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(Thursday 6:05am) 18 January 2001

Memorandum

To: Center for Clinical Trials faculty and staff

Fr: Curt Meinert

Re: Variance good practice policies and procedures (GPPP)

Definitions

adjudicated reading *n* - 1. The **reading** of a **discrepant record** as provided by an **independent** reader or panel, especially such a reading to be used for making a final classification or determination. 2. A reading provided by readers empaneled to review their discrepant readings for the purpose of arriving at a final or official reading.

duplication *n* - The act or process of **duplicating**. rt: **repetition**, **replication** ***Usage note***: Not to be confused with **replication**; see usage note for **replication**.

reliability *n* - The extent to which an **experiment**, **test**, **measurement**, or **analysis** yields the same results on **replication** under the same conditions; **repeatability**, **reproducibility**.

repeat reading *n* - A **reading** performed again; done by a different person or by the same person at different times.

repeatable *adj* - 1. Capable of being **repeated**. 2. The quality of an **experiment**, **study**, **test**, **measure**, or **analysis** to yield the same **result** when repeated under similar conditions; **reliable**, **reproducible**.

repeated measures design *n* - 1. A general class of **designs** having one or more **outcome measures** amenable to repeated measurement. 2. That subset of designs defined in defn 1 in which the **primary outcome measure** is amenable to repeated measurement. ***Usage note***: Note that defn 1 includes **crossover trials** and most trials having **parallel treatment designs** to the extent that the latter have at least one outcome measure amenable to repeated measurement. Defn 2 is limited to the set of designs in which the primary outcome measure (usually the **design variable**) is amenable to repeated measurement. Hence, in this sense, a trial having a parallel treatment design with mortality as the design variable is not a member of the class because the variable, death, is not amenable to repeated measurement. However, such trials, to the extent they involve other outcome measures amenable to repeated measurements (eg, a trial with mortality as the primary outcome measure and blood pressure change as a secondary

outcome measure, as observed at various points over the course of treatment) are members of the class as defined by defn 1.

replicate measure *n* - 1. Two or more **observations** of the same **variable** made under identical circumstances. 2. Two or more observations of the same variable made under near identical circumstances, eg, as with repeat observations made in close temporal proximity to each other. rt: **replication**

replication *n* - **Repetition** of a process, procedure, **study**, or **experiment** for the purpose of increasing the **precision** of an **estimate** or to confirm or refute some finding, **result**, or **conclusion** derived from an earlier execution of that process, procedure, study, or experiment. rt: **duplication**, **redundancy** ***Usage note***: Not to be confused with **duplication**. **Replication** is an essential part of the scientific method; duplication is not. For example, replication of an experiment is necessary to establish the plausibility of a result or finding, but repetition, once a result or finding is established, is an unnecessary duplication of effort.

variance *n* - [MF *variaunce*, fr MF, fr L *varianita*, fr *variant-*, *varians*, prp of *variare* to vary] 1. A **parameter** equal to the second **moment** of the underlying **variable** (or associated distribution function) about its **mean**. 2. The mean of the square differences about the mean of a **frequency distribution**; a similar quantity using **n** - 1 rather than **n** as a divisor. 3. The square of the **standard deviation**. rt: **standard deviation**

variance control *v* - Reducing or eliminating **variance** in some process or procedure; such reduction or elimination arising from **bias control**, **matching**, **stratification**, **monitoring**, or **adjustment**. rt: **bias control**

P&P 1: Enumerate variance control and reduction procedures to be practiced; enumerate during the design phase of the trial; review and update as the trial proceeds.

Comment

The usual methods of variance control or reduction are via routes suggested below.

Design

- Increased sample size
- Crossover designs
- Matching or pairing of assignment units

Patient selection and exclusion

Execution

- Stratification
- Blocking
- Standardization
- Ongoing surveillance and quality control
- Ongoing data editing
- Performance monitoring

- Treatment effects monitoring

Replication

- Double data entry
- Replicate laboratory determinations
- Multiple readings of records

Repeated measures

Analysis

- Use of baseline covariates for adjustment
- Multiple regression analysis
- Subgroup analysis
- Trimming and Winsorization

Other aids and strategies

- Written protocol
- Procedures handbook
- Outlier detection and trimming procedures
- Standardized equipment
- Central readings and determinations
- Training and certification
- Site visiting

P&P 2: Avoid exclusion as a means of variance control; limit to what is necessary for proper and safe administration of assigned treatments.

Comment

See *Screening and eligibility good practice policies and procedures (GPPP).*

P&P 3: Limit use of replication (eg, repeat laboratory determinations or multiple independent readings of a record) to measures that (1) are key to the trial and (2) where variance reduction is necessary to yield the desired level of precision for comparison.

Comment

Generally, the amount of precision provided for laboratory tests and readings is sufficient without replication.

P&P 4: A measure should not be combined by averaging (or other means) if it is not a **replicate measure** (see definition above).

Comment

The practice of repeating a measure at two or more visits prior to enrollment in order to obtain a "stable" baseline (eg, by averaging the values) is open to question under this P&P because the measure is not a replicate. Variables measured at different visits, even if in close temporal proximity, are not replicate measures because the conditions of observation and measurement are different.

P&P 5: Limit use of adjudication processes to what is necessary for the proper characterization or care of persons enrolled in a trial; avoid if in the critical time path for randomization.

Comment

There are considerable expenses in setting up and maintaining adjudication processes in trials.

P&P 6: Tilt in favor of local laboratories (vs central laboratories):

- For routine assays needed for care or management of patients
- For standard routine measures
- When shipping is not possible, impractical, or expensive
- When there is no cost advantage to central laboratories

Tilt in favor of central laboratories:

- For special assays not routinely performed in local laboratories
- When lab-to-lab variation is likely to be high and where reduction in variance is necessary to provide the desired level of precision
- Results of tests are to be masked to clinic personnel
- There are cost or logistical advantages to having a central laboratory

P&P 7: Tilt in favor of local readings (vs central readings):

- When real world conditions require reliance on local readings or where local readings represent "standard of care"
- For readings necessary in the routine care or management of patients
- When same-day readings are required

Tilt in favor of central readings when:

- Readings are subjective
- Readings are to be done by clinic personnel not masked to treatment assignment
- Clinic-to-clinic variation in readings is likely to be large
- Readings require special equipment or specially trained personnel
- Results of readings are to be masked to clinic personnel
- There are cost or logistical advantages to central readings