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Memorandum

To: Trialists

Fr: Curtis Meinert

Re: On investigator meetings and site visiting in trials

The recent publication of a re-analysis of the Mediterranean diet trial (NEJM June 13, 2018; doi: 10.1056/NEJMoa1800389) replacing the original publication of results in 2013 (NEJM. 2013; 368:1279-90. doi: 10.1056/NEJMoa1200303) raising questions as to the adequacy of oversight of operations when the trial was ongoing.

The trial was carried out in Spain in 169 clinics in 11 study sites. Enrollment started in June 2003 and was completed (database lock) September 2011.

The authors state "In 2013, we reported the results for the primary end point in the Journal. We subsequently identified protocol deviations, including enrollment of household members without randomization, assignment to a study group without randomization of some participants at 1 of 11 study sites, and apparent inconsistent use of randomization tables at another site. We have withdrawn our previously published report and now report revised effect estimates based on analyses that do not rely exclusively on the assumption that all the participants were randomly assigned."

Retraction and reanalysis is a trialist's worst nightmare, especially one that is five years in the making.

I was not involved in the trial so I have no knowledge of how it was organized and operated, but the fact that the problems leading to reanalysis were not discovered until after the results were published in 2013 suggests inadequate monitoring during the trial.

Bad things can happen, in spite of best efforts to protect against them. You write the best protocol ever written but it will misinterpreted or ignored by somebody. Amelia Bedelia is proof of how hard it is to write a protocol that cannot be misinterpreted.

When Mrs. Rogers was giving Amelia instructions before she left for the day, two of them were to dust the furniture and to change the towels in the bathroom. When Amelia set about her duties she did exactly as instructed. She sprinkled baby power on the furniture and cut the towels in half with scissors.

The problem with Amelia is that she is a literalist. As a protocol writer, the Amelias can drive you crazy, but the Loosey Goosey Harrys can do more harm by ignoring or "rewriting" those portions of the protocols they consider to be unreasonable or impractical and to do so without notice to study leaders. The scenario recited above by study investigators appears to be the work of Loosey Goosey Harrys.

The other problem in protocols are the Oversight Sallys. We see and hear what we want to see and hear. The UGDP required frequent glucose determinations done locally on persons enrolled. The protocol specified that clinics were to use whole blood for determining glucose, but four clinics used

serum rather than whole blood. There are reliable formulas for translating serum glucose to whole blood equivalents, but you have to be aware of the protocol deviation to apply the correction.

The way the problem came to light was during an investigator meeting and an innocent comment by an investigator about glucose determinations. That led to a comment by another investigator as to how they can use the method cited using whole blood.

"Whole blood? We are using serum"

"The protocol specifies whole blood."

"It does?"

Three things are essential if you want to minimize protocol deviations:
1: Face-to-face hell and damnation talks before starting a trial at investigator meetings,
2: Investigator meetings over the course of the trial,
and
3: Periodic site visits to clinics over the course of the trial.

The hell and damnation talks are meant to educate and put the fear of the devil in investigators regarding their responsibilities in the trial, the importance of following the protocol and randomization procedures, and consequences of violations.

The people who like to travel are those who haven't. By the time people graduate into trials they have had their fill of flights in sardine and airport meetings. If they can avoid travel they will.

The trend, increasingly, is to substitute webinars for face-to-face meetings. They appeal to investigators because it keeps them home and to funding agencies because it saves the cost of travel. So much so that it is possible now for investigators to do an entire trial and never meet face-to-face.

Webinars have their place but, they are not substitutes for face-to-face meetings. Conversation and dialogue, of necessity, is controlled in webinar settings. Interaction, of necessity, is ordered and stilted. It is unlikely we would have discovered the discrepancy in glucose determinations without the free flow of interaction in face-to-face dialogue.

The third element in trying to prevent and detect protocol violations is site visiting. That becomes increasingly difficult and time consuming as the number of enrollment and data collection sites increase. The study in question had 169 data collection sites. Making the rounds with that number is no small matter, but there is no substitute for site visiting. You have little chance of discovering protocol deviations without site visiting. If you do not want to create the structure for visiting and to fund it, you should not be doing trials.