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(Friday 6:59am) 16 June 2000

Memorandum

To: Center for Clinical Trials faculty and staff

Fr: Curt Meinert

Re: TEM good practice policies and procedures (GPPP)

Definitions

treatment effects monitoring *n* - 1. In **trials**, the act of or an instance of reviewing accumulated **outcome data** by **treatment group** to determine if the trial should continue unaltered. 2. The act or an instance of watching for **treatment effects** in an individual **patient**. syn (not recommended): **data monitoring**, **safety monitoring**, **data and safety monitoring** rt: **administrative review**, **efficacy monitoring**, **multiple looks**, **safety monitoring**, **treatment effects monitoring** ***Usage note***: See note for **treatment effects monitoring** *v* and notes for **administrative review**, **efficacy monitoring**, and **safety monitoring**.

treatment effects monitoring *v* - **Monitoring** done to assess the **effects** of **treatments** used in a **trial** as measured by designated **treatment comparisons** and for the purpose of deciding whether the trial should continue unaltered. Typically, a process starting early in the course of the trial and continuing to its planned end or until a decision is made to stop it as a result of the monitoring. The monitoring may be done in **masked** or **unmasked** fashion and may be done by a single individual or a formally constituted **treatment effects monitoring committee**. In **multicenter trials**, usually performed by such a committee using **treatment effects monitoring reports** prepared by the **data center**, **data coordinating center**, or **coordinating center**. syn (not recommended): **data monitoring**, **safety monitoring**, **data and safety monitoring** ***Usage note***: Harm, in the context of trials, can arise from use of a bad treatment or failure to use a good one. *Safety* in **safety monitoring** or **data and safety monitoring** suggests that the monitoring is concerned primarily with preventing harm arising from use of a bad treatment. The terms are largely silent on the aspect of harm arising from failure to use a good treatment. **Treatment effects monitoring** provides a better description of the process involved by keying on the focus of the monitoring (**treatment effects**) and avoids the one-sided emphasis by neutrality. The term **data monitoring**, while also neutral, is not informative. Technically, any ongoing process involving periodic assessments of **data** of any kind constitutes a form of data monitoring.

P&P 1: Assume the need for TEM when preparing a funding initiative.

Comment

See memo from CLM dated 26 April 2000.

The impact of the P&P is to make TEM the default condition. To be willing to forego monitoring it must be possible to argue convincingly that the treatments being administered are risk-free or that monitoring does not materially reduce the risk of harm to persons. Cost, inconvenience, or logistical difficulties are not admissible as reasons for not monitoring.

Most treatments carry risks, even if small. Therefore, arguments that treatments are "risk free" should be viewed with skepticism. Certainly, the mere fact that a treatment is "standard" is not sufficient to establish the treatment as "risk-free".

Similarly, one should not take the fact that the treatments being tested are innocuous as a basis for being "risk-free", because evaluation and data collection procedures carry risks. Indeed, some argue that the mere nuisance of being studied is itself a "risk". Hence, one should not be studying more people than necessary or for longer periods of time than warranted by available data.

P&P 2: Do not proceed with a funding initiative or continue in a collaboration where TEM is proscribed by the sponsor, or where it is uncertain whether or not the Center has the authority, means, or wherewithal to institute and perform adequate monitoring.

Comment

See memo from CLM dated 26 April 2000 and publications cited in that memo for foundations underlying this P&P.

P&P 3: Be explicit on need for TEM in funding initiatives (when the trial meets the test for requiring monitoring); make position clear in response to RFAs and RFPs in cases where need is not mentioned in RFA or RFP.

Comment

The purpose is to inform sponsors of the intent to monitor to allow them to decline funding if they are opposed to monitoring.

P&P 4: Establish and maintain procedures to ensure that investigators are properly empowered and informed regarding the approach to TEM, that they are involved in selection of persons to serve on the TEMC, and that they deliberate and vote on recommendations coming from the TEMC.

Comment

See memo from CLM dated 26 April 2000.

P&P 5: Recognize monitoring as a function to be vested in a properly constituted group.

Comment

The issues and problems in TEM are too complex to be entrusted to a single person. Competency can be achieved only by a collective effort involving the combined skills and disciplines of a variety of people.

P&P 6: Establish and maintain a body charged with responsibility for monitoring.

Comment

The body may be the investigators themselves, or a body consisting of persons independent of the trial and persons from the trial (eg, study officers).

P&P 7: Establish and maintain procedures to ensure timely data flow as needed to ensure adequate monitoring.

Comment

Monitoring is de facto inadequate if the lag in data flow is such that monitoring is rendered ineffective by virtue of the lag. See Controlled Clinical Trials (19:515-543, 1998).

P&P 8: Establish and maintain procedures to ensure completeness of data flow as needed to ensure adequate monitoring.

Comment

Monitoring is de facto inadequate if the TEMC does not have access to a complete dataset. This P&P implies real-time or near real-time processing of data and procedures for creating and maintaining datasets that incorporate data generated in the trial. Operationally, this means that batching of readings or specimens to be done at the "end" of the trial should not be practiced if the information to be generated is likely to have utility in monitoring. See Controlled Clinical Trials (19:515-543, 1998) for additional comments.

P&P 9: Establish and maintain procedures to ensure an inviolate linkage of the TEMC to investigators.

Comment

See memo from CLM dated 26 April 2000.

Consider the linkage to be violate if the TEMC reports to the sponsor in the absence of written assurance that recommendations will be passed to study investigators in a timely manner and without regard to whether the sponsor endorses the recommendation.

P&P 10: Do not impose or accept objectivity constructs in monitoring that are likely to reduce competency of monitors or constrain their actions.

Comment

See memo from CLM dated 26 April 2000.

P&P 11: Do not impose or accept objectivity constructs in monitoring that make data more difficult to interpret or that increase the risk of errors in analysis or monitoring.

P&P 12: Indicate the minimally acceptable standard for adequate monitoring in the initial submission to the parent IRB and in discussion with study investigators.

P&P 13: Notify the parent IRB and study investigators of demands or requests of sponsors having the effect of causing the CC to perform below standard.

P&P 14: Adopt procedures to suspend randomization while recommendations to stop, as issued from the TEMC, are being processed and debated.

Comment

The purpose is to avoid duplicity in the CC by continuing to randomize when a recommendation to stop is pending.

P&P 15: Notify investigators of meetings of the TEMC and of recommendations made by the TEMC. Notify IRBs as required by IRBs.