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Memorandum

To: Center for Clinical Trials faculty and staff

Fr: Curt Meinert

Re: Followup good practice policies and procedures (GPPP)

Definitions

active followup *n* - 1. **Followup** done by **direct contact** of the person of interest or via such contact with a member of the person's family or the person's guardian; may be by letter, telephone, or face-to-face by **home visits** or **clinic visits**. 2. The state of not being **lost to followup**. rt: **passive followup**

dropout *n* - 1. [general] One who terminates involvement in an activity by declaration or action or as deduced from an unbroken **sequence** of failed contacts or absences from scheduled activities; especially one who so terminates because of waning interest or for physical, practical, or philosophical reasons. 2. A person who **withdraws** (defn 2) from a **trial** or **followup study** by an announced unwillingness to continue to submit to the required procedures for **treatment**, evaluation, or **data collection** or as deduced in **retrospect** from an unbroken series of absences from scheduled contacts for such treatment, evaluation, or data collection. 3. A person who misses a **scheduled visit** or who is not contacted within the indicated **time window** for a scheduled contact. 4. [**trials**] 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 implied by 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 compliance**. 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, in fact, be treatment-related. Defn 2 includes those who actively refuse, those who passively refuse, as well as those who are simply unable to continue in a trial or followup study for physical or practical reasons, eg, because of having moved to a location where it is no longer possible or convenient to return for scheduled visits. Further, it 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

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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 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 global sense of that term. 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 if the outcome measure depends on data collected from **examinations** of the person. Similarly, the act of dropping out need not affect **treatment compliance** to the assigned treatment. 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 only 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**, such as in the Program on the Surgical Control of the Hyperlipidemias [Buchwald et al, 1990]. 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. See **withdrawal** and **endpoint** for additional comments.

follow up, **followed up**, **following up** *v* - 1. To maintain contact with a person or some larger **observation unit** through periodic **visits**, telephone calls, or letters so as to continue **observation** or to be in a position to do so when appropriate; in the case of **trials** typically done in relation to **treatment administration** or assessment of the effects of **treatment**. 2. To pursue in an effort to take some action or step; to take appropriate action, eg, to follow up on a lead. 3. To contact periodically in **trials** and other forms of **prospective followup** for the purpose of observing or **monitoring** the effects of some procedure or **treatment** or to note the occurrence of some **outcome** or **event** for **data collection**; the process implied proceeds forward in real time and typically involves **direct contact** with **study participants** or their **surrogates**. 4. Any of various kinds of activities or processes intended to generate **prospective data** for the object of followup. The activity or process for the object of followup starts at a point in time determined by some act, **event**, or **exposure** and proceeds in time from that point. The act, event, or exposure may have occurred in the past with followup proceeding to a point in the less distant past, to the present, or to a point in the future, or it may occur in the present with followup proceeding to a point in the future.

followup (Fu, FU) *n* - [also **follow-up**] 1. The act of or an instance of **follow up**. 2. Something done in or as follow up, eg, reexamination of a person as part of **scheduled**

followup. 3. Maintenance of contact with a person or **observation unit** for care or administration of **treatment**. 4. **patient followup**

followup, **follow-up** *adj* - 1. Done, conducted, or administered in the course of **follow up**, as in a **followup study**. 2. Of, relating to, concerned with, or being something done as a followup, especially in relation to previous actions, procedures, or **observations**.

ideal time window *n* - A **time interval** in a **permissible time window** within which an activity or procedure is ideally performed, eg, a 14 day interval centered at the **ideal visit time** within a permissible time window of 56 days similarly centered. rt: **permissible time window**

indirect followup *n* - 1. **Followup** absent **direct contact** with the person of interest. 2. Followup absent direct contact with the person of interest and members of the person's family or guardian, eg, as with **mortality surveillance** achieved by querying the **National Death Index** or by use of agencies specialized in tracing and locating persons. syn: **passive followup** ant: **direct followup**

locator information *n* - 1. **Information**, such as name, address, etc, collected as part of **baseline data** in **prospective followup studies**, used or intended for use in locating patients **lost to followup** (defn 1). 2. Information such as record number, form number, etc, used for locating **records** or **files**.

loss to followup *n* - Any **loss** of **followup data** on a person (or other **observation unit**) after **enrollment** into a **study**; loss may occur because a person cannot be located for required **data collection** or because the person is unwilling or unable to submit to required data collection procedures. rt: **lost to followup** ***Usage note***: The majority of losses to followup in **trials** occur because of **dropout** since most data in trials are generated via direct interview and examination of those enrolled. However, some forms of followup may continue even after a person drops out, as noted in a comment for **dropout**.

lost to followup *n* - 1. A person who cannot be found for **followup**. 2. An **observation unit** in a **followup study** that cannot be followed for some **outcome** or observation of interest. 3. A person considered unsuitable for followup because of some intervening condition or state, eg, in a **trial**, because the person is not receiving or taking the **assigned treatment**. rt: **losses to followup** ***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 true for data that can be collected by other means, eg, by telephone contact with the person. In good usage, the observation or

set of observations lost is specified. Do not use interchangeably with **dropout** or **drop out**. Even persons who refuse contact with study personnel can be followed for death.

missed study visit *n* - 1. A **required visit** that has been **missed**. 2. A **scheduled study visit** not made within the permissible **time window**.

passive followup *n* - 1. **Followup** that is a byproduct of another activity. 2. **indirect followup** ant: **active followup**

permissible time window *n* - The allowable **time interval** for performing a specified activity or procedure; usually centered at the **ideal visit time** and usually **contiguous** to adjacent time windows for **visit schedules**; **time window** in the absence of **ideal time window**. rt: **ideal time window**

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**. rt: **contiguous time windows**, **ideal time window**, **permissible time window**, **time interval**, **time measure**, **time period**, **time point** ***Usage note***: See **time measure**.

transfer patient *n* - [**multicenter trials**] 1. A **patient** seen temporally at a sister **study clinic**, eg, because of vacation or some other time limit move. 2. A patient removed from the from the **roll** of one **study clinic** and placed on that of another by agreement of the **transferring** and **transfer clinic** and patient; usually because of a job change or other life change taking the patient to a new locale. rt: **patient transfer**

treatment failure *n* - [**trials**] 1. The **failure** of a **treatment**, as administered to a person or **treatment unit** in a trial, to produce the 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 or treatment unit in question and accompanied by **cessation** of that treatment or a **treatment switch**. 3. A person or treatment unit **enrolled** in a **trial** no longer receiving the **assigned treatment**; especially when the cessation occurred 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. Its use should be limited to settings where there is supporting evidence indicating a failure. It should not be used simply as a synonym for **treatment cessation** regardless of reason, eg, in relation to defn 3. See note for **value-laden term** for additional comments.

P&P 1: Design followup to be independent of treatment status or compliance.

Comment

A common mistake is to regard "nonadherent" persons as "dropouts" and to stop collecting data on such persons. Followup and related data collection should continue regardless of treatment status.

P&P 2: Avoid language conventions that link followup to treatment, eg, as in defn 3 for **lost to followup**, defns 2 through 5 of **dropout**, and defn 3 of **treatment failure**.

Comment

See usage notes for the above mentioned terms.

P&P 3: Define **dropout** in terms of missed visits and independent of treatment status (eg, one who has missed 3 consecutive followup visits).

Comment

This P&P follows from P&P 1; see the usage note in the definition of dropout above.

P&P 4: Collect locator information on persons at the time of enrollment; update that information at periodic intervals over the course of the trial and on completion of the trial.

P&P 5: Trace persons lost to followup to maintain contact for determination of vital status (P&P 7) and to maintain the possibly of reinstatement to active followup.

P&P 6: Design the data system to allow for reinstatement of dropouts to active followup.

P&P 7: Arrange to follow all persons enrolled at periodic intervals over the course of the trial for vital status.

Comment

The P&P is necessary for ensuring a system of followup that allows investigators to categorize all persons randomized by whether dead or alive. Waiting until the end of trial is generally a mistake. Followup is best done when the trail is still warm. Further, the "end" can come any time, eg, because of a recommendation to stop based on interim results.

P&P 8: In multicenter trials, design data systems to allow for transfer patients.

Comment

There can be a sizeable number of "transfers" in long-term trials. Transfers occur when a person moves from one clinic area to another and is willing to continue under active followup.

P&P 9: Define missed visits in terms of permissible time windows; count visits as missed when not done within permissible time windows.

P&P 10: Design data systems to reject data not collected within permissible time windows.

P&P 11: Construct contiguous time windows.

Comment

Any other method of construction allows for "dark periods" in the followup schedule, ie, periods where nothing is due.

P&P 12: Specify ideal time windows for visits.

Comment

The windows provide targets for clinics in scheduling visits. They are also useful in performance monitoring.

P&P 13: Aim for followup schedules that are independent of treatment assignment, ie, where all persons, regardless of treatment assignment, are seen on the same schedule.

Comment

The more one looks the more one finds. Hence, differences in the time at which followup visits are done or in the amount of information that is collected can produce artifactual differences among the treatment groups. The risk of differential observation rates by treatment group is largely avoided in masked trials but can be a risk in unmasked trials, especially when the trial involves different modes of treatment (eg, as in trials involving surgical vs medical treatment). See also P&P 14.

P&P 14: Design the followup data system to count all patient contacts, scheduled and unscheduled.

Comment

The contact schedule may be different by treatment group if one treatment group has more unscheduled visits than another group. See also P&P 13.

P&P 15: Avoid mixed modes of data collection for any given scheduled followup visit, ie, if the visit is to take place in the clinic do not attempt to satisfy the requirements of the visit by a home visit.

Comment

In general, the nature and quality of information obtained can be expected to vary depending on where the data are collected.

P&P 16: Design data forms to include information on where or how information was obtained, if different modes of data collection are allowed.

Comment

See P&P 15.