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Memorandum

To: Center for Clinical Trials faculty and staff

Fr: Curt Meinert

Re: Bias control 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.

bias *n* - [fr OF *bias*, oblique, fr OProv, perhaps from Gk, *epikarsios*, oblique] 1. An inclination of temperament, state of mind, or action based on perception, opinion, or impression as opposed to fact, that serves to reduce rational thought or action, or the making of impartial judgments; a specified instance of such an inclination; **prejudice**. 2. A tendency toward certain **measurements** or **outcomes** over others as a result of a conscious or subconscious mind set, temperament, or the like; a specific expression of such a tendency. 3. **Deviation** of the **expected value** of an **estimate** of a **statistic** from its true value. See *bias* for list. ***Usage note***: Distinguish between uses in which **bias** (defn 1 or 2) is being proposed in a speculative sense as opposed to an actual instance of bias. Usages in the latter sense should be supported with evidence or arguments to substantiate the claim. Usages in the former sense should be preceded or followed by appropriate modifiers, explanatory clauses, or statements to make it clear that the user is speculating rather than stating a fact. Similarly, since most undifferentiated uses (in the sense of defns 1 or 2) are in the speculative rather than fact sense, prudent readers will treat all uses of the term as being in the sense of speculation, except where accompanied by data, evidence, or arguments to establish bias as a fact. See **prejudice** for additional comments.

bias control *v* - The exercise of restraint to reduce or eliminate the influence of **bias** on some process or procedure; such restraint as arising from **masking**, **standardizing**, **training**, and **certifying**. rt: **variance control**

frozen state of equipoise *n* - [**trials**] An **imposed state** intended to keep **study investigators** from knowing the nature or trend of **interim results**; achieved by proscription of interim analyses or by constructs to shield study investigators from results of interim analyses, eg, as in **apartheid treatment effects monitoring**. rt: **clinical equipoise**, **equipoise**, **equal ignorance**, **frozen state of knowledge**, **imposed state of equipoise** ***Usage note***: Not to be confused with

masked treatment administration. The state exists independent of **treatment masking** (eg, as in the **UGDP** — the oral hypoglycemic treatments in that study were administered in masked fashion; the monitoring was done by the directors and deputy directors of the various participating **centers** with interim analyses with treatments identified). Also not to be confused with **masked treatment effects monitoring**. The monitoring, whether or not done by study investigators, may or may not be masked. The state is maintained to the extent that investigators, individually and collectively, refrain from preforming their own interim analyses. That capability exists in **unmasked trials**, and in **masked trials** to the degree that treatments can be identified. The state may be imposed on all study investigators or on a selected subset, eg, all personnel involved in **treatment** or **data collection** (as in **apartheid treatment effects monitoring**). The state is imposed to reduce the risk of **treatment-related feedback bias**. Concerns regarding that bias are greatest in unmasked trials, but are present in masked trials to the extent that masking is ineffective. See **objectivity requirement** for additional comments.

selection bias *n* - 1. A systematic inclination or tendency for elements or units selected for **study** (usually persons in **trials**) to differ from those not selected. See **Berksonian bias** for a special type of selection bias. 2. **treatment-related selection bias** (not a recommended synonym) ***Usage note***: The **bias** defined by defn 1 is unavoidable in most trials because of selective factors introduced as a result of eligibility requirements for **enrollment** and because of the fact that individuals may decline enrollment (see **consent process**). The existence of the bias does not affect the **validity** of **treatment comparisons** within a trial so long as the bias is the same for all **treatment groups**, eg, as is the case when **treatment assignments** are made by **randomization**.

treatment-related bias *n* - 1. **Bias** related to **treatment**. 2. Bias related to **treatment assignment**. rt: **treatment-related feedback bias**

treatment-related feedback bias *n* - [**trials**] 1. **Bias** in an **observation**, **measurement**, **reporting**, **analysis**, or **administration** process or procedure due to knowledge of **interim treatment results** on the part of the one observing, measuring, reporting, analyzing, or administering. 2. Differential behavior of persons **enrolled** into a trial due to their having knowledge of interim treatment results, eg, a differential **loss to followup** due to differences in the willingness of persons to continue because of their having knowledge of **non-nil** interim treatment results. ***Usage note***: Use with caution as a claim or assertion. The existence of a **feedback bias** is difficult to establish. It does not operate in the absence of knowledge of interim results and is unlikely to operate in the presence of **nil** interim treatment results. Knowledge of an interim treatment result is not sufficient for the bias to operate. One must also be able to argue plausibly that that knowledge can produce the bias. It is difficult to do so in **masked trials**, and especially in **double-masked trials**. Even if a **treater** has access to interim results, that information, to translate into a **treatment-related bias**, must be related to individual patients and must influence how that person treats or observes in the trial. It is not possible to relate results to individual patients if the treater is effectively masked to **treatment assignment**. Further,

even if a treater or data collector is not masked, it is difficult to argue plausibly that a **treatment difference** is due to a treatment-related bias if the process or procedure in question is **robust** to the bias. For example, there is not much of an opportunity for the bias to operate if the measurement in question is not prone to **errors** of interpretation or reporting (eg, as with most event-type **outcomes**, such as death or events indicative of gross morbidity). Nor is there much room for the bias to operate if a process or procedure is well-defined (eg, as in a **treatment protocol** with explicit rules for when and how **treatments** are to be altered in the presence of specified conditions). Generally, the more **objective** the process or procedure, the more difficult it is to plausibly argue that knowledge of interim results can produce a treatment-related feedback bias. See **bias** for additional comments.

treatment-related selection bias *n* - Broadly, **bias** related to **treatment assignment** introduced during the selection and **enrollment** of persons or **treatment units** into a **trial**. Often, **selection bias** due to knowing treatment assignments in advance of use and using that information in the selection process. The **risk** of the bias is greatest in **unmasked trials** involving **systematic** assignment schemes (eg, one in which assignments are based on order or day of arrival of **patients** at a **clinic**). It is **nil** in trials involving **simple** (**unrestricted**) **randomization** but can arise in relation to **blocked randomization** if the blocking scheme is known or deduced. For example, one would be able to correctly predict one-half of the assignments before use in an unmasked trial of two **study treatments** arranged in blocks of size two, if the blocking was known or deduced. The chance of the bias operating, even if the blocking scheme is simple, is minimal in **double-masked trials** (because correct guesses are not likely to translate into a treatment-related selection bias when the treatments are masked).

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

Comment

The usual methods of bias control are via:

- Randomization
- Masking (patients, physicians, data collectors; readings; determinations; data analysts)
- Organizational and operational separations
- Frozen state of equipoise
- Training of clinic personnel
- Certification of clinic personnel
- Standardization (treatment procedures; data collection procedures; definitions)
- Surveillance and monitoring
- Adjudication

P&P 2: Minimize efforts in characterizing selection biases (defn 1) related to persons selected for study.

Comment

All trials involve select study populations. Patients enrolled into a trial can be expected to differ from the general population from in a host of ways; principally because of the select nature of clinics involved in any given trial and because one cannot study patients who do not consent to study. Efforts aimed at "defining" the population from which persons are recruited are not likely to particularly fruitful or informative.

P&P 3: If screening logs are desired, minimize effort in creating and maintaining such logs; avoid major effort in recording and keying such data.

Comment

See P&P 2.

P&P 4: In regard to bias control, concentrate efforts on control of treatment-related bias.

Comment

Treatment-related bias is, by definition, differential by treatment group and, therefore, can create bias in treatment comparisons thereby threatening the validity of the trial.

P&P 5: Regard randomization as essential in protecting against treatment-related bias; do not accept alternatives even if seemingly operationally equivalent to randomization.

Comment

The power and virtue of *randomized* trials flow from randomization.

P&P 6: Mask where it is possible, practical, and safe to do so.

P&P 7: Opt for the highest level of masking for treatment administration that is possible, practical, and safe; double masking if possible; single-masking if double-masking is not possible; no masking if double-masking or single-masking are not possible.

P&P 8: Avoid masked treatment administration for bias control if the masking carries risk for a patient, if the competency of those caring for a patient in the trial is reduced by masking, or if masking is impractical or ineffective.

P&P 9: Design performance monitor procedures to detect differential bias; to the extent possible, institute procedures to remove or reduce cause of such bias.

P&P 10: Avoid use of adjudicated readings as a means of bias control; limit use to cases where adjudication is considered necessary for the proper diagnosis and care of persons in a trial.

Comment

Any system of adjudication is complicated, time consuming, and energy draining. Treatment comparisons should be unbiased, even if readers are biased, unless those biases are related to treatment assignment – not likely if readers are masked to treatment assignment.

P&P 11: Set up and maintain procedures to monitor for evidence of treatment-related bias over the course of the trial.
