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Memorandum

To: Trialists

Fr: Curtis Meinert

Re: Counting 101

Counting is the most important thing you do in trials and it is your neck if you do not get counts correct. Just ask investigators in the VIGOR Trial involving Vioxx after letters of expressions of concern from the editors of the NEJM.

I am a counter. Back when my sisters and brother walked home from our country school, the road we walked crossed the Chicago Northwestern railroad line. Always we laid our ears to the rail to listen for the click-clack of an oncoming train. If we heard click-clacking we waited to wave to the engineer and count cars.

I soon learned we needed a protocol if there was to be any chance of getting the same count. We knew not to count the engine but what about the caboose (remember those?) and what about deadhead engines in tow? Did they count? Even with a protocol we rarely got the same count.

I used counting as a "treatment" for my oldest daughter's panic attacks in her young adult years. I got so I could recognize them. That is when I told her to walk around the block (about a mile) and count her steps. When she returned and did not look "cured" I would say go around again and count again. Usually the second trip was a "cure".

The reason why the "treatment" worked is because counting blocks out everything else. You think it is easy. Try counting your steps from where you park to your office. You have to concentrate and even then you will screw up.

It is about 1,700 steps round trip from our front door. You can mouth the words but once you get beyond 100 "mouthing" will slow your gait and upset your rhythm. You can count to hundreds and use the finger method of keeping count of hundreds. Whatever method she used she never got the same count twice.

You live by counts in trials. During the trial and when it is finished and results published. Often the most difficult job is to get counts to jibe.

Number randomized
Number randomized by treatment group
Number dropped out
Number missed visits
Number completed visits through a specified time
Number visits outside time windows
Number lost to followup
Number dead
Number with a specified clinical event
Number not on treatment
Number finishing the trial

To count reliably you need written definitions so counts can be reproduced.

When is a person enrolled? If the answer is "when randomized to treatment" then when is that? When the assignment is issued? When the assignment is revealed to the study patient? When the assigned treatment is actually administered? Do you count a person as enrolled if the person refuses the assignment? What about a person who never receives the assigned treatment? In regard to counts by treatment group, where do you count a person who received the wrong treatment?

When is a visit missed?

The visit schedule in the UGDP was at three month intervals over the course of followup after enrollment. Each visit consisted of a general examination and, depending on the quarter, an eye, heart, kidney, or peripheral vascular examination. Visits were numbered by quarter, i.e., FU 1 for the 3rd month after enrollment, FU 2 for the 6th month after enrollment, etc.

Well and good, except for what clinics did when people missed a visit. Suppose a person did not show up for the 6 month visit but does for the 9 month visit, i.e., the second followup visit for the patient, but the 3rd required visit according to protocol. Does the clinic do the kidney exam or the heart exam? Some clinics did the kidney exam and labeled the exam as an FU 3 and others did the heart exam and labeled it as an FU 2 visit. Needless to say, counting visits to produce performance statistics by clinic was impossible without hard and fast rules as to when a visit was counted as missed. The answer was contiguous time windows that specified limits within which a visit was to be done. Visits not done in the specified time interval were counted as missed.

Many of the lessons one learns in trials are "lessons" only because of shortsightedness. It should be apparent to anyone involved in long-term trials that one keeps track of everyone, even if they dropout, so that one can classify persons as to whether alive or dead at analysis time. Anyone in charge of such efforts knows that clinic personnel have to keep up-to-date "locator" information if there is to be any hope of tracing people. Even Inspector Clouseau knows that the chance of locating persons lost to followup diminish as a function of time last seen.

The protocol in the UGDP specified that clinics were to maintain "up-to-date" locator information for dropouts, but no one paid attention to the requirement. Hence, when it came time to produce the publication describing the tolbutamide mortality results, nine years after the start of enrollment, investigators had 23 dropouts in the tolbutamide-assigned group and 24 in the placebo-assigned group with unknown vital status. Clearly, a differential mortality rate among those could be large enough to explain the observed tolbutamide-placebo mortality difference. Hence, it was obvious that investigators would have to delay publication in order to locate dropouts to determine if they were alive or dead.

Ultimately, via those efforts, investigators were able to determine the vital status of everyone enrolled, except five; one person assigned to the tolbutamide treatment group, two persons assigned to the placebo treatment group, and the other two persons assigned to the insulin-variable treatment group.

The hard core unlocatables included a person by the name of Wong who moved to Chinatown in San Francisco. He was lost among 100s of Wongs there.

The lesson is to keep "locator information" current and engage in efforts to locate people lost to followup in an ongoing fashion over the course of the trial because you never know when the end comes.

Important counts should be made by two people, independent of each other without cross talk. Just as with my brother and sisters counting cars on trains, the chance of agreement is slim because of how counters deal with problem cases. Discrepancies should be reviewed by a 3rd party and resolved. The process should continue until counts agree.