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Memorandum

To: Center for Clinical Trials faculty and staff

Fr: Curt Meinert

Re: Laboratory, reading, and banking 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.

central laboratory (CL) *n* - 1. A **study center** in the structure of a **multicenter study**, such as a **multicenter trial**, responsible for performing specified **tests** (defn 2) on specimens collected by participating **field centers** or **clinical centers** from people enrolled or considered for **enrollment** into the **study**; as distinct from **local laboratory** (defn 1). 2. A facility within an **institution**, such as a hospital, responsible for performing a variety of tests or analyses, as ordered by and received from staff of the various departments or units of the institution having access to its services. rt: **local laboratory** See *center* for list.

good laboratory practice (GLP) *n* - A set of **guidelines** promulgated by an august body or regulatory agency as being good or desired in regard to the practices of laboratories; in the case of **trials**, such guidelines promulgated by the **Food and Drug Administration** or the **International Conference on Harmonisation**.

local laboratory *n* - 1. A **laboratory** that serves a single **center** in a **multicenter study**. 2. A laboratory located within the same geographic region as its users, eg, one located in the same city or institution as its users. 3. A laboratory set up and operated for the benefit of a specific person or set of persons in relation to some research activity or specialized function; especially one under the control of and located within one's own administrative unit and the services of which are available only to specified persons housed within that administrative unit. rt: **central laboratory**

specimen bank *n* - [**clinical research**] A **bank** containing biological specimens collected on persons evaluated for study or on persons **enrolled** into a **study**.

P&P 1: In multicenter trials, default to local laboratories in the absence of convincing rationales for central laboratories.

Comment

Generally, it is easier and less expensive to use local laboratories. Hence, the mind set in multicenter trials should be tilted in favor of local laboratories.

Central laboratories are necessary when local laboratories do not have the means or skill to perform the desired tests. They are desirable as well when there are legitimate reasons to for wanting to reduce variance by use of a single laboratory, with emphasis on *legitimate*. Usually, precision is more than adequate for most laboratory determinations in trials, even if subject to lab to lab variation.

The tendency on the part of investigators is to favor central laboratories over local laboratories. Usually, the supposition is that there is not much to be lost and a good deal to be gained. The usual arguments are:

- Not more expensive than local laboratories
- Eliminates need for certification, standardization, calibration, and for monitoring local laboratories for secular drift
- "Everybody else does it"
- The study will be criticized if local laboratories are used
- Improved precision of comparisons

The costs are greater for central than for local determinations. There are costs for packaging and shipping that are avoided with local on-site laboratories (to say nothing about time needed for preparation of specimens for shipment).

Sometimes the only option is local determinations, eg, when needed in a hurry for the diagnosis or immediate care of a patient. Central determinations can be problematic if they are used for determination of eligibility or for stratification if the turnaround is not compatible with the time constraints required for enrollment.

P&P 2: In regard to laboratory determinations, establish procedures for ongoing processing of specimens and for flow of results to the CC.

Comment

Timely processing and flow of information to the CC is necessary if the information generated is to be of value in monitoring.

P&P 3: In regard to specimen banks, avoid in the absence of plans for use.

Comment

Investigators are like squirrels when it comes to banking. The primary difference is that squirrels have an obvious purpose in mind when they bank.

There are costs in banking, hence, it should not be undertaken without an appreciation of those costs – costs for collection, processing, shipping, inventorying, storage, retrieval, analysis, and harvest of data from tests done on banked specimens.

Banks are meant for depositing and withdrawing. The tendency in design is to concentrate on deposit without much thought about withdrawal or who has "withdrawal privileges". Are such privileges limited to study investigators or should they extend to others outside the study? If so, what are the conditions for use outside the study?

P&P 4: In regard to readings, establish systems to provide timely readings and flow of readings to the CC.

Comment

The same as for P&P 2.

P&P 5: Build the primary system for reading on a per record basis, ie, build so each record is read independently of all other records.

Comment

The easiest and most robust reading system is one built on a per record system.

P&P 6: If paired readings are required to measure change (eg, by comparing a followup record to that obtained at baseline for a given person), perform those readings independently of the per record readings mentioned in P&P 5.

Comment

The purpose underlying the P&P is to avoid conditions that are likely to impede or delay the flow of information to clinics and to the CC from per record readings (P&P 5).

P&P 7: If paired readings are required (P&P 6), establish a system that provides such readings in a timely fashion over the course of the trial.

Comment

The desire, often, is to wait until the "end" of the trial to simplify the logistics of pairing and readings. However, that approach has the obvious shortcoming that the "end" in trials can come prematurely and, hence, the pairing may never get done. In any case, paired readings done at the end of a trial are not useful in monitoring for treatment effects during the trial.

P&P 8: If paired readings are done by comparison to records other than baseline records (eg, as in eye trials where the new base of comparison is provided by fundus photographs taken after a new course of treatment), establish such procedures with clear crisp definitions of the defining conditions calling for creation of a new "baseline".

P&P 9: In regard to central versus local readings, use the same philosophy as outlined for deciding on central versus local laboratory determinations (P&P 1).

P&P 10: Do not use central readings for diagnosis, care, or treatment of patients if the practice is to use local readings for those purposes.

Comment

The general goal in most large-scale multicenter trials is to conduct them under conditions as near real world as possible. Pursuit of that goal, in regard to readings of records and specimens used for diagnosis, care, or treatment of persons in trials, argues for isolating central reading processes from clinics, except where central readings represent normal practice.

P&P 11: If central readings are to be used for diagnosis of persons to be enrolled into a trial or for care or treatment of persons enrolled into a trial, then the system for central readings must be established and maintained to provide feedback to clinics within days of date of receipt.

P&P 12: In regard to repeat readings, tilt in favor of single unadjudicated readings.

Comment

Valid treatment comparisons can be made using single readings if they are made without knowledge of treatment assignment or course of treatment.

Adjudication processes are difficult to implement and maintain, especially those done with panels where readers have to assembled in a common location.