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(Thursday 9:59pm) 15 June 2000

**Memorandum**

To: Center for Clinical Trials faculty and staff

Fr: Curt Meinert

Re: Close-out good practice policies and procedures (GPPP)

**Definitions**

**anniversary closing date** *n* - [**trials**] A **date** for close of **followup** determined so as to be the same for all other persons **enrolled**; **common followup period patient close-out**. rt: **common closing date**

**anniversary date patient close-out** *n* - [**trials**] A method of **patient close-out** in which **patients** are separated from a trial on an **anniversary date** of **enrollment**, eg, separation after 26 weeks of **followup**. Operationally equivalent to **common date patient close-out** when **enrollment** has occurred within a short period of **time**, otherwise the amount of followup **person-time** will be less than that for common date patient close-out. rt: **common date patient close-out**

**close-out design** *n* - **Design** relating to **close-out** of an activity; **clinic close-out design**; **patient followup close-out design**; **trial close-out design**. rt: **start-up design**

**close-out followup visit** *n* - A **followup visit** performed in relation to **close-out**; **patient close-out followup visit**. rt: **close-out examination**

**close-out stage** *n* - [**trials**] 1. The close of **followup** for a person. 2. The **stage** in which persons are separated from the trial, especially in trials with **common closing date** designs and preceding the **termination stage**; typically starting with the first such separation and ending with the last. See **stage of trial** for list.

**close of trial** *n* - 1. The **point** at which **treatment** (as dictated under the **treatment protocol**), **scheduled followup**, and **data collection** end — typically marked by completion of the **close-out stage** of the **trial**. 2. The point at which treatment is stopped or suspended in a trial (not recommended usage); **treatment cessation** (defn 2); **treatment termination** (defn 2). 3. The point at which all activities related to the trial, including **data analysis**, end — typically marked by completion of the **termination stage** of the trial. 4. Termination of the **enrollment phase**. 5. Termination of funding for the trial. 6. **end of trial** ***Usage note***: Phrase subject to ambiguities, especially in settings in which **study treatments** are administered only once on **enrollment** or shortly thereafter and in which those so enrolled and treated are then simply

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followed for **outcomes** of interest. In one sense, in this setting, the trial is ended as soon as the last person enrolled has been treated, even though **followup** may continue for years thereafter. Usage should be restricted to settings in which all patient-related activities are terminated, including **scheduled followup visits** and related data collection. Avoid use in settings in which only specific activities or functions are terminated, such as enrollment but not followup; be specific in such settings about what has ended and what continues.

**cold turkey treatment withdrawal** *n* - Abrupt and complete **treatment withdrawal** without any tapering of dosage. ant: **step down treatment withdrawal**

**common closing date** *n* - [**trials**] 1. A **date** for the close of **followup** that is the same for all persons **enrolled**; **common date patient close-out**. 2. A date common to all **sites** in a **multi-center trial** for ceasing or closing some function or activity, eg, the use of the same date for **cessation** of **enrollment** regardless of when a clinic entered a trial. rt: **anniversary closing date**

**common followup period patient close-out** *n* - [**trials**] A method of **patient close-out** in which **patients** are separated from a trial after a specified period of **followup** (eg, after two years). Roughly equivalent to **common date patient close-out** when **enrollment** has occurred within a short period of time. syn: anniversary close-out rt: **common date patient close-out**

**protocol suspension** *n* - 1. **Suspension** of the **study protocol** or elements of it during the course of a **study**; such suspensions due to concerns or questions regarding the appropriateness or adequacy of the protocol or compliance to it. 2. **treatment protocol suspension** 3. Continuation of activities without the rigors of a protocol. rt: **enrollment suspension** ***Usage note***: Subject to confusion. Suspension does not imply a total cessation of activities. Sometimes used simply to indicate that activities and procedures performed after the suspension were not subject to the same requirements or standards of rigor as prior to the suspension (defn 3). See also usage notes for **enrollment suspension** and **treatment protocol suspension**.

**step down treatment withdrawal** *n* - **Treatment withdrawal** by tapering dosage until withdrawal is achieved. ant: **cold turkey treatment withdrawal**

**treatment protocol suspension** *n* - **Suspension** of the **treatment protocol** or elements of it during the course of a **trial**; especially when based on **treatment effects monitoring** or recommendations of a **treatment effects monitoring committee** because of concerns regarding **safety** or **efficacy** or because of the presumed **benefits** or harm associated with one or more of the **study treatments**. rt: **enrollment suspension**, **trial termination**, **treatment cessation**, **treatment suspension**, **treatment termination** ***Usage note***: Not to be confused with **trial termination**, **treatment cessation**, or **protocol suspension**. Usage generally implies that other elements of the **protocol** remain in force, eg, those having to do with **followup** and **data collection**. Hence, **patients** may continue to be seen according to the **data collection protocol**

of the trial and be treated according to best medical judgment. See also usage notes for **enrollment suspension** and **protocol suspension**.

**treatment withdrawal** *n* - 1. The act or instance of withdrawing **treatment** in a **treatment withdrawal trial**. 2. The act or instance of withdrawing treatment because of an **adverse event**. 3. **treatment cessation** (defn 2). rt: **cold turkey treatment withdrawal**, **step down treatment withdrawal**

**trial termination** *n* - 1. The **cessation** of **enrollment**, **treatment**, and **data collection** in a **trial**. 2. The cessation of all activities related to a trial, including **data analysis**, eg, in relation to the cessation of **funding**. syn: termination of trial rt: **protocol suspension**, **termination stage**, **treatment cessation**, **treatment suspension**, **treatment termination** ***Usage note***: See **trial stop**.

**washout** *n* - 1. The **washing out** or washing away of something. 2. The act or process of removing or facilitating the removal of an extraneous or foreign **substance** from a biological system. 3. The act or process of allowing for the **clearance** of a substance from a biological system by passage of time.

**washout period** *n* - 1. The **interval** of time considered necessary for a biological system to remove a foreign substance or to be free of its influence. 2. [**crossover trial**] The period of time separating the last administration of a **treatment** in one period of treatment and the first administration of treatment in the next period of treatment; an **n-period crossover design** may have n - 1 washout periods. 3. [**parallel trial**] A period of followup extending beyond the point of **treatment cessation** imposed in order to provide information on the effect of treatment cessation; such a period imposed in order to determine the degree to which a **treatment effect** remains after cessation of treatment.

**washout study visit** *n* - A **study visit** done in relation to **washout** (defn 3); a visit in a **washout period**. ***Usage note***: Use with caution because of unintended connotations in regard to persons making such visits; suggestive of being "washed out" of the study.

**P&P 1**: All other things being equal, opt for designs involving common closing dates.

**Comment**

Common closing date designs generate more follow-up person-time and are easier to implement and manage than anniversary closing date designs.

**P&P 2**: Implement treatment protocol suspensions using common closing date designs, even if the trial was designed for anniversary closing.

**Comment**

The luxury of closing over an extended period of time, as necessary with anniversary closing, does not exist if the treatment protocol is suspended.

**P&P 3**: In the case of masked trials, treatment assignment should be revealed to clinic personnel and patients in relation to close-out or protocol suspensions; the fact and date of disclosure should be recorded in the patient's record; the patient should be given a document confirming disclosure; the patient should acknowledge receipt of the information by signing and dating a disclosure form indicating the patient's treatment assignment and nature and amount of assigned treatment received; patient should be provided with a photocopy of the executed form.

**P&P 4**: The CC should prepare a Patient Notification Form; form should be distributed to clinics via a numbered memo with instructions for completion; form should provide information on date of notification, method of notification, and nature of information imparted; in cases where notification is not accomplished: an indication of effort made to find the patient or reason why notification was not possible or necessary.

**P&P 5**: Patients should be notified of protocol suspensions even if the suspension does not affect them.

**P&P 6**: In the case of changes to the treatment protocol because of evidence of benefit or harm, assume the need to reconsent persons remaining under treatment in the trial (see *Consent good practice policies and procedures*).

**P&P 7**: Retain the ability to track persons separated from the trial and to recontact them if necessary.

**Comment**

See P&P 18.

**P&P 8**: The data system for the trial should be designed to include patient notification; form should be keyed; CC should develop and implement system for ensuring notification.

**P&P 9**: In treatment trials, patients, on separation from the trial, should be informed of the treatment options open to them, whether continued treatment with the assigned medication is indicated, and how and where treatment may be obtained; compliance to separation process should be monitored by the CC.

**P&P 10**: A drug tested under an IND and found to be effective in treatment of a life-limiting disease should be provided to study patients until the drug is approved for marketing or longer.

**Comment**

The purpose is to avoid the Catch-22 where a drug treatment is shown to effective in a trial but patients in the trial cannot continue to receive the treatment or cannot be given the drug if they were in the control-treated group because the trial has been stopped and the drug has not yet been approved for marketing.

**P&P 11**: Patients should be informed of results leading to a protocol suspension before results are made public.

**P&P 12**: Establish procedures for investigators to receive, review, and accept or reject recommendations from the TEMC for treatment protocol changes.
**Comment**
See *TEM good practice policies and procedures*.

**P&P 13**: Specify procedures for withdrawing treatment when developing the close-out design (cold turkey or step-down); opt for cold turkey except where step-down is required for safe withdrawal.

**P&P 14**: Specify data to be collected on close-out; argue for minimal added data and no additional procedures on close-out; whenever possible, the data collection requirements at close-out should the same as for regular followup visits.

**P&P 15**: Close-out procedures involving placebo washouts should not be undertaken if treatment was effective and never without IRB review and approval.

**P&P 16**: In masked trials, consider collecting information on the effectiveness of the masking at the close-out visit.

**P&P 17**: Update locator information on separation of a person from the trial.

**P&P 18**: Retain the ability to track persons separated from the trial and to recontact them if necessary; alert patients to the possibility of recontact and subsequent followup on separation.
**Comment**
It is common, at least in long-term trials, to follow persons for mortality after the trial has closed by use of the National Death Index or other indirect means of followup.

The need for actual contact arises when investigators believe that information obtained by letter or telephone contact or from a clinic visit will provide information bearing on the utility or effectiveness of test treatments.

The need for contact can be compelling in cases where there is reason to believe that test treatments used in the trial may increase risks for certain kinds of cancers or other treatable conditions.

The need for recontact is why, in trials, it is unwise to destroy linkages to patients, even if deemed desirable by IRBs to protect patient anonymity and confidentiality.

**P&P 19**: When dealing with a recommendation from the TEMC calling for cessation or change of treatment, assume the need for urgency in implementing the recommendation; assume the need for clinics to contact all persons enrolled in the trial and to do so in short order following acceptance of the recommendation; assume the need for special clinic visits if treatment is to be stopped, switched, or otherwise adjusted.

**P&P 20**: Except as specified in P&P 19, arrange close-out in relation to scheduled followup visits.

**P&P 21**: In trials coming to a scheduled normal end, prepare patients for that end at visits preceding the final visit.

**P&P 22**: Do not regard recommendations from a TEMC to halt enrollment or cease treatment as synonymous with cessation of followup or "close of the trial".

**Comment**

Followup and "close of the trial" is independent of treatment.