewers to remind them of such basics as the treatments being tested, the sample size requirement, and the outcome measure. Surely, it is reasonable to assume that they will retain those basic facts from meeting to meeting.

**How to 11:** Do not provide a listing of members.

**Comment**

The rationale for this **How to** is similar to that for **How to 10**. Why run the risk of insulting the recall powers of members by providing such a listing?

**How to 12:** Do not provide name tags for members.

**Comment**

See **How to 10**.

**How to 13:** If place cards are provided print only on one side; arrange so as to readable only from across the table.

**Comment**

Since people seated next to one another introduce themselves, the time and effort needed for two-sided print is a waste.

Besides, because only half the place cards are readable when one enters the room, people have to mill around to find their rightful place. The milling increases the chance of people getting to know one another while hunting for their rightful places.

**How to 14:** Do not provide a table of contents for reports.

**Comment**

The absence of a table of contents makes going through reports more adventuresome.

**How to 15:** Do not provide minutes of meetings.

**Comment**

The rationale is largely the same as for **How to 10**.

**How to 16:** Do not provide an agenda.

**Comment**

A "let it roll" approach makes for more interesting meetings.

**How to 17:** Supply reports loose leaf.

**Comment**

The fear of "messing up" the report will cause members to treat them with respect (especially after the first "drop").

**How to 18:** Supply reports without page numbers.

**Comment**

See rationale for **How to 17**.

This **How to**, in combination with **How to 17**, creates what is known, in the trade, as "partial deck anxiety". The anxiety is the result of fear of having a report with missing pages. The anxiety makes for more attentive members.

The anxiety is most acute in members who have dropped their reports in sardine (usually while making room for an airline "snack"). Without page numbers, they will have no way of knowing if the recovery was "full" (unlikely without crawling on one's hands and knees after the plane has landed; even then the chance of a full recovery is roughly akin to the chance an astronaut has of retrieving a tool floating in space).

**How to 19:** If pages are numbered, vary location from table to table and use MRF (minimal readable font).

**Comment**

There is no agreement as to the MRF, though Microsoft seems to be the standard setter with its Windows products.

The use of a MRF for page numbering has a distinct advantage. The lack of legibility and the resulting "wrong page anxiety" make members less willing to talk, especially the more senior members (because of poor vision) – the people who tend to talk too much anyway!

**How to 20:** Produce tables using SAS or other similar products.

**Comment**

This **how to** is a natural consequence of **How to 19**. Even if the font is large enough, the formatting will be klutzy enough to make reading and interpretation difficult, thereby helping to make members more attentive.

**How to 21:** Use the MRF for explanatory notes to tables.

**Comment**

This rule stems from the general practice in everyday life of printing the things that are most important in a MRF. Continuing that practice when producing a TEM report helps to underscore the importance of notes and ensure that they are read.

**How to 22:** Vary terminology from table to table.

**Comment**

Doing so has the advantage of keeping members on their toes by using different terms to mean the same thing.

**How to 23:** Use terms such as dropout, withdrawal, and lost to followup, without definition.

**Comment**

The rationale is the same as for **How to 22**.

**How to 24:** Supply the report without a glossary of terms and abbreviations.

**Comment**

The advantage is the same as for **How to 22**.

**How to 25:** Regale members with a flurry of handouts during the meeting; distribute loose leaf and unstapled.

**Comment**

The flurry creates the impression of "timeliness".

**How to 26:** Delay instructing members as to where handouts go in the report.

**Comment**

Delay makes insertion challenging, especially when the report itself is not page numbered. The usual approach in such cases is for someone to direct the activity more or less as follows: "This page (holding it up), and the two after it in your folders, goes about this far into the report (measuring distance with thumb and forefinger). It goes after Table 7.1.2.4.1 and before Table 8.1." The diversion helps relieve boredom, likely to roll over the assemblage much like a Cape Cod fog about 2 hours into the meeting.

**How to 27:** Provide updates and corrections to the report in willy-nilly fashion over the course of the meeting.

**Comment**

A bumbling Colombo-type style, when properly maintained, conveys competence. The flipping around and backtracking inherent in the style can be useful in reminding members of things likely already forgotten.

**How to 28:** Vary denominators.

**Comment**

This **How to** is important in making discussion more enlivened by arguments concerning counts. The arguments will help keep the more passive members from dosing.

**How to 29:** Do not present totals.

**Comment**

The absence of totals will give members something to do while in sardine and during lulls in the meeting.

**How to 30:** Present tables with varying denominators.

**Comment**

The lack of consistency will serve to make members more attentive and pensive.

**How to 31:** Provide listings of adverse events without summary counts.

**Comment**

The approach has the advantage of making the flight to the meeting seem shorter because of time spent in compiling a summary table.

**How to 32:** Do not provide p-values.

**Comment**

Rationalize by arguments that p-values can be misleading.

The absence of summary statistics has the virtue of leaving members in the dark as to importance of differences and, hence, increases objectivity.

**How to 33:** Be cryptic in titling tables and figures.

**Comment**

The lack of crispness has the advantage of generating speculation as to the content of tables.

**How to 34:** Do not provide run dates or cutoff dates for data in the report.

**Comment**

See **How to 30** for rationale.

**How to 35:** Do not provide rules for quorums or for voting.

**Comment**

The absence of such rules makes for interesting discussion and debate when a vote has been taken.

**How to 36:** Give only rudimentary information as to location of the meeting.

**Comment**

Members should be smart enough to figure out where the meeting will be held. Those that are not probably should not be at the meeting anyway.

**How to 37:** For meetings held in hotels, make certain that the listing at the front desk does not correspond to anything members are likely to recognize.

**Comment**

This approach ensures that members will browse through the menu of meetings and, hence, provide an opportunity to do other things if the meeting ends early.

**How to 38:** Arrange to have the meeting in a small room.

**Comment**

The advantage of crowding is that it keeps the meeting from running too long and keeps members in shape for the ride back home in sardine.

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