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(Thursday 7:55am) 15 June 2000

Memorandum

To: Center for Clinical Trials faculty and staff

Fr: Curt Meinert

Re: IRB good practice policies and procedures (GPPP)

Definitions

institutional review board (IRB) *n* - A **committee** or **board**, as set forth in guidelines and regulations emanating from the **United States Public Health Service** concerning research involving human beings, appointed by authorities within a research **institution** and constituted to review and approve studies to be carried out on human beings by **investigators** from that institution. The review focuses on the **ethics** and legitimacy of the proposed research from the perspective of **risk-benefit** and on the adequacy of the proposed safeguards for would-be volunteers or individuals put at **risk** in or by the research. The risk may be a **direct** consequence of procedures performed or may be an **indirect** consequence of the work (eg, invasion of privacy or breaches of confidentiality). The review deals with, but is not restricted to, the nature and adequacy of the **consent process** and related **consent statement** when there is to be **contact** with individuals, and in all cases, whether or not there is contact, to a review of the adequacy of procedures to preserve individual anonymity and confidentiality of the information provided or obtained. Technically, the guidelines and regulations apply only to projects funded or to be funded by the federal government, but most institutions require IRB review and approval of all research involving human beings before it may be undertaken, regardless of funding source. The name arises from the regulations issued by the US Public Health Service and is, in one sense, unfortunate in that it is not suggestive of the functions actually performed. See also note for **involve**. syn: **ethics committee**, **ethics review board**, **Helsinki committee**, human experimentation committee, human volunteers committee rt: **central institutional review board**, **commercial institutional review board**, **independent institutional review board**, **institutional animal care and use committee**, **institutional review board approval**, **institutional review board approval renewal**, **institutional review board of record**, **parent institutional review board**

institutional review board approval *n* - **Approval** from one's **IRB** allowing one to proceed or continue with a specified **project**; approvals communicated in writing and, typically, good for one year from date of issue (may be for lesser time at the discretion of the IRB). Approvals are contingent on compliance with reporting procedures mandated by the IRB in relation to **adverse events** (where applicable). rt: **approved consent form**, **institutional review board approval renewal**

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institutional review board approval renewal *n* - **Renewal** of an existing IRB approval; required prior to expiration of an existing approval for a **project** to continue; request initiated by **investigator of record** with submission of progress report and details concerning extant consent procedures and **consent forms**. Renewal may be contingent on changes to consent procedures or forms, as dictated by one's IRB. Typically renewed approval are good for one year from date of issue (may be for lesser time at the discretion of the IRB). rt: **institutional review board approval**

institutional review board of record *n* - 1. The **IRB** to which one submits. 2. The IRB having signatory authority regarding one's **project**. 3. The IRB of the institution at which a project is conducted. 4. The IRB of the institution housing an **investigator** reporting an **adverse event** for a **patient of record** at that **site**. rt: **parent institutional review board**

parent center *n* - 1. A **center** that gives rise to or nurtures other similar centers. 2. A center that has administrative or operational primacy over others. 3. A center having an **affiliate**, **associate**, **field**, or **satellite center**. rt: **lead center**

parent institutional review board *n* - [**human research**] 1. The **IRB** of the **institution** housing the **principal investigator** of a **human research project** involving affiliate **sites** subservient to **affiliate IRBs**. 2. The IRB of the **parent center**. 3. The IRB of the **coordinating center**. rt: **affiliate institutional review board**, **central institutional review board**, **local institutional review board**

direct funding award *n* - A **funding award** (**grant** or **contract**) received directly from the **sponsor**. ant: **indirect funding award**

indirect funding award *n* - A **funding award** made to a **site** by another site with funds from a **sponsor**, as in a **consortium funding award**. ant: **direct funding award**

minimal risk *n* - In the setting of research involving human beings, a **risk** that is considered to be not more than that of routine daily life, defined in the Code of Federal Regulations for protection of human subjects as meaning that *the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests*. (§46.102(i)) rt: **more than minimal risk**

more than minimal risk *n* - A **risk** of harm, injury, or insult considered to be in excess of a **minimum**; in the setting of research involving human beings, the minimum is that of routine daily life. Research considered to not involve more than minimal risk are eligible for **expedited review**. rt: **minimal risk**

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protocol amendment *n* - 1. A proposed change to an **approved protocol**. 2. A **protocol change** that has been implemented. 3. A proposed protocol change submitted to an **IRB**; such a proposed change approved by an IRB. ***Usage note***: Subject to varying use. Technically, any change to an approved protocol is an amendment. Best reserved for changes submitted to IRBs for review and approval – generally, any change that can be reasonably argued as having the potential of changing the **risk-benefit ratio** for persons studied, or having potential to influence a person's decision as to whether to **enroll** or to remain in a **study**. In **trials**, including changes to the **treatment protocol**, study procedures, schedule of **study visits**, or period of **followup**; especially any change considered to require changes to existing **consent forms** or to require **reconsent**. Avoid in relation to changes due to spelling errors or minor wording changes on **data collection forms**.

P&P 1: Submit and operate under a parent IRB model.

Comment

The rationale underlying the P&P is to impose order and to ensure uniformity across IRBs in regard to what they receive. Absent order some imposed order, every center will be on its own in regard to when and how it submits, and in regard to the content of consent statements presented to study subjects.

The most practical way to impose order is by the parent IRB model (as described in the article in IRB referred to in the 26 April memo from CLM to me). The order is achieved by forestalling submissions to local IRBs until the protocol and consent form has cleared the parent IRB.

The intent to employ the parent model should be made clear in the initial submission from the CC to its IRB. Investigators should be informed early on of the intent to impose a parent IRB model and appraised of its operational implications.

Getting investigators to hold submissions until the parent has acted may be difficult. It can be if the parent is seen as being "slow" or if they think the order imposed will impede their progress.

Use of the model obligates the CC to proceed with deliberate speed in getting its submissions to the parent. It may also require dialogue with the chair of the parent IRB to "educate" in regard to responsibilities as a parent.

P&P 2: Submit and obtain an IRB approval for the CC, independent of all other IRB submissions.

Comment

The rationale underlying this P&P is to twofold: (1) to ensure a review concentrated on CC activities and (2) to ensure a direct and unfettered line of communication between the CC and its IRB of record.

A direct line of communication between the CC and its IRB of record requires submissions by the PI of the CC. Direct lines of communications are not assured when the CC approval is covered by submissions of the Study Chair.

The option of "piggy backing" in regard to the CC IRB submission exists only when funding is indirect and then only when the CC funding comes from the Office of the Study Chair or from another center located in JHU; presently the case for CBET, WGET, and ADAPT (see attached table).

Problems in "piggyback" IRB coverage arise when and if the CC is required to report directly to the IRB, or when the CC PI wishes to report to the IRB and the signatory refuses to do so. (In general, IRBs are loathe to accept or act on communications from subordinate investigators.)

The need for independent communication can arise if the IRB wishes to know treatment assignment (eg, in regard to adverse events) when that information is not to divulged to the signatory. It can arise also if the CC is obliged to report interim results by treatment group and that information is not to revealed to the signatory.

Of the IRBs serving the JHMI, the one best "schooled" in CC activities is the CHR, and therefore is the IRB of choice. However, the IRB to which one submits here is determined by the primary appointment of the signatory (PI in the language of IRBs). If the primary appointment is in the SHPH and the project does not involve JHMI patients, the submission is to the CHR. If the submission involves JHMI patients, the submission is to the JCCI, even if the primary appointment of the signatory is in the SHPH.

The rules of the JHMI are designed to avoid dual submissions. That is, there is reciprocity among IRBs of the JHMI. Approval by the JCCI covers the CC if its activities are included in submissions to that IRB, even if the CC is headed by a person from the SHPH.

Routinely, the CHR defers to the JCCI in cases where an application qualifies for submission to CHR or JCCI.

The recommendation, regarding CBET, WGET, and ADAPT, is to partial the CC activities out of the existing approvals and to submit and obtain approvals independent of the Study Chairs.

P&P 3: Submit applications for CC activities to the CHR regardless of place of appointment of the CC PI.

Comment

See P&P 2.

P&P 4: Make the initial submission under the assumption that TEM is necessary.

Comment

The rationale is to make monitoring the default condition. The operational implications of the P&P is that monitoring will be proposed. If not, the CC is obliged to explain why monitoring is not necessary (see 26 April 2000 memo).

P&P 5: Outline minimally acceptable monitoring procedures in the initial submission of the CC to its IRB.

Comment

The purpose behind the P&P is to limit the role of sponsors and TEMCs in setting monitoring procedures. Adherence to the P&P means that practices suggested or imposed by sponsors or TEMCs considered to reduce competency in monitoring will not be implemented by the CC unless or until expressly reviewed and approved by the CC IRB.

P&P 6: Disclose and justify proposed objectivity constructs in submissions to the CC IRB.

Comment

See 26 April 2000 memo.

Disclosures and justifications should be provided for randomization, masking, censoring, or other objectivity constructs imposed on study participants, study investigators, or on the TEMC. To be justifiable, it must be possible to argue convincingly that a proposed construct does not carry more than a minimal risk of harm (direct or indirect) for study subjects. It must be possible, in the case of constructs considered to reduce competency, to show that the reduction does not increase the risk of harm to study subjects.

P&P 7: Set up and maintain procedures to ensure compliance to procedures and rules of the parent IRB and all other associated IRBs.

Comment

It is the responsibility of the CC PI to ensure that activities in the CC are fully and properly reviewed by its IRB and to ensure that activities in the CC do not proceed or are halted in the absence of valid IRB approvals for the CC. The CC PI has a duty to cease operations if the CC IRB approval lapses or is withdrawn.

Good procedures include, but are not limited to, the following: (1) maintenance of a file of all CC IRB submissions and associated correspondence, arranged in order by date; (2) maintenance of a file of all approved (IRB date stamped) prototype consent statements; (3) a system for receiving, filing, and tracking queries from the CC IRB to ensure timely reply and resolution; (4) maintenance of a file of all IRB approvals and of IRB date stamped consents for participating clinics; (5) systems to remind centers of approvals near lapse.

P&P 8: Set up and maintain procedures to block randomizations at a clinic in the absence of a valid IRB approval for the clinic.

Comment

Adherence to this P&P requires systems of randomization that are controlled from the CC. Systems in which clinics are free to start enrollment and randomization without external controls or checks are not consistent with CC GPPP.

The P&P implies a system in which clinics are required to provide the CC with documentation of valid IRB approvals and with copies of approved consents before being cleared to randomize.

P&P 9: Set up and maintain procedures to inform all investigators, and via them, their respective IRBs, of reports of adverse events.

Comment

The presumption, in multicenter trials employing common treatment protocols, is that an adverse event in any clinic is an event that is to be reported to all other sites operating under the protocol. There may be additional requirements extending even to sister trials in the case of IND trials involving proprietary products. See also P&P 7.

P&P 10: Notify the CC IRB if the CC is unable to ensure an inalienable linkage of the TEMC to study investigators.

Comment

The requirement for inalienable linkage (see memo of 26 April 2000 from CLM) is evident in codes underlying research on human beings. The expectation is that the linkage is inviolate. The CC PI has the duty to notify the CC IRB if the linkage is not assured and to be guided by the dictates of the CC IRB in regard to ensuring linkage.

P&P 11: Disclose financial, relational, and philosophical conflicts of interest of CC personnel in submissions to the CC IRB; update as necessary.

P&P 12: Disclose major financial, relational, and philosophical conflicts of interest represented in the collective investigatorship of the trial in communications to the parent IRB.

P&P 13: Set up and maintain a system of numbered memos to communicate matters of interpretation of protocol and protocol amendments to clinics.

P&P 14: Develop prototype consents for submission to the parent IRB; supply approved prototypes to clinics for use in preparing consents for submission to local IRBs.

P&P 15: Review approved local consents against prototypes; note deficiencies in local consents; work with local site to correct deficiencies.

P&P 16: Set up and maintain a system for ensuring review and approval of amendments to the protocol.

Comment

Technically, any change to the study protocol, even trivial wording changes in study forms, are amendments to the protocol and subject to review and approval by all associated IRBs. However, some triage is necessary to keep from flooding IRBs with trivial changes.

Formal processes for clearance and communications of amendments to participating clinics should be established for amendments meeting the test implied in the usage note in the definition for **protocol amendment** (above).

Amendments and instructions for clinics to submit same to their respective IRBs should be communicated via numbered memos (see P&P 13).

P&P 17: Notify parent and local IRBs of close of a trial, procedures to be followed in separating persons from the trial, and procedures for disclosing results and treatment assignment (in the case of masked trials) to participants and investigators.