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(Thursday 5:12pm) 9 November 2000

Memorandum

To: Center for Clinical Trials faculty and staff

Fr: Curt Meinert

Re: Substudy, ancillary study, and auxiliary study good practice policies and procedures (GPPP)

Definitions

ancillary study *n* - 1. A supplementary **study** done in association with a **parent study**. 2. Such a study done by personnel associated with a parent study. rt: **daughter study**, **sister study**, **substudy** ***Usage note***: Subject to misuse when used interchangeably with **substudy**. A substudy is part of the parent study, an ancillary study is not. Ancillary studies are the result of the varying interests and pursuits of investigators in the parent study. Most **multicenter trials** have procedures for reviewing and approving proposed ancillary studies. Generally, investigators must satisfy the reviewing body of the parent study that the proposed studies are impact neutral. Studies seen as having a likely adverse impact on the parent study are not usually approved. Proposals calling for the collection of additional data or the conduct of additional procedures on persons enrolled in the parent study are not approved when seen as interfering with data collection procedures or requirements of the parent study, or when seen as increasing the risk of **dropout** or **missing data**. Studies are expected to be resource neutral from the perspective of the parent study. Studies calling for use of treatment-related data are assumed to be impact negative and are not approved, or are approved with the proviso that such data are not to be released or used until the parent study has been completed. See also **substudy**.

auxiliary study *n* - 1. An **ancillary study** done by personnel not associated with a **parent study**. 2. A study involving **data** or material from a study, done independently of that study and by personnel not associated with it. rt: **ancillary study**, **substudy**

co-enrollment *n* - [**studies**] 1. **Enrollment** of a person into a study while enrolled in a related study. 2. Simultaneous enrollment into two or more related studies. 3. An arrangement in which procedures performed and data collected on a person enrolled in one study serve to satisfy requirements for another study in which also enrolled; usually made to reduce time, inconvenience, or superfluous procedures. ***Usage note***: Assume usage is in the sense of defns 1 or 2 in the absence of supporting detail to justify use in the sense of defn 3. Largely, the arrangements required under defn 3 are difficult to achieve, even when the studies are done by the same group and generally not possible when the studies are done under different organization structures. Avoid as a jargonistic expression to imply the coordination and integration of approaches and protocols to allow for the sharing implied by defn 3.

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main study *n* - The portion of a **study** addressing the **primary objective** of a study, especially in the presence of **substudies** or **ancillary studies**. rt: **parent study**, **secondary study**

parent study *n* - 1. **main study** 2. A **study** having one or more **ancillary** or **substudies**.

secondary study *n* - 1. The portion of a **study** addressing a **secondary objective**. 2. **substudy** rt: **ancillary study**, **main study**, **substudy**

substudy *n* - A **study**, regarded to be within the work scope of the **parent study**, but performed only on selected study participants; selection may be by sampling or other means (eg, in the case of **multicenter studies**, performed at **clinics** with people having the interest, abilities, or facilities needed to perform said study; may be performed on all or selected participants at those sites). rt: **add-on study**, **ancillary study**, **daughter study**, **sister study** ***Usage note***: Not to be used interchangeably with **ancillary study**. A substudy is part of the work scope of the parent study, an ancillary is not.

Substudy

P&P 1: Avoid creating substudies.

Comment

Operationally, it is easier to design and manage one protocol than two or more.

There is the temptation, when investigators are split on an issue of method, to resolve the conflict by creating a substudy simply to still the argument. Generally, the better solution, even if more time consuming, is to talk and argue until a consensus is reached as to the method or procedure of choice.

P&P 2: Avoid use of substudies as "rewards" to investigators for participation.

Comment

"Why not let centers having the equipment and expertise needed to make the proposed crème de la crème measurement while the rest stick with the bare bones measurement?" The trouble with the solution lies in the added work in coordinating different versions of a protocol.

In any case, once the flood gates are open it may be difficult to close them. If Rudy satisfied his interests with a substudy why can't I?

P&P 3: Avoid substudies involving visit schedules different from those in the parent study.

Comment

The more you look the more you see. Hence, different visit schedules can lead to differences due simply to differences in the frequency of contacts.

P&P 4: Be skeptical of schemes to reduce data collection requirements by sampling, eg, a scheme in which a particular battery of laboratory tests is done only on persons having Id numbers divisible by 10.

Comment

Sampling schemes are difficult to implement and maintain by clinics and the CC.

P&P 5: Develop policy and procedures for review and approval of substudies.

Comment

One of the advantages of formal procedures and rules is that they reduce the propensity for substudies. Suggested rules and procedures:

- A rule precluding investigators from proposing and voting on a substudy at the same meeting
- A rule serving to preclude the steering committee from acting on a substudy until the coordinating center has conducted and reported an "environmental impact" analysis to the steering committee; report to provide information on the cost and logistical implications of the substudy at clinics and in the coordinating center
- A mandatory "cooling off period" following a proposed substudy; eg, a rule proscribing a formal vote on a substudy proposal within 30 days of proposal.
- Requiring a written protocol prior to taking a final vote
- Requiring a 2/3rd majority vote from the steering committee

Ancillary study

P&P 6: Define ancillary study; define during design phase; define to differentiate from auxiliary study and from substudy.

Comment

When defining, take care to exclude activities that do not meet requirements for being an ancillary study. Broadly, to qualify as an ancillary study, it should be possible to answer *yes* to both questions below:

- The activity is undertaken to address a question or issue of relevance to the parent trial.
- The activity involves contact with persons enrolled in the parent trial for collection of additional data, requires use of specimens from or records generated on persons enrolled in the parent trial, or requires access to data from the parent trial to analyze or interpret results from the proposed ancillary study.

The enrollment of persons from the parent trial into some other study not associated with the parent trial does not qualify as an ancillary study if it is not possible to answer yes to both questions. See P&P 9.

P&P 7: Establish procedures for proposing ancillary studies; produce a form in which the investigators provide:

- Title of project and purpose
- 250 word abstract description

- Principal investigator; other investigators
- Performance site(s)
- Nature and extent to which proposed study is likely to impact the parent trial
- Type and amount of specimens or records required from the trial
- Type and amount of data to be generated in the study
- Type and amount of data required from the trial
- Amount of effort required from the CC to support or analyze the study
- IRB reviews and approvals
- Source of funding

P&P 8: Establish review procedures and criteria for approval; design the review to ensure that:

- Conduct of the study will not adversely impact the trial
- Funding for the study, if required, will be obtained and provided independently of funding for the trial
- Need for and limitations on access to study data and records are made explicit prior to approval
- The proposing investigator has the means and resources to conduct the study including those needed for data analysis; if help is needed for data analysis those requirements should be made explicit prior to approval and the analysis center should indicate a willingness to provide that support
- The proposing investigator understands the conditions and restrictions imposed in regard to use of data or materials provided, including conditions for review of manuscripts prior to publication and on authorship and credit listings

P&P 9: Establish policy regarding limits of review prerogatives.

Comment

The prerogative for review and approval should be limited to studies rising to the level of ancillary study. However, the reality is that groups are territorial and, therefore, likely to extend their reach to activities not meeting the definition for ancillary study.

Policy calling for mandatory review of such activities is, at best, difficult to enforce and, in addition, has the potential of being resented if seen as an effort to assert "ownership" and control over persons in the trial.

The more reasonable policy is to educate investigators on the possible contaminating effects of extra study activities and to encourage investigators to request courtesy reviews when in doubt as to whether the influences are disqualifying.

P&P 10: Maintain a list of approved ancillary studies; update periodically; review progress periodically.

P&P 11: Establish policy friendly to the design and conduct of ancillary studies.

Comment

One of the fringe benefits of labor in a clinical trial is the opportunity it provides for ancillary studies. Providing a climate conducive to spawning and conducting such studies can be a win for the trial and for investigators conducting them.

P&P 12: Establish authorship policy along lines suggested in *Publication and presentation good practice policies and procedures*.

Auxiliary study

P&P 13: Define auxiliary study as implied in defn 2 above for that term.

P&P 14: Give priority to proposals for ancillary studies over auxiliary studies in the case of competing proposals.

P&P 15: Establish procedures for proposing auxiliary studies akin to those for proposing ancillary studies (see P&P 7).

P&P 16: Establish review procedures and criteria for approval; design the review to ensure that the proposing investigator:

- Understands conditions for approval
- Provides written assurance of willingness to limit use of data and records to that indicated in the agreement
- Agrees to conditions, if any, imposed when granting the approval in regard to manuscripts generated, including right to review manuscripts prior to publication

P&P 17: Maintain a list of approved auxiliary studies; update periodically.