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(Wednesday 6:46am) 31 January 2001

Memorandum

To: Center for Clinical Trials faculty and staff

Fr: Curt Meinert

Re: Treatment effects monitoring committee good practice policies and procedures (GPPP)

Definitions

advisory-review and treatment effects monitoring committee (ARTEMC) *n* - A **committee** that performs the functions of both the **advisory-review committee** and **treatment effects monitoring committee**. A **key committee** in the organizational structure of **multicenter treatment trials**. See *committee* for list.

advisory-review committee (ARC) *n* - A **committee** in the organizational structure of a **trial** that is responsible for reviewing the design and operations of the trial for the purpose of advising the **steering committee** and **sponsor** on matters related to the trial; voting members usually not involved in the execution of the trial or associated with any of the participating **centers** or **sponsor** of the trial. Selected **investigators** from the trial may serve as nonvoting members. A **key committee** in the organizational structure of some **multicenter treatment trials** with method of appointment and route of reporting similar to that described for **treatment effects monitoring committee**. syn: advisory board, advisory committee, policy-advisory board, policy-advisory committee, policy board, policy committee See *committee* for list.

efficacy monitoring *v* - [**trials**] 1. **Monitoring** (defn 2) for **efficacy**, as performed at periodic time points over the course of a trial, to determine whether the trial should be stopped or modified; as distinct from **safety monitoring**. 2. **efficacy review** (defn 1) 3. **treatment effects monitoring** rt: **safety monitoring**, **treatment effects monitoring**, **interim look**, **interim result** ***Usage note***: Often used in contradistinction to **safety monitoring** in settings where the user wishes to distinguish between **interim looks** performed for efficacy monitoring versus those made for safety monitoring; eg, in settings where looks for safety monitoring are not counted as looks for purposes of adjusting **p-values** for **multiple looks**. The distinction is predicated on the assumption that safety and efficacy are **independent** dimensions of **treatment** — often not the case. Use **treatment effects monitoring** when the distinction is unimportant or where the monitoring performed is for efficacy and safety. See also notes for **administrative review**, **safety monitoring**, and **treatment effects monitoring**.

safety monitoring *v* - [**trials**] 1. **Monitoring** (defn 2) performed at periodic time points over the course of a trial, to determine whether the trial should be stopped or modified because of safety

considerations; as distinct from **efficacy monitoring**. 2. **safety review** (defn 1) 3. **treatment effects monitoring** rt: **data and safety monitoring**, **efficacy monitoring**, **treatment effects monitoring**, **interim look**, **interim result** ***Usage note***: Often used in contradistinction to **efficacy monitoring** in settings where the user wishes to distinguish between **interim looks** performed for efficacy monitoring versus **safety monitoring**; eg, in settings where looks for safety monitoring are not counted as looks for purposes of adjusting **p-values** for **multiple looks**. The distinction is predicated on the assumption that safety and efficacy are **independent** dimensions of **treatment** — often not the case. Use **treatment effects monitoring** when the distinction is unimportant or where the monitoring performed is for safety and efficacy. See also notes for **administrative review**, **efficacy monitoring** and **treatment effects monitoring**.

treatment effect *n* - 1. A quantity representing the **change** in **response** produced by a **treatment**, as in models for **analysis of variance**. 2. An **effect** (**adverse** or **beneficial**) attributed to the **test treatment**; in **trials**, usually inferred or **estimated** from a **comparison** of the **test-** and **control-assigned groups**. 3. The effect (adverse or beneficial) produced or assumed to be produced by a treatment in a **treatment unit**, usually assessed by **measurements** made before and after administration of the treatment in that unit. 4. **treatment difference** rt: **adverse treatment effect**, **beneficial treatment effect**, **therapeutic effect**

treatment effects and performance monitoring committee *n* - A **committee** having responsibility for **treatment effects** and **performance monitoring**. See **performance monitoring committee** and **treatment effects monitoring committee**.

treatment effects monitor *n* - One who **monitors** for **treatment effects**, especially one seated on a body charged with or constituted to perform **treatment effects monitoring**.

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.

treatment effects monitoring and analysis committee *n* - A **committee** having responsibility for **treatment effects monitoring** and **data analysis**. See **treatment effects monitoring committee** and **analysis committee**. rt: **external treatment effects monitoring committee**, **internal treatment effects monitoring committee**

treatment effects monitoring committee (TEMC) *n* - [**trials**] A standing **committee** in the structure of **single** or **multicenter trials** responsible for the periodic review of accumulated **data** for evidence of **adverse** or **beneficial treatment effects** during the **trial** and for making recommendations for modification of a **study treatment**, including termination, when appropriate. One of the **key committees** in the organizational structure of a multicenter trial. Usually constituted such that voting privileges are restricted to members not directly involved in the execution of the trial and not associated with participating **centers** or **sponsors** of the trial. Others, such as **officers of the study** or other key **study investigators**, if included as members, serve without vote. Voting members are appointed by the **sponsor** (defn 2) or **research group**, often with the advice and consent of the other party. The committee reports to the appointing authority and usually to the other party via the appointing authority or directly. syn (not recommended): **data monitoring committee**, **data and safety monitoring committee**, ethical committee, **ethics committee**, **safety monitoring committee** rt: **advisory-review and treatment effects monitoring committee**, **external treatment effects monitoring committee**, **internal treatment effects monitoring committee** ***Usage note***: **Data monitoring committee**, though commonly used, is not recommended because the most common usages of **data monitoring** occur in relation to **data collection** and **quality assurance**. **Safety monitoring committee** is not recommended because of the implication that the monitoring relates only to **safety** and not to **efficacy**. Perhaps, the most common name is **data and safety monitoring committee** but it suffers from all the drawbacks listed above; hence is not recommended. The preferred descriptor is *treatment effects monitoring*; preferred because of its currency in suggesting what is done and because of its neutrality with regard to safety versus efficacy. The committee may have a compound name when the treatment monitoring function is vested in a committee having other broad responsibilities, eg, **advisory-review and treatment effects monitoring committee**.

treatment effects monitoring report *n* - A **report**, prepared during the course of a **trial** that uses accumulated **data** and provides a **comparison** of the various **treatment groups** represented in the trial for the **outcomes** of interest. It is used by those reviewing it as a vehicle for deciding whether the trial should continue unaltered. Typically prepared by the **coordinating center**, **data coordinating center**, or **data center** and reviewed by the **treatment effects monitoring committee** in the case of **multicenter trials**.

P&P 1: Review and follow policy and procedures outlined in *TEM good practice policies and procedures* (GPPP).

P&P 2: Ensure the existence of a written document detailing the following before proceeding to create a TEMC:

- Charge
- Membership (voting and nonvoting)
- Method of appointment
- Length of service
- Payment (voting members only)
- Meeting mode (face-to-face; conference telephone)
- Frequency of meetings
- Requirements for attendance
- Voting rules
- Routing of recommendations to study investigators
- Requirements for disclosure of conflicts of interest
- IRB tutorial and certification of members

P&P 3: Regardless of who produces the written document in P&P 2, ensure that the document is reviewed and discussed by the SC, that it is revised accordingly, and that the revised document is formally accepted by a 2/3rds vote of the SC.

Comment

Sponsors can be expected to question, if not sometimes outright resist, elements of this P&P since it has the effect of reducing the sponsor's prerogatives in regard to control of the trial. Typically, that resistance is likely to be greatest with high profile trials. However, that resistance should not dissuade investigators from insistence on the principles of this P&P.

P&P 4: Limit the charge to treatment effects monitoring; resist expansion of the charge to include other duties or functions, eg, as represented for advisory-review committees.

Comment

The added functions detract from the monitoring function. The imposition of other review and approval functions, especially those related to approval of the study and policy issues affecting conduct, has the effect of blurring lines between the SC and TEMC and has the potential for creating an adversarial relationship with the TEMC.

P&P 5: Specify composition of the TEMC in the study protocol; indicate the disciplines and types of expertise to be represented; the number of voting members independent of the trial and the number of nonvoting members form the trial.

P&P 6: Outline procedures for appointment of voting members; provide for an advise and consent process involving study investigators and the sponsor; appoint for term of trial with meeting attendance clauses as discussed in *Organization good practice policies and procedures*.

P&P 7: Establish requirements for disclosure of conflicts of interest in the membership and methods for addressing and resolving conflicts of interest.

Comment

See *Conflict of interest disclosure and redress good practice policies and procedures*

P&P 8: Specify the minimum frequency of meetings and modes of meeting.

Comment

If the primary mode is by conference phone, require at least one face-to-face meeting in relation to the start of monitoring and a face-to-face meeting as indicated in P&P 11.

P&P 9: Require all members of TEMC to be IRB trained and certified.

P&P 10: Specify payment to be provided to voting members for each meeting.

Comment

When setting payment, be mindful that large sums may render members reluctant to stop a trial.

P&P 11: Require that votes to stop a trial be taken at face-to-face meetings.

Comment

Conference phone is not suitable for discussing and debating motions to stop a trial.

P&P 12: Establish protocol for transmitting recommendations to study investigators and IRBs; establish protocol for providing summary reports to IRBs following each meeting of the TEMC.

P&P 13: Specify voting rules and quorum requirements in the specification for the committee; specify whether a simple majority or a 2/3rds vote is required to suspend the protocol or to stop a trial, whether proxy votes are permitted (not recommended), and whether members not present may be polled for a vote (not recommended).

P&P 14: Avoid imposition of restrictions on the TEMC in regard to the number of looks that can be made or in what may be looked at; avoid restrictions in which TEM is limited to safety monitoring.

Comment

The line of demarcation between safety and efficacy is murky. The issue of safety is relative to efficacy, hence, it rarely makes sense to monitor for safety without also monitoring for efficacy.

P&P 15: Do not mask the TEMC.

Comment

See *Masking good practice policies and procedures*.

P&P 16: Design the TEM report to include a summary of adverse events by treatment group.