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Memorandum

To: Center faculty, staff, and friends

Fr: Curt Meinert

Re: Internal presentation of results

This is the seventh in a series of memos concerning issues in the presentation and publication of results from trials. Previous memos have dealt with the obligation to publish, investigator right of primacy, limits to that right, type and place of publication, deposit of finished datasets, and external presentation of primary results.

It is a given that results presented at scientific meetings are seen, first, by study investigators. It is obvious as well that, whether or not results are presented at a scientific meeting, investigators have to see results in relation to recommendations for change coming from a TEMC and on completion of the trial. The issue here is whether investigators should see treatment results at other times over the course of the trial.

The operating philosophy of the UGDP was for investigators to see results by treatment group. Indeed, the SC was responsible for monitoring the trial and it was that body that decided to stop use of tolbutamide and later on phenformin based on results they saw as the trial proceeded.

The picture today is different. The "norm" is for investigators to be shielded from interim results; to know nothing of treatment results until the trial is finished or until they are presented in conjunction with a recommendation for change from the TEMC. The rationale for the shielding arises from the concern that knowledge of results will lead to treatment-related feedback.

treatment-related feedback bias *n* - 1. Bias in an observation, measurement, reporting, analysis, or administration process or procedure due to knowledge of interim treatment results on the part of the one observing, measuring, reporting, analyzing, or administering. 2. Differential behavior of persons enrolled into a trial due to their having knowledge of interim treatment results, eg, a differential loss to followup due to differences in the willingness of persons to continue because of their having knowledge of non-nil interim treatment results. ***Usage note***: Use with caution as a claim or assertion. The existence of a feedback bias is difficult to establish. It does not operate in the absence of knowledge of interim results and is unlikely to operate in the presence of nil interim treatment results.

> Knowledge of an interim treatment result is not sufficient for the bias to operate. One must also be able to argue plausibly that knowledge can produce the bias. It is difficult to do so in masked trials, and especially in double-masked trials. Even if a treater has access to interim results, that information, to translate into a treatment-related bias, must be related to individual patients and must influence how that person treats or observes in the trial. It is not possible to relate results to individual patients if the treater is effectively masked to treatment assignment. Further, even if a treater or data collector is not masked, it is difficult to argue plausibly that a treatment difference is due to a treatment-related feedback bias if the process or procedure in question is robust to the bias. For example, there is not much of an opportunity for the bias to operate if the measurement in question is not prone to errors of interpretation or reporting (eg, as with most event-type outcomes, such as death or events indicative of gross morbidity). Nor is there much room for the bias to operate if a process or procedure is well-defined (eg, as in a treatment protocol with explicit rules for when and how treatments are to be altered in the presence of specified conditions). Generally, the more objective the process or procedure, the more difficult it is to plausibly argue that knowledge of interim results can produce a treatment-related feedback bias.
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> (*Clinical Trials Dictionary*; Meinert, 1995)

The norm is for trials to operate under an imposed frozen state of equipoise – a state achieved and maintained by a results blackout[2] and apartheid treatment effects monitoring structures.

frozen state of equipoise *n* - An imposed state intended to keep study investigators from knowing the nature or trend of interim results; achieved by proscription of interim analyses or by constructs to shield study investigators from results of interim analyses, eg, as in

[2] There is evidence that the blackout construct may be crumbling. The AIDS trials have created cracks in the construct. More recently, the requirement that investigators provide IRBs with reports from TEMCs serves to increase the probability of glimmers in the blackout. A guideline promulgated in 1998 (18 June 1998; grants.nih.gov/grants/guide/notice-files/not98-084.html) specifies that: *IRBs should be provided feedback on a regular basis, including findings from adverse event reports, and recommendations derived from data and safety monitoring* and in an 11 June 1999 guideline (grants.nih.gov/grants/guide/notice-files/not99-107.html) that: *In lieu of receiving individual adverse event reports from each of the clinical sites, the IRBs should receive from the investigator a written summary report whenever a data safety monitoring board (DSMB) review has taken place. ... The DSMB's summary report should provide feedback at regular and defined intervals to the IRBs. The Institutes and Centers should assure that there is a mechanism in place to distribute the report to all participating investigators for submission to their local IRBs.*

apartheid treatment effects monitoring. ***Usage note***: Not to be confused with masked treatment administration. The state exists independent of treatment masking (eg, as in the UGDP — the oral hypoglycemic treatments in that study were administered in masked fashion; the monitoring was done by the directors and deputy directors of the various participating centers with interim analyses with treatments identified). Also not to be confused with masked treatment effects monitoring. The monitoring, whether or not done by study investigators, may or may not be masked. The state is maintained to the extent that investigators, individually and collectively, refrain from performing their own interim analyses. That capability exists in unmasked trials, and in masked trials to the degree that treatments can be identified. The state may be imposed on all study investigators or on a selected subset, eg, all personnel involved in treatment or data collection (as in apartheid treatment effects monitoring). The state is imposed to reduce the risk of treatment-related feedback bias. Concerns regarding that bias are greatest in unmasked trials, but are present in masked trials to the extent that masking is ineffective.

(*Clinical Trials Dictionary*; Meinert, 1995)

results blackout *n* - 1. Any of various imposed constructs intended to keep treatment results from being revealed or made known to the public until presented or published by study investigators. 2. Any of various constructs imposed during the conduct of a trial to keep all but those persons responsible for treatment effects monitoring blinded to interim results, eg, as required in imposed states of equipoise.

(*Clinical Trials Dictionary*; Meinert, 1995)

apartheid treatment effects monitoring *n* - Treatment effects monitoring performed in such a way so as to keep study clinic personnel and study patients from seeing or knowing interim treatment results; typically done by constituting a treatment effects monitoring committee absent study clinic personnel, by closed deliberations, and by proscription of dissemination or discussion of interim results (except within the committee) until the trial is completed or until it has produced an actionable interim treatment result (defn 2). ***Usage note***: The origins of this form of monitoring had to do with concerns regarding treatment-related feedback bias and the desire of organizers of trials to preserve treating physicians from conflicts of interest (defn 2). The apartheid notion is contained in a recommendation of the NIH Clinical Trials Committee. It recommended (in regard to treatment effects monitoring committees for multicenter trials) that: *The unit should consist of clinicians expert in the disease under investigation, biostatisticians, and scientists from*

> *other pertinent disciplines. Physicians engaged in the care of study patients or directly responsible for evaluating clinical status are excluded.*[3]
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> (*Clinical Trials Dictionary*; Meinert, 1995)

Given the blackout norm, what can investigators see routinely? Obviously, they must see results related to performance because they are responsible for the trial. There is also no reason to shield them from descriptive information concerning the study population, including baseline data by treatment group.

But what else? How about results over time for one of the treatment groups or for all the treatment groups combined? Usually the answer is no for trials operated under the blackout mode.

Of the two options, the second is least defensible. The trend observed provides clues as to treatment differences. For example, if the trend displayed is flat, it must be because of counterbalancing treatment effects or because none of the treatments are effective.

The first option avoids such speculations or "inferences". Indeed, the option has some appeal when the control group is untreated. For example, investigators in the CDP, while shielded from results by treatment group, routinely saw results for the placebo-treated group and they used results from that group to produce a number of "natural history" papers over the course of the trial.

However, the option is not viable when the control group is treated and is not usually exercised even when the control group is untreated because of concerns of biasing the trial in some way or for fear of exposing it to avoidable criticism.

[3] A word of caution: One can argue that monitoring bodies devoid of study investigators or that are appointed by and report to sponsors are unethical in that they do not provide an inviolate linkage to investigators. All ethical codes, starting with the Nüremberg Code, make it clear that investigators are responsible for ensuring the safety and well-being of those they study. The duty cannot be assigned to third parties. The required linkage is assured when investigators are seated as members of the TEMC (usually as non-voting members) and when the TEMC reports directly to study investigators, or simultaneously to investigators and sponsor. Arrangements in which that body is devoid of study investigators and reports to the study sponsor have the potential of severing the linkage.