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(Wednesday) 23 August 2000

Memorandum

To: Center for Clinical Trials faculty and staff

Fr: Curt Meinert

Re: Screening and eligibility good practice policies and procedures (GPPP)

Definitions

enrollment *n* - 1. The action of **enrolling** as defined by some action or **event** that marks the beginning of a person's participation in a **research study**. 2. The state of having been or of being **enrolled**. 3. **patient enrollment** ***Usage note***: The term is subject to a fair amount of confusion in **trials**, especially when used in contexts where there is no landmark demarcating enrollment. The usual landmark is **treatment assignment** or **treatment initiation**. Persons passing the landmark are considered enrolled and are counted in the **denominator** for the trial. Use in contexts where the landmark is not specified is likely to leave readers uncertain or confused as to the true denominator for **treatment comparisons** and with concerns as to whether the treatment groups are free of **treatment-related selection biases**, especially in **unmasked trials**. See **patient enrollment** for comments.

recruitment log *n* - A **log** maintained by a **recruiting study site**, such as a **clinic** in a **trial**, of persons considered for **enrollment** into a **study**. Usually maintained to provide a description of the characteristics of the **population** screened for enrollment; **screening log**.

registration *n* - 1. The act of **registering**, as in entering one's name and other pertinent information into a **register**. 2. **enrollment** 3. A **document** certifying an act of registering. 4. The granting of an **application** or **license**; in regard to a **new drug**, the approval of a **new drug application** by the **Food and Drug Administration**. ***Usage note***: Registration (defn 1) may or may not correspond to enrollment. Usually the act of registration (defn 1) is a necessary but not sufficient condition for enrollment. Hence, the two terms should not be used interchangeably. In the case of **trials**, registration typically takes place at the first contact with a person during the **enrollment process**; signaled by the act of entering the person's name into a register or **log** or issuing an **identification number** for the person. The act of enrollment takes place when the **treatment assignment** is revealed or **treatment** is initiated and usually after **baseline** evaluations have been completed and **consent** has been obtained.

screening *n* - 1. A search for persons with an identifying **marker** or characteristic, as determined by results from some **test** or **observation**, known or believed to be associated with some **disease** (or health condition presumed to have adverse health implications); see also **case detection**,

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mass screening, and **multiphasic screening**. 2. The process of evaluating **study candidates** for **enrollment** into a **study**. 3. Any of a variety of procedures applied to **data** to identify **outlier** or questionable values. 4. A 100% inspection of items, such as in a manufacturing process, in which unacceptable items are rejected.

screening log *n* - 1. A list or **register** of people **screened** or to be screened. 2. **recruitment log**

P&P 1: Persons may not be screened or assessed for eligibility without consent.
Comment
See Consent/assent good practice policies and procedures (GPPP).

P&P 2: Information provided when obtaining consent for screening should include:
1. Why the person is being screened
2. What is involved in screening
3. The risks of being screened
4. The consequences of screening positive
5. What will happens if the person screens eligible

P&P 3: Consent for eligibility assessment should include:
1. Why the person is being assessed.
2. What the assessment entails.
3. The risks of assessment.
4. The options a person has if assessed to be eligible for enrollment.

P&P 4: Minimize exclusions.
Comment
Recruitment is always difficult. The more selective one is, the more difficult recruitment becomes.

P&P 5: Limit exclusions to those necessary for safe and proper treatment of persons being considered for enrollment and, when applicable, to those necessary to protect fetuses from harm and to protect reproductive capability.

P&P 6: List proposed exclusions and the reasons for use; prune to eliminate exclusions not pertinent to P&P 5.

P&P 7: Avoid exclusions based on age, gender, or ethnic origin, except as necessary for P&P 5 or in achieving the objective of the trial.
Comment
See stratification GPPP for rationale.

P&P 8: Do not exclude on the basis of age, gender, or ethnic origin because the number expected in a particular demographic subgroup will not be sufficient to draw a meaningful conclusion.

Comment

Some information across the demographic spectrum is better than none. Further, for the most part, treatment effects are likely to be independent of demographics. That is, treatments that work tend to work across both gender groups, over a broad age range, and regardless of ethnic origin of persons treated.

P&P 9: Do not exclude on the basis of literacy or language if outcomes can be assessed independent of literacy or language.

Comment

Exclusions based on literacy or language have negative connotations for the public at large.

P&P 10: Do not randomize a person until eligibility has been determined and the necessary baseline data have been collected.

Comment

See Randomization GPPP.

P&P 11: Screening variables should not be used as baseline variables.

Comment

The distribution of a variable used for screening is effected by its use as a selection variable. To establish a reliable baseline for screening variables, the variable should be observed independent of screening and prior to randomization.

P&P 12: Be wary of screening logs for defining base populations of trials.

Comment

Trials, by definition, involve select populations. Generally, it is not possible to define or characterize the base population of trials. The only exceptions are where screening is done in a systematic fashion or where only persons having certain tests are screened, eg, as in CASS. Usually screening is ad hoc and there is no way to know whether the log maintained by a clinic is complete.

Generally, screening logs are best reserved for uses in which there is a desire to monitor the activity level of clinics in screening or in which the information recorded on logs as to why persons screened where not or could not be enrolled is used to revise eligibility criteria.

P&P 13: Forego entry of data on registered but not enrolled persons if screening is ad hoc.

Comment

Largely, data on screened persons is of marginal use in relation to the trial. Usually, the effort and cost associated with data entry and processing is not justified relative to the information obtained.

P&P 14: Copy for recruitment materials (ads, mailed fliers, letters, informational brochures, etc) should be reviewed by IRBs before distribution or release; in the case of direct mailings, the submission to the IRB should include information on the nature of the mailing and the mailing list to be used.

P&P 15: Direct mailing No recruitment effort should not be undertaken prior to review and approval by IRBs. .

P&P 16: Do not waive eligibility requirements related to P&P 5.

Comment

A protocol is a protocol. If the exclusion in question exists because of requirements under P&P 5, any relaxation of the requirement, no matter how well intentioned or justifiable, is a violation of protocol. Overrides of medical exclusions are not likely to be seen kindly by IRBs and can result in punitive action by the FDA.

P&P 17: If a person is waived into a trial by overriding fail-safe procedures to protect against enrollment of persons with excluding medical conditions, set up procedures to ensure that:

- The responsible study physician requests the override in writing, and that the request includes the reasons for the request and the reasons why the enrolling physician believes it is safe to enroll the person in question.
- The request to override is subject to review by a party or parties independent of the requesting physician
- The order to override and issue a randomization is not given in absence of written justification or in the face of doubt regarding the potential of risk of harm to the person, if enrolled.
- The enrolling investigator is made to notify his or her IRB of the override and the reasons for it within three working days of the override, and the notification and acknowledgment of the notification is on file at the investigator's institution and at the CC.

P&P 18: Instruct staff of the CC to refuse release of randomization via an override of a medical eligibility requirement without the authorization of the Director or his or her designee.