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Memorandum

To: Trialists

Fr: Curtis Meinert

Re: Counting protocols

Living through the 2020 presidential election we got schooled in counting, recounts, and re-recounts. If there was anything to learn from that, it is that counting is difficult and that counts are never the same.

I was born a counter. I went to a country school about 100 yards from the Chicago-Northwestern railroad line. On the way home my sister and I would lay our ears to the rails and listen for the characteristic clicking of an approaching train. If we heard clicking we sat and waited to count cars and wave at the conductor in the caboose.

Even though we had a counting protocol, we rarely got the same count.

Our farm was on US Highway 14 – the Black-Yellow Route (because it went though the Black Hills and terminated at the entrance to Yellowstone).

When I was bored, I counted cars. I quickly learned the need for rules.

Did I count cars from both directions or just from the east or west? What about pickups? Did they count? What about a car in tow? What about cars on car carriers? Did they count? What about motorcycles? What about tractors and four wheel utility vehicles?

I did not know then that counting would be central to my career as a trialist years later.

The foundation for counts in trials is persons enrolled. To count you have to have some indelible event which, when transpired or encountered, the person is counted as enrolled.

Simple enough. The hard part is choosing the event marking enrollment. What is it? When the assignment is issued, when disclosed to personnel in the study clinic, when disclosed to the study subject, or when the treatment is administered? Assignment is predicated on the assumption that the person has been informed about the trial and associated risks and benefits, has agreed to accept whatever treatment is assigned, and has consented to enrollment.

The standard approach is to count everyone assigned, and to count to the treatment group to which assigned even if the person did not get any treatment or received the wrong treatment, i.e., counting by assignment as issued or counting by “intention to treat”.

The primary analysis should be by these counts. It does not preclude other analyses based on other counting schemes.

In an ideal world, everybody enrolled in trials would be followed to the appointed end of the trial for the design variable (the variable used for determining sample size in planning a trial), but the

world of trials is far from ideal. The focus of counts can change mid-course if differences emerge for a higher order outcome (e.g., mortality differences in a trial with a clinical event as the design variable).

In the typical trial there are dropouts, dropins, losses to followup, and withdrawals, and even, perhaps, treatment mixups.

A practice sometimes pushed by IRBs is to allow people to withdraw study data after enrollment. The practice is ill-conceived.

The enrollment consent should make it clear that persons can withdraw at any time during the trial without consequence, but that data collected during the trial cannot be withdrawn. Ill-conceived because once data are collected they can reside in dozens of files for processing and storage. Operationally it is virtually impossible to expunge them once in data systems.

Typically counts by treatment group are done several times over the course of a trial in relation to treatment effects monitoring; aka data and safety monitoring. A good practice in producing those reports is for two people, independent of each other, to replicate essential counts and to adjudicate differences. Counting errors can be embarrassing.

The problem is keeping track of losses to followup. Differential losses may be evidence of adverse side effects of the treatment. Keeping track of dropouts requires ongoing effort over the course of the trial. You never know when you may need to know about them if differences approach stop conditions during the trial.

Counting vocabulary

Adapted from *Clinical Trials Dictionary: Terminology and Usage Recommendations*; 2nd ed; John Wiley and Sons; 2012

baseline (Bl, BL) *n* - 1. An observation, set of observations, measurement, or series of measurements made or recorded on a person just prior to or in conjunction with treatment assignment that serves as a basis for gauging change in relation to treatment assignment. 2. An observation, series of observations, measurement, or series of measurements made or recorded at some point after enrollment in relation to some act or event that serves as a basis for gauging change thereafter (e.g., a blood pressure measurement made in relation to an increase in dosage of an anti-hypertensive drug to measure the effect of the increase). ***Usage note***: Subject to varying uses. Typically, in trials, unless otherwise indicated, the term should be reserved for characterizations that are consistent with defn 1. Baseline observations in most trials arise from a series of baseline examinations, separated in time by days or weeks. Hence, the time of observation for one baseline variable, relative to another, may be different.

drop-in *n* - 1. A person who receives a study treatment different than the one assigned in a trial. 2. A dropout who returns to a study for active followup and treatment.

dropout *n* - 1. One who terminates involvement in an activity by declaration or action; especially one who so terminates because of waning interest or for physical, practical, or philosophical reasons. 2. A person who withdraws from a trial. 3. A person who fails to appear for an unbroken sequence of scheduled followup visits, e.g., a person so classified after having failed to appear for three consecutive followup visits as defined by specified visit time windows. 4. One who refuses or stops taking the assigned treatment. 5. One who stops taking the assigned treatment and whose reason for doing so is judged not to be related to the assigned treatment. ***Usage note***: Use should be limited to that of defns 1 and 2. Most trials require continued data collection regardless of course of treatment. Hence, a "dropout" in the sense of defns 4 and 5 will continue to be an active participant in regard to scheduled data collection. Persons meeting the requirements of defns 4 or 5 are better characterized in relation to treatment adherence. Avoid uses in the sense of defn 5 because of difficulty in making reliable judgments regarding the reason a person stops taking the assigned treatment. The stated reason may not be the real reason and seemingly vague reasons, which on the surface do not appear to be related to treatment, may be treatment-related. Defn 2 includes those who actively refuse, those who passively refuse, as well as those who are simply unable to continue for physical or practical reasons, e.g., because of

having moved to a location where it is no longer possible or convenient to return for scheduled visits. Further, the definition allows for the possibility of a person being designated a dropout as a result of failure to return for scheduled contacts. Hence, one who misses a specified number of consecutive visits may be classified as a dropout. Similarly, the definition implies that the state is transitory. Most long-term trials will have provisions for reinstating persons classified as dropouts if and when they return to a study clinic for required data collection. Avoid in the sense of defn 3 in relation to a single visit or contact in the absence of other reasons for regarding someone as a dropout. Use other language, such as missed visit or missed procedure, to avoid the connotation of dropout in the broad global sense of usage. The term should not be confused with lost to followup, noncompliant, withdrawal, or endpoint. A dropout (defn 2) need not be lost to followup if one can determine outcome without seeing or contacting the person (as in some forms of followup for survival) but will be lost to followup if the outcome measure depends on data collected from examinations of the person. Similarly, the act of dropping out need not affect treatment compliance. A person will become noncompliant upon dropping out (or soon thereafter) in settings where dropping out results in discontinuation of an active treatment process (as in the case of a drug trial where patients are required to take a daily dose of a drug or matching placebo and where the process of supplying them with the assigned treatment depends on visits to the study clinic). However, there may be no effect on treatment compliance in settings where the assigned test treatment is administered once on enrollment and where that treatment is not routinely available outside the trial, as in a surgery trial involving a special operation and where there is no established standard treatment. Similarly, the term should not be confused with or used as a synonym for withdrawal (defn 2), since its meaning is different from that for dropout.

end point *n* - 1. A point that marks the end of a line segment or interval. 2. A point marking the completion of a process or a stage of a process. 3. Limit or boundary value, as in the end point of a range.

endpoint *n* - 1. Limit or boundary value, as in the end points of a range. 2. end point (defn 2) 3. outcome measure 4. A primary or **secondary outcome measure**, especially one recorded as an event such as death or a nonfatal event such as a myocardial infarction, that results in termination or alteration of treatment or followup of the person. 5. Any primary or secondary outcome measure recorded as an event observed during the course of treatment or followup regardless of whether it results in an alteration of treatment or followup. 6. Any outcome measure recorded as an event. 7. early stopping 8. stopping rule ***Usage note***: Best avoided because of misuse and potential for confusion. Use end point in the sense of defns 1 and 2. Use outcome, outcome measure, or event in the sense of defns 3, 4, 5, and 6. Most "endpoints" noted over the course of followup in trials are not indicators of "end" in regard to treatment or followup. Most protocols call for followup, and often treatment as well, over a defined period of time even in the presence of and following intercurrrent events. As a rule, there are no endpoints in this operational sense of usage, except death. Use of the term in protocols and manuals for trials can cause personnel at clinics to stop treatment and followup on the occurrence of an "endpoint" (morbid event) if they regard the term as having operational meaning. Avoid as a generic label for morbid and fatal events, and especially in settings where such events are devoid of operational implications in regard to followup or treatment. Avoid in the sense of defns 7 and 8 and especially in contexts where the term is likely to be confused with usages in the sense of defns 4, 5, or 6.

intention to treat (ITT) *n* - [trials] A philosophy in which there is an intent to account for all persons enrolled in a trial and to perform analyses by assigned treatment, regardless of observed course of treatment. ***Usage note***: Subject to varying interpretations and uses. Use only in the presence of language detailing the operational definition of the intent. The term was used by Hill in his book *Principles of Medical Statistics* (7th ed; 1961; pg 259) in relation to differential exclusions from trials. The concept of intention to treat as an analysis principle is implicit to the essence of the pragmatic trial, as discussed by Schwartz and Lellouch (1967).

lost to followup *n* - 1. A person who cannot be found for followup. 2. A person who cannot be followed for some outcome of interest. 3. A person considered unsuitable for followup because of some intervening condition or state. ***Usage note***: Generally, best avoided in the sense of defn 3; especially in trials where the intent is to maintain followup regardless of treatment status. Typically, the characterization is applied to a person who is unwilling or unable to return to a

study clinic for followup examinations, but such uses are also best avoided because they imply that missing clinic visits is tantamount to being lost to followup. That is true for data that cannot be collected in any other way, but it is not for data that can be collected by other means, e.g., by telephone contact with the person. Do not use interchangeably with dropout. Even persons who refuse contact with study personnel can be followed for death.

missed visit *n* - 1. A scheduled visit that is missed. 2. missed study visit 3. A visit not made within the specified time window. *rt*: **missed contact** ***Usage note***: Not synonymous with missed contact. Subject to confusion when used in relation to contacts done by telephone or mail; limit use to visits to study clinics or visits of study personnel to study participants' homes.

outcome *n* - 1. [general] Something that follows as a consequence of some antecedent action or event; a natural result or consequence. [trials] 2. An event or measure observed or recorded for a particular person or treatment unit in a trial during or following treatment and that is used to assess the safety or efficacy of a study treatment. 3. Primary or secondary outcome measure, especially one measured or recorded as an event; outcome variable. *syn*: **endpoint** (not recommended) ***Usage note***: Preferred to endpoint; see endpoint for reasons.

outcome variable *n* - [trials] An observation variable recorded for persons at one or more time points after enrollment for the purpose of assessing effects of the study treatments. *syn*: **outcome measure**

primary analysis *n* - 1. The analysis of greatest relevance to the objective of the research. [trials] 2. Treatment comparisons involving the primary outcome. 3. Treatment comparisons based on analyses by assigned treatment; analysis by intention to treat.

protocol *n* - [MF *prothocole*, fr ML *protocollum*, fr LGk *prōtokollon* first sheet of a papyrus roll bearing date of manufacture, fr Gk *prōt-* prot- + *kollon* to glue together, fr *kolla* glue; akin to MD *helen* to glue] 1. Specifications, rules, and procedures for performing some activity or function. 2. study protocol 3. data collection schedule 4. treatment plan ***Usage note***: Subject to varying use. Often used as a synonym for treatment, as in "on protocol".

time window *n* - The time interval for performing a specified activity or procedure. In trials and other followup studies, usually the window for performing a specified examination or type of data collection, such as for a baseline or followup visit

treatment adherence *n* - 1. The degree to which a person adheres to the treatment schedule in a trial. 2. treatment compliance

treatment assignment *n* - 1. The process of assigning people to treatment in a trial. 2. The treatment assigned to a particular person in a trial. 3. The treatment to be administered to a person as indicated in a treatment assignment schedule.

treatment compliance *n* - 1. Compliance to treatment requirements or procedures. 2. The degree to which a person or the person's treater follows the assigned treatment regimen. *syn*: **treatment adherence** *ant*: **treatment noncompliance**

withdrawal *n* - 1. The act of withdrawing. 2. The removal of a person from a life table analysis at the cessation of followup for that person or at the occurrence of the event of interest; removal due to cessation of followup may occur as a consequence of when the person was enrolled (e.g., calculation of a three-year event rate is based on data provided by those who were enrolled at least three years prior to the date of the analysis) or because the person dropped out. [trials] 3. dropout (not a recommended synonym) 4. One who has been removed from treatment; treatment withdrawal (not recommended usage). 5. One who is not receiving or taking the assigned treatment (not recommended usage). *rt*: **censor** ***Usage note***: Usage should be limited to those implied in defns 1 and 2. The term should not be used as a synonym for dropout or loss to follow for reasons discussed in usage notes for those terms. The term, when used in the context of treatment, has different meanings and should be avoided or accompanied with detail indicating nature of use. Use in the sense of defn 5 is as an indicator of action taken by study personnel to

forego or halt use of the assigned treatment, usually because of lack of benefit or bad effects (e.g., as used in the Consolidated Standards of Reporting Trials (CONSORT). Use in the sense of defn 4 is broader and is as an indicator of those persons no longer taking or receiving the assigned treatment, whether due to choice or direction of study personnel. In either use, it is important to recognize that withdrawal from treatment, for whatever the reason, does not remove the effect of treatment. One can be withdrawn from treatment but not from its effects.