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May 26, 2005

Dockets Management Branch
Food and Drug Administration
(HFA-305)
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket Number 2005D-0103; Draft Guidance for Industry on Using Centralized Institutional Review Boards Process in Multicenter Clinical Trials; 70 Federal Register 15635; March 28, 2005

Dear Sir/Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) welcomes the opportunity to comment on the above referenced proposed draft guidance issued by the Food and Drug Administration (FDA). PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer, healthier, and more productive lives. Investing more than \$38 billion during 2004 in discovering and developing new medicines, PhRMA companies are leading the way in the search for cures.

PhRMA commends the FDA for the preparation of the Draft Guidance on "Using a Centralized IRB Review Process in Multicenter Clinical Trials". PhRMA strongly supports the finalization of a guidance to encourage the efficient use of a centralized process for the ethical review of research in multicenter settings. The efficiencies to be gained with a central review are significant. Considering that under 21 CFR Part 56, each Institutional Review Board (IRB) must minimally have 5 members, most of whom are medical professionals, which must review initial research at convened meetings as well as provide continuing periodic review of that research, a 50 site study may require multiple reviews by no fewer than 250 individuals if each institution required full review by its own IRB. Additionally, some sites, regardless of pre-study evaluations by the sponsor, and commitments by and best intentions of investigators, may recruit no subjects to the research protocol for a variety of reasons. The local review done by that clinical investigator's IRB then amounts to wasted resource.

PhRMA therefore welcomes FDA's initiative, as it will provide needed guidance in an area which can greatly improve the efficiency of multi-center clinical trial as well as reduce the burden of multiple redundant reviews. As noted in a draft report from a forum between PhRMA and the Association of American Medical Colleges (AAMC) held in 2001 (provided as an appendix to these comments), the use of central IRBs is considered a very sensible approach to dealing with the complexities associated with large multicenter clinical trials.

As highlighted in the FDA draft guidance, large multicenter clinical trials are now common place (particularly for the clinical development of products targeted for marketing authorizations such as New Drug Applications). It is therefore an appropriate time to consider promoting greater

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efficiency than the current duplicative and inefficient process by which much research is reviewed. The implementation of a centralized process would reduce the review load on each participating IRB and allow it to more effectively and thoroughly review that research that it chooses to continue to review within its institution.

Many PhRMA companies have experience with centralized IRB reviews conducted on studies that are run from investigators' private offices, not otherwise affiliated with an institution that requires its own IRB's review. These reviews are efficient and thorough. Central IRBs are well aware of their role in adequately assuring that the rights and welfare of human research participants are protected. PhRMA company experience has been that central, commercial IRBs are adequately resourced to perform a full and comprehensive review of the research protocol.

While the FDA has never prohibited the use of a centralized IRB review, it has not been widely adopted by many institutions. The reasons for this are varied and complex, and may include a desire to maintain local control over research conducted within their institution, doubts about the qualifications or processes used by other IRBs, and concerns about their institution's liability should they delegate review to another IRB.

Within the context of the draft guideline, all of these challenges can be addressed to alleviate the specific concerns, resulting in an improved, more efficient process and greater protection for research participants. PhRMA is pleased to offer the following comments on this draft guidance.

Local Aspects of IRB Review:

The draft guidance suggests that any central review process needs to include mechanisms to ensure meaningful consideration of relevant local factors. Requirements for local knowledge in the guidance document may be too vague and would likely be viewed as requiring formal input from sites or more representation on central IRBs. This section leaves much room for interpretation for defining the relative weight and roles of local and central IRBs for a trial. This is likely to create an approach where redundant reviews would forfeit the efficiency benefits of a single central review. PhRMA suggests that the guidance include a list of general topics that the central IRB should evaluate as important local considerations. While no checklist could encompass every aspect that every locality might consider significant, such a checklist would promote consistency of review and provide greater assurance that the local factors identified by the FDA as most important are considered. Central IRBs might also adopt a process of including ad hoc members that could represent geographical regions, or specific patient populations. These members could reside in those areas, be connected by phone at convened meetings, and provide information on local medical practice and prevailing community attitudes on research. It is not necessary that all members be physically present so long as they can participate in the deliberations, and have access to all the review materials.

In the same context, to provide further guidance, it would be valuable for the guidance document to include minimum requirements that a central IRB must meet in order to conduct their review. PhRMA also suggests that the final guidance recommend that IRBs which fulfill the role of a central IRB should be accredited for this function.

The guidance does not discuss the use of central IRBs in the context of global trials that are run in parallel in multiple countries. PhRMA recommends that the guidance indicate the best approach would be to assure review is done by at least one IRB within each country where the

research will be performed. However in those countries where there may be no established IRBs, or where neither sponsor nor investigator can locate an IRB willing to review the research (e.g. not willing to review research that may be conducted outside the specific institution that sponsors that IRB), the FDA should permit an established central IRB in another country to review the research. This should require the approval of the authorities within the country where the research will be performed. The central IRB should also identify a medically qualified individual within that country, who is not otherwise associated with the research, to participate in the IRB's deliberations as an ad hoc member, to provide information on local medical practice and prevailing community attitudes on research.

Documenting Centralized IRB Agreements

The FDA provides reference to an OHRP sample IRB authorization agreement. PhRMA suggests that the FDA develop a template acceptable to them using this model authorization, to further promote the efficient review of clinical research.

Use of a Central IRB for a Clinical Study at an Unaffiliated vs. Affiliated Site

The draft guidance introduces the terms "affiliated site" and "unaffiliated site", where an "affiliated site" refers to an Investigator's site for conduct of clinical research that has a local, site-associated IRB that serves as the usual and customary IRB overseeing research in human subjects at that site. An "unaffiliated site" appears to refer to an Investigator's site for conduct of clinical research that does not have a local, site-associated IRB that serves as the usual and customary IRB overseeing research in human subjects at that site. The draft guidance states it is a "common practice" (line 206) for unaffiliated sites to "rely on the review and oversight of a central IRB" (line 206); PhRMA agrees that this is a common practice and this practice fully complies with all requirements of 21 CFR Parts 50, 56, and 312.

However, the draft guidance also states that affiliated sites are expected to work with a site-associated IRB, or only work with a Central IRB if a documented agreement is in place between the Central IRB and the site-associated IRB (e.g., see line 25 and lines 155-156). These provisions of the draft guidance seem to exceed the scope, content, and detailed regulatory requirements pertaining to IRBs as stated in 21 CFR Part 56.

Importantly, the current regulatory requirements governing IRBs, as well as the obligations of investigators and sponsors pertaining to protection of the rights and welfare of human subjects, are fully open with respect to the ability of an Investigator at an "affiliated site" to satisfy the relevant requirements through use of a site-associated IRB or a Central IRB, with no unique or special requirements imposed for studies using a Central IRB (e.g., see 21 CFR 56.114). This is appropriate and wise in that a uniform standard for the protection of human subjects should indeed continue to apply, regardless of the nature of the IRB.

Multicenter Clinical Trials

Lines 53-54 (and references 4-6) in the draft guidance recognize that multiple reviews of an individual protocol, intended for conduct by a team of investigators at multiple study sites, is inefficient, increases burden on the overall human subjects protection system, and creates unnecessary duplication of effort and delays. In PhRMA's view, the current regulations in 21 CFR Part 56 fully allow a single central IRB to review and oversee all investigators conducting a

multicenter study, yet in practice this rarely occurs due to some considerations included in this draft guidance. PhRMA encourages FDA to utilize this draft guidance to emphasize to stakeholders the provisions of the current regulations in 21 CFR 56.114, which state that ". . . institutions involved in multi-institutional studies may use joint review, reliance upon the review of another qualified IRB, or similar arrangements aimed at avoidance of duplication of effort". The inefficiency and misuse of limited IRB resources should move FDA to change this draft guidance to include statements, such as the following:

It is acceptable (as well as timely and efficient in many cases) to have a single central IRB review and oversee all investigators and all study sites conducting a single multicenter study. This practice is consistent with the provision in 21 CFR 56.114 in current FDA regulations. Of course, this central IRB must meet all regulatory requirements in 21 CFR Part 56, including proactive attention to and documentation of mechanisms used by the central IRB to consider local community attitudes and practices in their review.

Inclusion of such statements in a revised draft or final guidance would serve the interests of multiple stakeholders, including settings for multicenter trials (including not only such studies sponsored by one or more pharmaceutical companies, but also by government-affiliated consortia such as the AIDS Clinical Trials Group or the multiple oncology collaborative study groups). A number of public discussions have occurred on the gains that could be achieved through increased reliance on central IRBs for review and oversight of multicenter clinical trials. One such forum was the 39th meeting of the National Bioethics Advisory Commission where Dr. Bert Spilker (Senior Vice President for Science and Regulatory Affairs, PhRMA) testified in favor of this role for central IRBs in an effort to reduce the workload burden on site-affiliated IRBs and reduce duplication¹. He shared with the Commission information from discussions among PhRMA, FDA, and OPRR that could be further consulted prior to preparation of revisions to this draft guidance.

Potential Roles for a Site-Affiliated IRB

The utility of the draft guidance would be enhanced if it gave some additional examples of potential roles for a local, site-affiliated IRB in the context of a multicenter study for which all investigators have review and oversight by a central IRB. In this context, PhRMA suggests that the central IRB could collect local information from some site-affiliated IRBs on topics such as (a) information on whether similar studies have previously been conducted in the institution, (b) information on whether the proposed Investigator has conducted other studies, including similar studies, in the institution, (c) qualifications of the Investigator, (d) appropriate reimbursement to subjects for local transportation to a study site, or (e) identification of a local person to contact in the event of research-related injury to a subject.

Possible Mechanisms for Considering Local Information

Lines 146-164 of the draft guidance focus on information to further encourage central IRBs to appropriately consider local community attitudes and practices. PhRMA recommends that the draft guidance expand this section to also encourage site-affiliated IRBs to similarly consider

¹ National Bioethics Advisory Commission. 39th Meeting. Loews L'Enfant Plaza Hotel, Washington, DC. April 7, 2000.

local community attitudes and practices. The physical proximity of a site-affiliated IRB to the investigator and community does not, in itself, provide assurance that site-affiliated IRBs are diligent in considering local community attitudes and practices. Public records from inspections of site-affiliated IRBs, including those at some widely recognized major academic institutions, by FDA and other agencies have shown that the need for appropriate consideration of local community attitudes and practices applies to both site-affiliated IRBs and central IRBs. The draft guidance should be revised to assure that this burden is clear and equitably applied to both institutional IRBs and central IRBs.

Clinical Trials Including Ex-US Study Sites

The draft guidance is silent with respect to two practices that occur regularly.

- First, US-based sponsors (including government institutions, academic institutions, and pharmaceutical companies) sometimes conduct an IND-governed study in ex-US locations. In such situations, PhRMA suggests that the draft guidance acknowledge that the ICH E6 GCP standard, including the provisions for protection of human subjects, is the uniform standard to which all IRBs (site-affiliated and central) should adhere.
- Second, sponsors sometimes conduct an IND-governed, multicenter clinical trial with investigators in multiple countries. In such situations, PhRMA suggests that the draft guidance acknowledge that the ICH E6 GCP standard, including the provisions for protection of human subjects, is the uniform standard to which all IRBs (site-affiliated and central) should adhere.

Other general comments

Some aspects of responsibilities of IRBs would benefit from additional guidance from FDA. Although some elements included in the following comments would not only be relevant to Central IRBs, the following are given to the FDA for consideration: To promote consistency amongst IRB, the guidance could include further details on the agency's expectations regarding Quality Control of IRB processes, the constitution of IRBs, the processes whereby information (for example safety information) is reviewed and/or communicated between the various parties (including FDA, IRB(s), institution(s), Clinical Investigator(s), and the Sponsor).

PhRMA appreciates the opportunity to comment on this guidance document and again commends the FDA for preparing this important document.

Sincerely,



Appendix

CENTRAL INSTITUTIONAL REVIEW BOARDS (IRBs) IN CLINICAL RESEARCH

Draft Report from the PhRMA-AAMC Clinical Trial Forum

August 2001

A. General Background

The primary function of Institutional Review Boards (IRBs) is to protect the rights, welfare and safety of human subjects involved in clinical investigations. IRB existed as early as 1961 and in January of 1981 the final regulations on operation of IRBs and informed consent were published by the Department of Health and Human Services (HHS) and the Food and Drug Administration (FDA). These regulations were subsequently amended in 1990, 1991, and 1996. Currently, there are two federal agencies falling under the auspices of the HHS that are responsible for IRB oversight. These are the Office for Human Research Protection (OHRP) and the FDA, which have dissimilar operating objectives and look at different types of research, in terms of funding source. The FDA regulates IRB conduct and procedures for the pharmaceutical industry.

In June 1998, the Office of the Inspector General (OIG) from HHS issued several findings regarding the challenges confronting IRBs within today's research environment. This report raised major concerns listed below regarding the effectiveness of IRBs. PhRMA does not agree with these points in full.

1. IRBs face major changes in the research environment, (e.g., a proliferation of multi-center trials, an increased number of research proposals)
2. Many IRBs were said to review too much, too quickly, with too little expertise
3. IRBs conduct minimal continuing review of approved research
4. IRBs face conflicts that threaten their independence
5. IRBs provide little training for investigators and IRB board members
6. Neither IRBs nor HHS devote much attention to evaluating IRB effectiveness

A number of other articles and reports have recently questioned the adequacy of IRBs in meeting their charge to protect the rights and welfare of human subjects. For example the highly publicized Office for Protection from Research Risks (OPRR) review of Duke University Medical Center found that the Center did not have adequate written policies and procedures for the IRB to address a number of required activities. The burden of a large volume of research for which the IRB had responsibility (often several thousand clinical trials at a single institution) was a major issue.

New treatment modalities, increased drug testing, and increased complexity of clinical trials presented to IRBs for review have created new demands on IRBs for expertise that is not always present on the IRB. Healthcare cutbacks and cost containment at institutions have

concomitantly led to limited funds for administration of IRBs. Some IRBs have decided to charge investigators to review protocols submitted as a means of paying for their administrative costs and staff.

B. IRB Workload and Efficiency

The rise in multi-center trials has been a major factor in the increased workload of IRBs. Each site involved in a multi-center trial must have its own IRB approval of the protocol and informed consent form. Thus for a three-center trial, for example, three separate IRBs may have different comments, suggestions and requirements for changes in the protocol, informed-consent form and/or data collection forms they review. For a 100-site trial the issue is greatly compounded. The premise of a multi-center trial is that every site uses the same protocol. Protocol changes required by one IRB must be sent to all of the others for their review and approval, no matter how many sites are involved. While minor changes may be approved in some cases through expedited procedures, the Chair may desire that an entire IRB consider any changes required by another IRB. Because IRBs generally meet monthly, and sometimes every six weeks, the review and approval process can take a considerable amount of time before a multi-center trial is initiated.

In some cases, such as treatment INDs, a single IRB has served as a "central" IRB to provide a single review for all sites involved in that trial, and the individual local IRBs used an expedited review process.

C. PhRMA's Perspective on IRBs

PhRMA's interest is in promoting innovative research and the swift development and approval of safe and effective treatments for unmet medical needs in a cost effective manner. This includes an expectation that all clinical research is held to an appropriate level of ethical scrutiny whether conducted by a PhRMA company or not. As such, PhRMA believes that the IRBs are a critical safeguard to ensure the rights and safety of patients entering clinical trials. There are currently over 1000 investigational drugs in development and PhRMA members are estimating spending 30.6 billion dollars on R&D in 2001.

PhRMA believes that the current regulations and guidelines for IRBs are not flawed and can still deliver the appropriate protection of human subject rights and welfare. However, PhRMA also believes that modest reforms can be made within the current legislative structure to improve the overall effectiveness of the IRB process, reduce duplication of efforts in multi-center trials and address a number of the findings highlighted in the June 1998 OIG report.

PhRMA believes that there are several methods that can be employed to reduce non-value added redundancy by local IRBs for multi-center trials and to improve their efficiency. It is important that any new measures introduced ensure continuing protection of subjects, while improving the review and oversight process by IRBs and not creating additional undue burden to the research process.

D. Proposal

This proposal seeks to improve the efficiency and effectiveness of IRBs while working within the current legal framework. It seeks to expand the central IRB system to ensure IRBs can meet relevant regulations, yet review multi-center clinical protocols much more rapidly. There are numerous models of central IRBs and this proposal does not endorse a single model, but rather endorses many models.

We propose that the FDA and OHRP jointly:

1. Encourage the process of accreditation of IRBs that wish to obtain such accreditation.
2. Encourage all IRBs, whether accredited or not, to accept a review of a multi-center trial from an accredited IRB by having an expedited review (or no review), in lieu of conducting their own detailed review.

E. Models of Central IRBs

When Dr. Greg Koski of OHRP spoke at a recent AAMC-PhRMA Forum, August, 2001, he described multiple models of Central IRBs in use.

1. Any accredited IRB may serve as a central IRB for a clinical trial.
2. Any organization or multiple institutions can form a new IRB that serves its member institutions for selected trials. The IRB formed may be made up of members from each or only some of the institutions that will accept the findings of the IRB. An example is the Cancer and Leukemia Cooperative Group B (CALGB) cooperative group for oncology trials. The National Cancer Institute (NCI) formed a new IRB with members of selected institutions who accept the results of this IRB's findings, and is currently conducting a pilot trial. NCI's model allows for >1000 sites across the U.S. (Central Gatekeeper Model). A single review is done and then "offered" to many sites. (Still need to have local implementation apparatus). The IRB of record is the Central IRB.
3. Any organization of multiple institutions can utilize the IRB review of any of its members, and does not need to form a new IRB for this purpose. An example is the Multi-center Academic Clinical Research Organization (MACRO) group, composed of 5 universities. These universities are University of Pennsylvania School of Medicine, Baylor College of Medicine, Vanderbilt University, Partners Healthcare System (Harvard Medical School-affiliated, Massachusetts General and Brigham and Women's Hospital), and Washington University School of Medicine (St. Louis). It is similar to a distributed network model. They have reviewed about 12 protocols to date where 2 or more institutions are involved.
4. A full-time ("professional") IRB may act as a Central IRB for certain studies, including treatment INDs and those conducted in community settings. Western IRB is the most well known group, but various others have served this role.
5. A network of 60 sites in the NYC area including Columbia and Cornell Medical Schools have centralized their IRBs (the original group used 14-IRBs). The scientific content of protocols is reviewed at an Academic IRB first, and then the protocol goes to Western

IRB, which becomes the IRB of record for the trial, especially for those protocols conducted at most of the 60 non-medical school sites.

6. Six institutions in Kansas City are pooling their resources to start a foundation that will have a single IRB. To obtain details, one could contact Midwest Bioethics Center in K.C. and speak with Mary Faith Marshall.
7. Other models are possible.

It is definitely possible, if desired, to centralize the ADR reporting for a large trial through a single group. Each academic site in a trial approved by a Central IRB will have local implementation apparatus (usually an IRB) in place and there must be a communications line between local and Central groups. It is essential to build the organization appropriately so that each group knows what they are responsible for and how to achieve their tasks. Greg Koski "encourages use of Central IRBs", but noted that it "has to be done right and with current standards.

F. Mutual Recognition of IRB Review of Multi-center Trials

The "PhRMA AAMC Forum" postulates that a public endorsement of the central IRB concept by OHRP and FDA, either jointly or independently, would lead to an increasing number of multi-center protocols being reviewed by a single IRB with accreditation or by well established IRBs with national reputations of excellence, until the accreditation system is operational.

This process would mean (for example) that instead of a large Southwest Oncology Group (SWOG), Eastern Cooperative Oncology Group (ECOG), or Pediatric Oncology Group (POG), multi-center trial being submitted to each local IRB, it would be submitted to a single well-known IRB (and in the future to an accredited IRB) for reviewing oncology protocols and its results, discussions and conclusion submitted to each local IRB with a request for expedited review or a complete waiver from local IRB review. This form or letter would be signed by the local IRB chair or his/her designee. Local IRBs would continue to receive (if desired) all reports of the clinical trial from the local investigator (e.g., annual report, every expedited IND safety report).

This practice would markedly decrease the workload at the local IRB level and allow them more time to focus on studies being conducted only at their institution, and to focus on reviews of ongoing trials they previously approved.

While the local IRB may be asked if it is willing to waive its review of a multi-center trial, this would not be a requirement, and it would have the right to conduct an independent review. Market factors would come into play, as IRBs that insisted on local reviews and refused to waive this right might be bypassed by some sponsors (government or industry) who felt that certain IRBs were frequent sources of delay in implementing a trial.

There are some situations (e.g., community trials) in which there is no local IRB. The central IRB could review clinical studies in such situations.

A two-day meeting held in Arlington, Virginia in October 1998, sponsored by PRIM&R discussed the above topic and there was general agreement that a system of having a single competent IRB review a multi-center trial made a great deal of sense and would save significant time and ease the workload on local IRBs.

Whether the term given to the reviewing IRB is “national,” “central,” or “regional” is not important. What is important is that:

- No one is suggesting the creation of new IRBs with a new function.
- Any IRB may function in the capacity of a “Central” IRB.
- No local IRB would be forced to accept the decision of a “Central” (reviewing) IRB for a multi-center trial.

No new laws are required to expand this process.