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Memorandum

To: Trialists

Fr: Curtis Meinert

Re: On the difference between design variables and outcomes in trials

In the lexicon of trials, a *design variable* is a variable used for determining sample size in planning a trial. *Outcome*, in the lexicon of trials, is an event or measure observed or recorded for a particular person or treatment unit in a trial during or following treatment and used to assess the safety or efficacy of a study treatment.

A *primary outcome* (Meinert; John Wiley and Sons; 2012) is:
1. The event or condition the trial is designed to treat, ameliorate, delay, or prevent.
2. The outcome of interest as specified in the primary objective of the trial.
3. The foremost measure of success or failure of a treatment in a trial.
4. The actual occurrence of a primary event in a study participant.

Usage note: Not to be used interchangeably with design variable. The modifier, "primary", should be used sparingly, since primariness depends on perspective.

ClinicalTrials.gov does not define *design variable* but defines *primary outcome measure* as the planned outcome measure that is the most important for evaluating the effect of an intervention/treatment.

The reference to “planned” implies it is one and the same as *design variable* but that is not always so, especially with “early stops”.

Consider the following.

Suppose high serum rhubarb levels are widely considered to increase risks for CV deaths in adults and that the Fly-by-Night Drug Company has a promising drug touted to reduce serum rhubarb levels.

Representatives of the company approach you about doing a trial to assess the benefits of reducing serum rhubarb levels in adults with a prior history of CV disease.

You push for a trial with death as the outcome, but the sample size measures in the thousands and the length of time to do the trial measures in decades, so you use change in serum rhubarb levels as a surrogate outcome measure, hoping that reductions in serum rhubarb levels will translate to reduced CV mortality.

You do the trial. About half way through you discover, in spite of marked reductions in serum rhubarb levels achieved with the drug, that mortality in the drug-assigned group is much higher than in the placebo-assigned group.

You stop the trial and publish the mortality results and end up with a brick bath by a medical community that believes in the drug. You are accused of data dredging because the trial was not designed to detect mortality differences and, hence, that you had no business looking at mortality.

Bottom line: Not all outcomes are equal. Higher order outcomes trump lower order outcomes, even those used in designing trials. You have a responsibility to publish. Brick bath or no brick bath.