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Memorandum

To: Trialists

Fr: Curtis Meinert

Re: Troublesome words

A recent posting to trialsmeinertsway.com is a log of responses to an e-mail sent 29 June 2012 asking recipients to provide their lists of troublesome words. Now it is my turn. My list is:

1. Protocol
2. Random/randomized
3. Placebo
4. Baseline
5. Dropout
6. Endpoint
7. Lost to followup
8. Treatment failure
9. Off study
10. Withdrawal

The definitions and usage notes below are from *Clinical Trials Dictionary: Terminology and Usage Recommendations*, 2nd ed (Meinert; Wiley 2012).

Protocol

protocol *n* - 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".

Comment: First on my list because it is used as if it has a precise meaning, but, in fact, means different things depending on who uses the term.

Protocols in trials, at best, are rough guides. They are purposely written to allow latitude for study physicians as to how treatments are administered and patients managed.

The view as to how protocols are seen depends on perspective. The FDA is likely to view protocols as blue prints whereas study physicians see them as guides.

Multicenter trials operate under a common protocol but that is more hypothetical than real. The requirements for approval by individual IRBs may well lead to differences in the way the protocol is administered unbeknownst to coordinating centers.

Random/randomized

random *adj* - [lay usage] 1. Having or appearing to have no specific pattern or objective. 2. Of or designating a process in which the occurrence of previous events is of no value in predicting future events. 3. haphazard [scientific usage] 4. Of or relating to a sequence, observation, assignment, arrangement, etc., that is the result of a chance process with known or knowable probabilities. 5. Of or relating to a process that has the properties of one that is random. 6. pseudorandom 7. Of or relating to a single value, observation, assignment, or arrangement that is the result of randomization.

randomized *n* - [trials] The condition of having been assigned to a treatment via a random process; normally considered to have occurred when the treatment assignment is revealed to any member of the clinic staff, e.g., when an envelope containing the treatment assignment is opened at the clinic.

Usage note: Subject to misuse. Avoid in the absence of a probability base; use haphazard or some other term implying less rigor than random. Misuse in the context of trials arises in relation to characterizations of treatment assignment schemes as random that are systematic or haphazard. In scientific discourse, reserve the descriptor for uses in the sense of defns 4, 5, 6, and 7.

Comment: There is a lay tendency to characterize anything lacking apparent order as "random". Indeed, most desk dictionaries equate haphazard and random. The label "random" as in "randomized trial" carries an aura of respectability and, hence, a tendency to use the term even though some lesser term would be more appropriate; e.g., as with "haphazardly controlled trial" versus "randomized controlled trial" but do not bank on getting results published with that label.

Placebo

placebo *adj* - 1. Of or relating to the use or administration of a placebo. 2. Of or relating to something considered to be useless or ineffective.

placebo *n* - 1. A pharmacologically inactive substance given as a substitute for an active substance, especially when a person is not informed whether it is an active or inactive substance. 2. placebo treatment 3. A sugar-coated pill made of lactose or some other pharmacologically inert substance. 4. Any medication considered to be useless, especially one administered in pill form. 5. nil treatment 6. An ineffective treatment.

Usage note: Avoid nonsensical uses such as an adjective for patient or group, as in "placebo patient" or "placebo group"; use placebo-assigned or placebo-treated instead.

Subject to varying uses as a noun. Avoid in the sense of defns 4, 5, and 6. The use of a placebo should not be construed to imply the absence of treatment. Virtually all clinical trials involve care and investigators conducting them are obligated to meet standards of care, regardless of treatment assignment and regardless of whether or not masked. A control treatment involving use of a placebo is best thought of as a care regimen with placebo substituting for one element of the care regimen. Labels such as "placebo patient" or "placebo group" create the impression that patients assigned to receive placebos are left untreated. The labels (in addition to being wrong in the literal sense of usage) are misleading when placebo treatment is in addition to other treatments (e.g., as in the

University Group Diabetes Program where all patients received dietary counseling or in a vaccine trial where infants receive vaccines for diphtheria and tetanus in addition to a pertussis vaccine or matching placebo for the pertussis vaccine).

Comment: Subject to misuse. One obvious misuse is regarding placebo treatment as tantamount to no treatment and regarding sham treatments as "placebo" treatments. Especially annoying are uses in which "placebo" is used to characterize persons rather than treatment, e.g., "placebo patients" or the "placebo group". There are placebo-assigned patients and placebo-assigned groups, but no placebo patients or placebo groups.

Baseline

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 (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.

Comment: As noted from the definitions above, "baseline" has a variety of meanings, the most common of which is defn 1. Technically, the baseline period of observation ends the moment treatment assignments are revealed to clinic personnel. Difficulties come with tendencies to stretch the baseline period beyond that point to allow opportunities to collect "baseline" data after the close of the period.

Dropout

dropout *n* - 1. Broadly, 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 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: Subject to varying usage. 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 persons who actively refuse, those who passively refuse, as well

as those who are simply unable to continue followup 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 as a dropout as a result of failure, for whatever the reason, to return for scheduled contacts. Hence, one who misses a specified number of consecutive visits may be classified as a dropout. 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 (e.g., as in some forms of mortality followup) 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 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 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, since its meaning is different from that for dropout.

Comment: Clinics are loathe to call somebody a dropout. Hence, it is important to have operational definitions as represented by defn 3.

Endpoint

endpoint *n* - 1. Limit or boundary value. 2. end point 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: Use outcome, outcome measure, or event in the sense of defns 3, 4, 5, and 6. Most "endpoints" 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 intercurrent events. As a rule, there are no endpoints in this operational sense of usage, except death. Use of the term in protocols and manuals can cause personnel at clinics to stop treatment and followup on the occurrence of an "endpoint" 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.

Comment: If I ever get to be president, I will ban the use of the term in clinical trials. The trouble with the term is its operational meaning. Groups regard the occurrence of an "endpoint" (meaning an outcome; event) as a reason to stop followup and data collection. You can talk until you are blue in the face in front of groups about not equating "endpoint" to stopping followup, but never with much success.

Lost to followup

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, e.g., in a trial, because the person is not receiving or taking the assigned treatment.

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 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.

Comment: The label is largely just an excuse to give up on a person; to forget about trying to find the person. Unless there is a plan to periodically contact persons lost to followup they will be lost even for mortality followup.

Treatment failure

treatment failure *n* - [trials] 1. The failure of a treatment to produce a desired effect or result. 2. Such a failure as observed, inferred, or declared by a study physician or other study personnel from measurements, evaluations, or observations on the person in question and resulting in cessation of the treatment or a treatment switch. 3. A person in a trial no longer receiving the assigned treatment; especially cessation of treatment occurring because of concerns regarding the safety or efficacy of the treatment.

Usage note: The term should be used with caution because of the implied conclusion regarding the treatment itself and value-laden meaning. Its use should be limited to settings where there is supporting evidence indicating failure. The term should not be used as a synonym for treatment cessation.

Comment: The term implies people know more about how treatments work than is usually the case. All we really know is that persons receiving the treatment did not get better. Whether that was due to failure of the treatment or other factors is a matter of conjecture.

Off-study

off-study *adj* - 1. Of or relating to not being on-study. 2. off-protocol

Usage note: If used, provide details to make nature of use clear. Subject to confusion because use may relate to treatment or to data collection. A person can be off-study in regard to treatment but on-protocol in regard to scheduled data collection.

Comment: Once a person is enrolled there is no way to be "off study" unless the person walks out the door. Short of that, they are still "on-study" even if off treatment.

Withdrawal/withdrawn

withdrawal *n* - 1. The act of withdrawing. 2. The removal of a person from a lifetable 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 4. One who has been removed from treatment; treatment withdrawal. 5 One who is not receiving or taking the assigned treatment.

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 followup. 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. 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.

Comment: Common usage is in regard to "withdrawal of consent" as an explanation by clinic personnel as to why a study participant is no longer under followup. The language implies a declaration by study participants declaring their desire to be out of the study, but most such "withdrawals" are passive, absent any declaration. The unfortunate part of the label is that it is preemptive. Once applied by a clinic, even if not by declaration of a study participant, it is interpreted as barring any future contact, even if only to determine if the person is willing to return to study.