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Memorandum

To: Center for Clinical Trials faculty and staff

Fr: Curt Meinert

Re: Randomization good practice policies and procedures (GPPP)

Definitions

baseline *adj* - 1. Of, relating to, or concerned with that which occurs just prior to or in conjunction with some act or **event**. 2. Of, relating to, or concerned with that which occurs in close proximity to some act or event, prior to or following the act or event. ***Usage note***: Limit to uses in the sense of defn 1. Avoid in the sense of defn 2. See also notes for **baseline** *n* and **baseline period**.

baseline (Bl, BL) *n* - [general] 1. A **time point** or **period** (as in **baseline period**) from which subsequent **measurements** or activities are timed. 2. A **point** or **measure** for assessing subsequent **change**. 3. An observation or series of observations made on an **observation unit** or **treatment unit** at a designated point in **time** or within a designated **time interval** that serves as a basis for gauging change from that point forward in time for that unit. [**trials**] 4. **baseline period** 5. An observation or set of observations made or recorded on an observation or treatment unit just prior to or in conjunction with **treatment assignment** or initiation of treatment that serves as a basis for gauging change for that unit over the course of the trial. 6. An observation or set of observations made or recorded on an observation or treatment unit at a time point after the close of the baseline period that serves as a basis for gauging change for that unit from that time point forward over the course of the trial (eg, an eye trial involving the use of photocoagulation for treatment of microhemorrhages by use of readings from a set of fundus photographs taken on a **patient** just having received an additional course of treatment for such a condition to provide a new baseline for assessing future changes in the eye). ***Usage note***: Subject to varying uses in the context of trials, especially in relation to uses in the sense of defns 5 and 6. Most uses are in the sense of defn 5 but may, on occasion, be in the sense of defn 6. Typically, in the context of trials, unless otherwise indicated, the term should be reserved for characterizations that are appropriately thought of as being at baseline in the sense of defn 5 (see note for **baseline** *adj*) or in the sense of defn 1 for **baseline period**. However, even if the user is careful to limit usage to observations made prior to treatment assignment or initiation, ambiguities can still arise when the term is used as if always applying to a single time point (eg, as implied by the phrase *at baseline*) when that is not the case. Baseline observations in most trials arise from a series of **baseline examinations**, separated in time by days, weeks, or, in some cases, months (see **baseline period**). Hence, the time of observation

for one baseline variable, relative to another, may be different (eg, as would be the case with baseline blood pressure measured at the **randomization visit** and baseline body weight measured one week prior to that visit at a prior baseline examination). The user is responsible for making the time differences among the variables represented in the baseline **dataset** known when describing the trial and its results. A certain amount of variability in the timing of one baseline observation or measurement relative to another and in the amount of time preceding the point of treatment assignment or initiation is unavoidable (except in cases where all required observations can be made at the same **clinic visit** and where that visit also serves as the **treatment assignment visit**). Unacceptably large variation is typically avoided by use of **time windows** specifying permissible **time intervals** within which the different observations are to be made and the maximum permissible separation allowed for any single observation relative to the point of treatment assignment or initiation. The size of permissible separations will be a function of the importance of proximal linkages of one observation to another and of the individual observations to the point of treatment assignment or initiation. Observations considered to be highly correlated and where the **correlations** are important for establishing **valid** baselines will be required to be more closely linked in time than where such correlations are modest or unimportant. Similarly, observations subject to wide variation from one time to another for the same person may be observed several times at different time points in the **baseline period** and averaged, or may be required to have been made in a narrow time window with its upper limit affixed to the act of treatment assignment or initiation.

baseline period *n* - [general] A **period** of **time** that is used to perform procedures needed to assess the suitability and eligibility of a **study candidate** for **enrollment** into a **study**, to collect required **baseline data**, and to carry out **consent processes**. [**trials**] 1. The period for a person or **treatment unit** defined by the start of the first **data collection visit** and ending with **assignment** to **treatment** or start of treatment. 2. Such a period ending with a **visit** or time point occurring shortly after **assignment** to **treatment** or the start of treatment. 3. A period of time during the course of treatment or **followup** of a person or treatment unit, usually marked by some **event**, process, or procedure, in which new **measurements** or **observations** are made to serve as a base for gauging subsequent change. 4. **enrollment period** rt: **treatment period**, **followup period**, **treatment and followup period**, **close-out period**, **baseline observation period**, **lead-in period**, **run-in period** ***Usage note***: Avoid in the sense of defn 2 without qualification (see note for **baseline** *adj*) and in the sense of defn 4. Provide qualifying detail for uses in the sense of defn 3. Traditionally, the point defining the end of the **baseline period** in trials is marked by the **treatment assignment** or initiation of **treatment**. The tendency to "stretch" the baseline period as in defn 2 arises from a desire to reduce missing **baseline data**. Clearly, the utility of an observation as a baseline, in the strict sense of usage, is diminished if there is any possibility of the observation being influenced by treatment. Hence, the practice is not recommended, even if the time interval following treatment assignment or initiation of treatment is small and even if the likelihood of treatment having had an effect on the **variable** being observed within that interval is small. See also notes for **baseline** *adj* and for **baseline** *n*.

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random *adj, general* - [ME impetuosity, fr MF *randon*, fr OF, fr *randir*, to run, of Gmc origin, akin to OHG *rinnan* to run] 1. Having or appearing to have no specific pattern or objective. 2. Of or designating a **chance** process in which the occurrence of previous **events** is of no value in predicting future events. 3. **haphazard** syn: **chance**, **casual**, **haphazard** ***Usage note***: Avoid; use **haphazard**, **casual**, **chance**, or **quasirandom** to avoid confusion with **random** *adj, scientific*. See also note for **lottery**.

random *adj, scientific* - 1. Of or relating to a value, **observation**, **assignment**, arrangement, etc, that is the result of **chance**. 2. Of or relating to a **sequence**, **observation**, **assignment**, arrangement, etc, that is the result of a **chance** process in which the **probability** is known or can be determined. 3. Of or relating to a **pseudorandom** process that has the properties of one that is random. 4. Of or relating to a single value, observation, assignment, or arrangement that is the result of **randomization**. syn: **chance**, **lottery** (not recommended synonyms, except in lay usage, as in **consent statements** describing the **treatment assignment process**) ant: **nonrandom** rt: **pseudorandom** ***Usage note***: Subject to misuse. Avoid in the absence of a probability base (as in *random blood sugar* in reference to routine blood sugar determinations); use **haphazard** or some other term implying less rigor than does **random**. Misuse in the context of trials arises most commonly in relation to characterizations of treatment assignment schemes as **random** that are **systematic** or **haphazard**. See also note for **lottery**.

randomization *n* - 1. An act of assigning or ordering that is the result of a **random process** such as that represented by a sequence of numbers in a table of **random numbers** or a sequence of numbers produced by a **random number generator**, eg, the **assignment** of a **patient** to **treatment** using a **random process**. 2. The process of deriving an order or sequence of items, specimens, records, or the like using a **random process**. rt: **haphazardization**, **quasirandom** ***Usage note***: Do not use as a characterization except in settings where there is an explicit or implied mathematical basis for supporting the usage, as discussed in usage notes for **random** *adj*. Use other terms implying less rigor than implied by **randomization**, such as **haphazardization**, **quasirandomization**, or **chance**, when that basis is not present or evident.

P&P 1: Limit use of *random* and *randomization* to settings where the probability base for the terms is satisfied, as defined above for **random** *adj, scientific*.

P&P 2: The consent form presented to study candidates should detail, in lay language, the reason for doing a randomized trial and what it means to be "randomized" to treatment.

Comment

The P&P is necessary for proper, informed, consents.

P&P 3: The treatment assignment schedule should be documented and reproducible.

Comment

One of the hallmarks of a sound randomization system is for the schedule to be reproducible. That is, someone else using the documentation should be able to produce the exact same schedule

and should be able to do so years after the trial is completed. Without this requirement, the basis for the claim of *randomization* is tenable.

Operationally, the requirement serves to rule out schemes, such as coin flips, that may, in fact, be random, but which are not reproducible.

P&P 4: The randomization scheme should be concealed to clinic personnel and study candidates.

Comment

This requirement is paramount if the scheme is to be protected against treatment-related selection bias. The likelihood is that such bias will be present if the randomization scheme is not concealed. The possibility remains that, if clinic personnel or study candidates know assignments to be made, this information will influence decisions regarding enrollment.

P&P 5: The release of assignments should be controlled by computer or a third party.

Comment

The most bias-robust systems are those in which assignments cannot be obtained until essential conditions have been met for release. Protection against premature release may be achieved by computer, programmed to withhold assignments until the necessary data have been keyed and edited or by manual systems of release operated from the CC. In general, self-administered envelope schemes of assignments in which clinics determine when an envelope is opened are suspect because of the absence of controls protecting against premature release.

P&P 6: A treatment assignment should not be released or revealed until or unless:

1. The person has consented to be randomized.
2. A consent form has been signed and dated.
3. The person is known to be eligible for treatment and eligibility has been documented.
4. The person has been evaluated for the presence of conditions excluding enrollment or treatment.
5. Essential baseline data have been collected.

Comment

Regulations governing research on human beings are explicit on the requirement for consent (conditions 1 and 2). The need for satisfying conditions 3 and 4 derives from P&P 7. A randomization is a randomization. They all count even for those persons subsequently found to be ineligible or where treatment is contraindicated because of some excluding condition.

The requirement of condition 5 derives from the fact that, by definition, the only observations qualifying as "baseline" are those made at or prior to randomization.

P&P 7: A person should be counted as randomized when the assignment is revealed to clinic personnel or to the study subject.

Comment

Good systems require an indelible landmark event serving to mark the point of randomization. That point should be when the assignment is released. Operationally, that is the time when the assignment envelope is opened in the case of self-administered schemes or in schemes where the assignment envelope is mailed from the CC (eg, as in the CDP), when the assignment is communicated to clinic personnel by voice or fax, or when it is printed or displayed on the screen of an onsite computer.

P&P 8: Set up and maintain a system of safeguards to prevent release of an assignment until data needed for establishing and documenting eligibility have been collected, recorded, and checked.

Comment

Eligibility in this context means the absence of any disqualifying condition and presence of all qualifying conditions. Hence, the system must be designed to monitor for excluding conditions as well as for qualifying conditions. The absence of data, for whatever the reason, should be sufficient to cause an assignment to be held.

P&P 9: Set up and maintain procedures designed to eliminate or minimize overrides of the system represented in P&P 8.

Comment

Overrides occur when the conditions necessary for release of an assignment have not been met, but the assignment is released nonetheless.

P&P 10: If overrides are allowed, institute a system requiring the review and concurrence of a second person to override and for detailing and documenting the fact of overrides.

Comment

The second person should be a senior CC person and the mind set the person should be to refuse to override in all cases except where there are cogent reasons for the overrides. The underlying purpose is to make overrides difficult and to ensure proper documentation when they occur.

P&P 11: The fact of randomization should be documented by an indelible audit trail.

Comment

The requirement for an indelible audit trail is to ensure that the trialist can demonstrate that persons were properly randomized during or after completion of the trial.

P&P 12: Masked treatment assignments should remain masked, unless unmasking is necessary for protection of persons from harm.

Comment

The purpose of masking is to protect against treatment-related bias. Unmasking increases the risk of such bias.

In general, unless the information is needed for the proper care or management of a person's health condition, the assignment should remain masked. The usual approach in masked trials is to stop use of the assigned treatment without revealing its identity.

P&P 13: The randomization scheme should be designed and administered in such a way so as to prevent prediction of the next assignments from past assignments.

Comment

In general, the more restricted the randomization schedule, the greater the likelihood of "prediction". For example, consider the case of a 1:1 assignment scheme administered in blocks of size 2. Half of the assignments are predictable if clinic personnel know or learn of the blocking scheme and if assignments are not masked.

The more elaborate the blocking scheme (eg, use of blocks of varying sizes) the less the risk of prediction. The risk is reduced if the nature of the blocking is not revealed during conduct of the trial. The risk may be nil when treatment assignments are masked, assuming the masking is effective.

P&P 14: The details of randomization should be reported in the primary publication. Details should include the following:

1. Method of generation (eg, via use of a table of random numbers or via use of a named pseudorandom generator).
2. The assignment ratio specified in the design of the trial.
3. Stratification variables; number of strata.
4. Blocking.
5. Method of release (eg, via onsite computer or by CC personnel).
6. Safeguards for protecting against premature release of assignments.
7. Provisions for unmasking in the case of masked treatment.