



22 June 2016

Memorandum

To: Trialists

Fr: Curtis Meinert

Re: Things learned from a half century of trials

Even robots learn, so there is no doubt I have learned from my years of doing clinical trials. I could probably write a book on the topics but, here, I limit myself to a few lessons gleaned over the years.

Avoid trials with numbers in their names

This rule is a corollary to one I taught my kids to avoid movies with numbers in the title because they are usually not as good or interesting as the originals.

Stay out of trials with names that can be pronounced

This rule is because of the abuse you can suffer when people play games with the name, e.g., as with MRFIT (Multiple Risk Factor Intervention Trial) that became Mr Fit and than Ms Fit by critics who were incensed because the trial involved only males.

The reality is that even if you stick to the rule, there is no guarantee that the letters you use to create a name will not work against you. My first trial was the University Group Diabetes Program or UGDP. Critics, when we produced results they did not like, referred to it as the GD UP.

Steer clear of trials with contrived pronounceable names

Unfortunately, here I violated my own rule by getting involved in STURDY: *Study to Understand Fall Reduction and Vitamin D in You*. It is a randomized trial, but you would not know that from the name.

The person with the shortest distance to travel will be the last to arrive

Meetings adjourn with the first departure for the airport

Working lunches don't work

It is easier to keep order in meetings held by conference phone than when face-to-face

I learned this early on from involvement in the UGDP. UGDP investigators were an unruly bunch. The best that could be hoped at meetings was for no more than three people talking at the same time. If anyone was familiar with Robert's Rules of Order it was not readily apparent and, indeed, when someone attempted to restore order by citing one of his rules the citation was more likely to produce debate about the rule than order.

Yet, this same group, when convened by conference telephone, was polite and conversations orderly. This contrast led me to suggest, during a particularly chaotic debate at a meeting, that the group retire to their respective rooms and have the hotel telephone operator arrange a conference call.

It will take you twice as long to get half the planned sample size and the event rate will be half that used when planning the trial (the rule of twos)

Those who love to travel haven't

Document!

I learned the importance of documentation on the farm, so it was no surprise, having created the randomization scheme for the UGDP, that I documented the scheme.

Ten years later, soon after the start of the firestorm of criticisms of the UGDP tolbutamide results, the International Biometrics Society was asked to review the UGDP. The Committee came calling in August of 1972. The first thing its members wanted to see was the “recipe” for randomization and the methods of administering the schedule.

Accordingly, people in the Center were sent scrambling to locate said documentation. About 30 minutes later in comes a person with the desired documentation – presented with obvious pride with a filing system capable of yielding a document as obscure as the one desired.

I then proceeded to read the document for the Committee, but after a few sentences I realized it was not written in English. Sentences, obviously crystal clear when I put pen to paper years back, were now strangely incomprehensible. Clearly, something had happened to the words during those many years in a dark filing cabinet!

The lesson overlooked was to have someone read what I had written to make certain it was written in English before “filing” away. That step was skipped in the “recipe” documentation.

The time to produce policy is before it is needed

The tolbutamide mortality difference emerged over time. At first, it was a matter of indifferent curiosity to investigators, but eventually the indifference turned to concern. The difference became a focus of concern by 1967. By 1968 there were a few investigators suggesting that the prudent course was to stop use of tolbutamide.

The trend was evident in the results presented at the 1969 spring meeting of study investigators. After considerable discussion, a motion was made to stop tolbutamide. A vote was taken. The vote carried, but just barely, too close to make the group comfortable with taking any action.

The voting policy (established early on) was two votes per center – two for each of the twelve clinics and two for the coordinating center (one vote for the center director and one for the deputy director) – but without any clear policy on proxy votes, “stand in” voters, or the designation, “deputy director.” The ambiguities were noted when the policy was drafted, but considered not important because voting would be unnecessary in the expectation that major decisions would be by “consensus”.

The time to figure out who has a vote is before there are issues to vote. Consensus is wonderful, but it is certain only in groups of size one.

Publish first, present later

I am a member of the "publish first, present later" school when it comes to results of trials, even though that rule was violated in my first trial with the UGDP tolbutamide results.

When you produce results the world does not want to hear, the problem is with you, not the world