Cooperative Research Ethics Review Boards: A Win-Win Solution?

by Greg Koski, Jessica Aungst, Joel Kupersmith, Kenneth Getz, and David Rimoin

Enhancing public participation in research is one of the central challenges facing the clinical research enterprise in the United States, and one of its highest priorities. Public concern about the safety of participating in research is increasing, reflected in a rising tide of litigation, negative articles in the popular press, and other published commentaries. Part of this concern focuses on Research Ethics Review Boards (Research ERBs)—the entities responsible for ethical review and oversight of human research. These bodies, referred to in federal regulations as Institutional Review Boards (IRBs), are overburdened and often characterized as inefficient and ineffective. The increasing number of multi-center studies is exacerbating current problems, as they often require duplicative reviews. Multiple submissions of a single protocol and its associated consent documents to several Research ERBs for review and alterations create redundancy without necessarily enhancing the protection of research subjects.

Many parties, including the Institute of Medicine (IOM), the National Bioethics Advisory Commission (NBAC), and the Department of Health and Human Services (DHHS), note that these duplicative reviews can actually detract from subject protections by diverting time and resources from more effective uses; they have suggested streamlining review through the use of alternative models. Collaborative approaches to ethical review that capture the best of both central and local processes could be more efficient, less costly and less demanding of limited resources, and also be more effective. They may allow for more timely data collection and analysis of adverse events, address the problem of institutional conflict of interest, and offer more options for unaffiliated investigators and patients with rare diseases.

Central review boards have taken on increasing importance in recent years. Reference to a “central IRB” does not necessarily mean that one Research ERB is always the IRB of record; use of the term “cooperative review” may more accurately reflect the emerging approaches discussed in this article. In a survey by the Association of American Medical Colleges (AAMC) of research deans at institutions using a Central IRB (defined as any non-institutional board or cooperative arrangement), 53% agreed that its use shortened time to approval of research protocols. Eighty-four percent were pleased with the Central...
IRB review, and 77% indicated that they were able to maintain excellent local oversight of studies approved by a Central IRB.\(^8\) Notably, some highly respected academic institutions have turned to well-established commercial review boards after deficiencies in their local boards and processes resulted in significant enforcement actions by federal regulatory agencies. One of these private boards was among the first human research protection programs (HRPP) to receive full accreditation by the Association for Accreditation of Human Research Protection Programs (AAHRPP); the Partnership for Human Research Protection (PHRP) also has accredited independent review boards.

Many institutions are hesitant to use cooperative review mechanisms for a variety of reasons. According to the AAMC survey, those who have not used Central IRBs (76% of respondents) did not do so because of concerns about liability (73%), additional costs (60%), the absence of local representation (86%), and the inability to assess the quality of the services (56%). Federal regulations require that research review boards have “sensitivity to such issues as community attitudes,” and many institutions feel that local review is an essential component of ethical research; to what extent this view also reflects a desire to maintain institutional autonomy is unknown. Both the Office for Human Research Protections (OHRP) and the Food and Drug Administration (FDA) have responded to the increasing number of multi-center trials by clarifying that existing regulations permit institutions to use joint review, rely on another qualified IRB, or make similar arrangements to avoid duplication of effort for cooperative research.\(^9\) In this paper, we describe several models of cooperative review, many of which were presented at the meeting. These models include the Multicenter Academic Clinical Research Organization (MACRO), the Biomedical Research Alliance of New York (BRANY), independent Research ERBs, the NCTs Central IRB, and Regional Ethics Organizations (REOs). Many of these models are in the formative stages, and REOs, which are now utilized in the United Kingdom, do not exist in the U.S. at this time.\(^10\)

Therefore, key evaluative data regarding existing central review mechanisms are not presently available; indeed, more data are needed to assess both traditional and cooperative review mechanisms and to more fully and scientifically compare these options. Our assessment is based upon the best available data about these efforts. Key issues about centralized review relate to perceived legal liability by cooperating academic institutions regarding the ability to fully reflect and address local concerns.

Models for Streamlined Research ERB Review

- **Multicenter Academic Clinical Research Organization (MACRO).** Created in 2000, MACRO is an alliance among Baylor College of Medicine, the University of Alabama at Birmingham, the University of Pennsylvania School of Medicine, Vanderbilt University, and Washington University School of Medicine. The participating institutions recognize the need to both expedite and improve the process for sponsors, patients, and academics as well as to respect the local culture.\(^11\) MACRO relies on “limited IRB reciprocity,” meaning that institutions within MACRO can accept the reviews of other MACRO institutions while also addressing local concerns. In practice, one primary reviewing institution shares information with the other trial participants who can perform a local administrative review to assess any local concerns. This arrangement is allowed under a special cooperative amendment to the institutions’ Multiple Project Assurances.

MACRO is a distributed network model with standardized operating procedures and performance indices. However, it still relies on its existing local Research ERBs; it is therefore dependent upon their schedules and currently has no central auditing or data collection. The lead Research ERB is responsible for ongoing review of trials. The MACRO review process costs only marginally more than individual Research ERB review and is considered, though not yet proven, to save money and
time by reducing redundancy. MACRO is voluntary and supported by its member institutions, but its membership is limited and legal liability is still a concern. Although MACRO has now been operational for a few years, the actual use of MACRO by the participating institutions has been limited and there are yet no performance indices to measure the quality of the review or its efficiency.

**Biomedical Research Alliance of New York (BRANY).** BRANY, formed in 1998 by an initiative of the New York Academy of Medicine, offers a variety of research administration services, including a central Research ERB. The alliance membership includes more than 100 institutions and practice settings mainly in the New York area. The central BRANY Research ERB holds an OHRP Federalwide Assurance (FWA). It meets every two weeks, with membership drawn from participating institutions, especially chairs or vice chairs of Research ERBs at home institutions.

Research ERBs at member institutions initially were reluctant to accept delegation of authority to the central body. The support of institutional leadership, institutional representation, and good communication, as well as modified FWAs, were essential to BRANY’s success.

BRANY tracks relevant metrics monthly and performs audits. According to Eileen Hilton (personal communication), Chief Executive Officer of BRANY, Research ERB review for a standard trial protocol (not vulnerable subjects) costs about $2,000, with no costs for the volunteering members’ time. IRB members are not compensated for their involvement in BRANY, which reduces the overall cost of the process, but this must be considered when comparing cost-effectiveness of this model to other “business models” in which IRB members are paid for their service.

**Independent Institutional Review Boards.** A growing number of independent Research ERBs (i.e., boards that are independent of organizations that conduct research and are often for-profit ventures) review both industry- and government-sponsored trials. Though services are variable by organization, the better known independent Research ERBs conduct both initial and continuing review of protocols and some related services. According to CenterWatch, independent Research ERBs provide Research ERB services for as much as 40 percent of the market for industry-sponsored trials and review an increasing amount of DHHS-sponsored research since receiving permission from DHHS to use them in 1995.

It is inaccurate to suggest that independent boards “control” that segment of the market, because many sites conduct full IRB review regardless of whether an independent IRB has previously reviewed the protocol. This duplication of review creates significant redundancy that could be reduced through more effective use of cooperative models.

The primary advantage of independent Research ERBs over institutional IRBs is faster turnaround times. For example, whereas Western IRB generally completes reviews in 10 days, estimates for many local Research ERBs are 46-102 days. Also, some independent Research ERBs have developed the capacity to offer specialized review boards (e.g., pediatrics) that might not otherwise be achievable except at specialty centers. On the other hand, independent Research ERBs may find it challenging to achieve critical mass of expertise in highly specialized areas.

At independent Research ERBs, members are sometimes paid a stipend for their time, and panels meet more frequently than local Research ERBs. They operate on a fee-for-service model charging, on average, $1,300 for review of a new protocol. These fees and the professional business management of the process allow independent Research ERBs to bolster their infrastructure and offer timely reviews at a relatively low cost.

While use of independent Research ERBs raises certain conflicts of interest concerns, it can also eliminate those related to institutions that may have financial interests in protocol approval not unlike those of corporate sponsors. Independent Research ERBs may be insulated from such pressures. Further, possible loss of business because of FDA or OHRP citations creates independent incentives to conduct high-quality reviews. Independent Research ERBs also are eligible for accreditation, and a number of them have met the standards of the AARPP and of PHRP. It is, of course, important to acknowledge that there are as yet few data available to assess the “quality” of either independent reviews or those performed at academic sites, nor is there an a priori reason to assume that there is a difference in quality, particularly by fully accredited programs. Indeed, what constitutes quality review has yet to be clearly defined.

**National Cancer Institute Central IRB.** The NCI Central IRB (CIRB) pilot program began in August 1999 in consultation with OHRP to determine whether a CIRB could alleviate some of the burden of local Research ERBs in NCI phase three multi-center trials. When the NCI CIRB approves a protocol, it
notifies local investigators about the approval and sends documents to the local Research ERB chair or a subcommittee for review and approval regarding local concerns. Thus, the central review board operates in tandem with local review boards through a “facilitated review” process that takes account of local considerations before initiation of the research. The NCI CIRB, which meets monthly, becomes the Research ERB of record and therefore handles amendments, continuing review, and adverse event reports centrally, allowing local Research ERBs to focus on oversight of local performance. The CIRB is funded by NCI at a cost of $50,000 a year in the “gearing up” stages.24

As of March 2002, the majority of CIRB protocols were subject to full, rather than facilitated, review by local Research ERBs.25 However, the initial number of participating sites was too small to provide meaningful data, so NCI has expanded the initiative to 100 local Research ERBs. Review time has decreased as the NCI CIRB has gained experience, but there are still complaints about timely approval of protocol amendments.26 Benefits include using a single and briefer application document rather than multiple forms for multiple Research ERBs, improved adverse event review, and quicker and less burdensome approval by local Research ERBs. This could allow for a greater number of open trials and could make trials for rare diseases more feasible. In addition, community physicians could have greater access to trial participation. Ultimately, over 800 sites could operate under the facilitated review and oversight process. However, if the local Research ERBs continue to use full review, the CIRB process will be at least as burdensome and duplicative as the current “one institution, one IRB model.” This challenge, which is not unique to the NCI model, will probably also hold true for any cooperative review process, including independent Research ERBs.

Regional Ethics Organizations. A system of 10-20 U.S. Regional Ethics Organizations (REOs) responsible for regional review, monitoring, training, and ethical policy formulation has recently been proposed.27 Each REO would consist of a Protocol Review Committee (PRC), an Ethics Policy Committee (EPC), liaisons, and ombudspersons. The PRCs would perform a function similar to Research ERBs, conducting prospective ethical reviews of the research studies in their region. Each REO would have a large number of PRCs also coordinate REOs to share best practices, ethical policies (which could vary by region), educational programs, and performance data.

Establishing a system of REOs would require a serious overhaul of the current system. It would meet resistance from those concerned about the lack of local context, those who perceive such centralization simply as increased bureaucracy, and institutions that have invested money and effort to create robust human participant protection systems. Conversely, small institutions that do not have many resources may find the regional boards a positive option to pool resources to provide effective protections. Creation of such bodies would necessitate a reevaluation of current regulations that largely rely on the premise of local Research ERB review. Changes to regulations are burdensome, and many people would prefer to emphasize the flexibility of the current regulations, while others have called for a reassessment of the regulations to reflect the changed research landscape.28

In Europe, regional ethics committees have been tried, first in the United Kingdom,29 and more recently in other countries including Denmark30 and the Netherlands.31 Initially, the UK approach was faced with the very challenges already described and was not well accepted. The recent implementation of the European Directive on Clinical Trials, which requires a “single opinion” from each member state within a relatively short time frame for all industry-sponsored clinical trials, is likely to give more impetus to adoption of collaborative and regional models in Europe, and these initiatives will be worth watching closely.32

IRBNet. Another recent development worth watching is known as IRBNet, a web-based interactive communications tool established by Dartmouth College and the
Children’s Hospital of Philadelphia.34 The IRBNet seeks to streamline the exchange of information among researchers, IRBs, and sponsors, thereby facilitating the review and oversight process when multiple centers are involved with a single protocol. This is a low-cost approach to facilitated review, and possibly cooperative review, that relies upon technology and the willingness of sites to use it.

Financial Considerations of Cooperative Models

Wood et al. estimate that the current system of 4,000-6,000 Research ERBs costs between $300-$400 million a year, not including payment for members’ time.35 The full costs of operating Research ERBs are difficult to estimate, particularly because they are part of a larger system of protections, but one recent study by Wagner et al. estimates that operating high-volume Research ERBs costs about $770,674 and operating low-volume Research ERBs costs about $76,662.36 Those authors also note that cooperative Research ERBs could be more cost efficient than local Research ERBs because of economies of scale. What proportion of this cost could be eliminated by collaborative models for review and oversight is unknown, but savings may be substantial. As innovative approaches to collaborative review are evaluated, careful consideration should be given to how they will be funded. While reducing costs is a reasonable consideration and a generally desirable goal, provision of adequate funding to sustain effective approaches is equally important for success of the clinical research enterprise.

Conclusions

Each of the models presented in this paper has benefits and drawbacks. Although there are no sufficient metrics at this time to measure the efficiency and effectiveness of Research ERBs and thus no meaningful data on these variables, centralized models could offer greater potential for cost savings, greater efficiency, less demand on limited human resources, greater consistency of reviews, more wide-scale data collection and analysis, less concern about institutional conflicts of interest, and more options for unaffiliated investigators to obtain ethical reviews. In addition, cooperative Research ERBs can more easily specialize in a particular area of research expertise such as pediatric or rare disease trials. These benefits would apply to continuing oversight as well as initial reviews.

However, increased centralization raises concerns about a lack of local context, the lack of beneficial redundancy in the safety net, the potential for increased bureaucracy, and the need to reevaluate current regulations. The consequences of member bias are potentially much greater for research involving a large number of sites and subjects than for a single site. More importantly, one committee’s oversight of a critical safety issue could fail to adequately protect human subjects. Nevertheless, all of these alternative models offer greater flexibility, accountability, cost-effectiveness, and efficiency than the highly redundant and inefficient “one-institution, one IRB” model that dominates the current system. If the quality of the review process can be similarly enhanced and trusted, the impact of the streamlined review on the research process could be beneficial.

While these cooperative models could offer many advantages, they may not enhance protections for human subjects when compared with the existing system. Any safety system benefits from some measure of redundancy, and some argue that the present system, even if inefficient, may afford greater protection. In practice, there is little more than anecdote to support this view. Still, this criticism of central models is valid and underscores the need for more consistent and effective performance of review boards however and wherever they operate. Toward this end, continuous quality improvement programs, independent performance assessment, and standardized accreditation of human research protection programs are likely to become essential and valuable components of a more efficient and effective systems approach to human subjects protection.37

The success or failure of any of these models ultimately depends upon institutions’ willingness to relinquish some measure of autonomy and to trust Research ERBs that operate outside each institution’s primary community.38 This is a special concern in an increasingly litigious environment, as the institution is ultimately responsible for research conducted at its site(s). Each of the current models has addressed legal concerns through amended Multiple Project Assurances and similar legal arrangements and have mechanisms to address local issues. Moreover, current federal regulations allow cooperative review, and such mechanisms have been recognized and accepted by OHRP and FDA. However, these provisions alone appear to be insufficient motivation for local bodies to pursue cooperative review mechanisms.

Clarifying the roles of the local and cooperative Research ERBs, particularly regarding continuing review functions, could facilitate the use of cooperative review mechanisms.39 The cooperative Research ERB would examine the “big picture” issues that affect the overall trial such as adverse events; this would generate the type of data needed to effectively assess safety in multi-site trials and to evaluate and improve the overall system. The system of protections as a whole could benefit from the reduced burden on local HRPPs, which could, in turn, refocus and better align time and
resources. The current system of redundant, overlapping reviews can be wasteful and frustrating; even more importantly, this system does not appear to enhance participant protections. Working in concert with an effective central Research ERB, local HRPPs could focus on improving the actual conduct of trials at their sites by ensuring investigator and staff education, reviewing consent procedures, and providing ongoing monitoring of trial conduct.

Further experience with these models is necessary to evaluate which are most effective. As the models gain credibility, more institutions may choose to use them, and the models may improve as a result. If these models prove to be effective and can deal with local and liability concerns, institutions may become more comfortable with more centralized approaches, changing the balance of benefits and drawbacks and, ultimately, improving the level of safety and ethical treatment of clinical research volunteers.

Disclaimer
The views presented in this paper are those of the authors and not the Institute of Medicine, the Institute of Medicine's Clinical Research Roundtable, or the Roundtable's sponsoring organizations.

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References
9. 45 CFR 46.107(a); 21 CFR 66.107(a).
10. 45 CFR 46.114, Cooperative Research, states "Cooperative research projects are those projects covered by this policy which involve more than one institution. In the conduct of cooperative research projects, each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with this policy. With the approval of the Department or Agency head, an institution participating in a cooperative project may enter into a joint review arrangement, rely upon the review of another qualified IRB, or make similar arrangements for avoiding duplication of effort; 21 CFR 56.114. Cooperative Research, states, "In complying with these regulations, 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."
15. The "owner institutions" are Montefiore Medical Center, Mount Sinai School of Medicine, New York University School of Medicine, North Shore-Long Island Jewish Health System, and Saint Vincent Catholic Medical Centers. See http://www.brancion.com for more information.
22. See ref. 8, Loh 2003.
Influences on IRB Decisionmaking

In their article, “Just-In-Time IRB Review: Capitalizing on Scientific Merit Review to Improve Human Subjects Research Compliance” (IRB, March-April 2003), Kelly and Johnson have not addressed what are subtle effects on IRB approval considerations caused by previous positive funding decisions—effects I have witnessed during 20 years of membership on both university and community hospital IRBs.

Once the decision has been made that funds will go to the institution if a proposal is approved, two things can happen. One is that IRB members can believe that because an outside agency—especially if it is a federal agency—has approved the project for funding, the proposed project gains overall credibility, including its appropriate use of humans as subjects. Even though this is not the intent of such funding decisions, some sort of halo effect will be present.

Secondly, with the prospects of funds flowing to the institution if and when the proposal is given IRB approval, the financial interests of the institution can influence members of the IRB. Although the IRB is supposed to be independent of the institution, the appointment of IRB members is the responsibility of the institution, and, most often, the great majority of the IRB members are employees of the appointing institution.

Therefore, while prior funding approval can act to decrease the number of proposals an IRB must review and therefore decrease its efficiency, such prior approval can also improperly influence the IRB’s decisionmaking.

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IN THE FIELD

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SACHRP Recommendations for Review of Children's Research
Requiring DHHS Secretary's Approval

Federal regulations for research involving human
subjects include special protections for children
under 45 CFR 46 Subpart D. Unlike other sec-
tions outlining protections for the general population
and other vulnerable groups, Subpart D delineates three
risk-benefit classifications for research that can be
independently approved by a local Institutional Review
Board (IRB) and a fourth classification that requires
Department of Health and Human Services (DHHS)
review. IRBs can independently approve research with
children

1) that does not involve greater than minimal
risk if the IRB finds that adequate provisions have
been made for parental permission and child assent
(46.404).

2) that presents greater than minimal risk but
offers a potential for direct benefit for the individ-
ual subject, or by a monitoring procedure that is
likely to contribute to the subject's well-being, if
the IRB determines (a) the risk is justified by the
anticipated benefit to the subject; (b) the risk bene-
tit assessment is at least as favorable as available
alternative approaches; and (c) adequate provisions
are made for soliciting parental/guardian per-
mission and child assent (46.405).

3) that presents greater than minimal risk but
offers no potential for direct benefit for the indi-
vidual subject if the IRB determines: (a) the risk to
subjects is a minor increase over minimal risk;
(b) the intervention and procedures present sub-
jects with experiences that are reasonably com-
mensurate with those inherent in their actual or
expected situations; (c) the research is likely to
yield generalizable knowledge of vital importance
for the understanding or amelioration of the sub-
jects' disorder or condition; and (d) adequate pro-
visions are made for soliciting parental/guardian
permission and child assent.

If an IRB determines that the proposed research does
not meet one of the requirements described in the sec-
tions above, and it presents a reasonable opportunity to
further understanding, prevention, or alleviation of a
serious problem affecting the health or welfare of chil-
dren, an IRB may submit the protocol to DHHS's Office
for Human Research Protections (OHRP) for determina-
tion whether the research can go forward. The 46.407
review process involves consultation with experts and
public comment on the proposed research.

In 2003 the Secretary's Advisory Committee on
Human Research Protections (SACHRP) undertook a
review of the process for conducting a 46.407 review of
pediatric research proposals. SACHRP developed recom-
endations for this review process and forwarded them
to the DHHS Secretary; in late 2004 the Secretary
approved the recommendations for implementation by
OHRP.

SACHRP Endorsement of the 46.407 Process and
Procedural Goals

SACHRP endorsed the 46.407 process for the follow-

ing reasons: 1) a national perspective that includes
scientific experts, bioethicists, and the public is re-
quired for research that an IRB believes is worthy but
that does not satisfy the criteria for approval under 46.404,
46.405, and 46.406; 2) the 46.407 process provides a
critical forum for protocols in which the risk level
requires special scrutiny or no clear national consensus
exists on the ethical matters under consideration; and
3) adequate transparency in the 46.407 process provides
the public and IRB community with a body of case
test examples that can inform future deliberations.

Although research reviewed to date under the 46.407
review process represents a very small minority of pedi-
atriic studies conducted under the jurisdiction of DHHS,
SACHRP members considered it important to have a
well-developed 46.407 review process based upon the
following factors:

- The expectation that research involving children not

Celia B. Fisher and Susan Z. Kornetsky, "SACHRP Recommendations for
Review of Children's Research: Requiring DHHS Secretary's Approval," IRB:
otherwise approvable will increase in light of the Children's Health Act directing the DHHS Secretary to require all research involving children (including clinical investigations involving products regulated by the Food and Drug Administration [FDA]) to be in compliance with subpart D (Public Law 106-310, October 14, 2000) and the Best Pharmaceuticals for Children Act re-authorizing pediatric exclusivity incentives for drug products (January 4, 2002).

- Institutions that have submitted protocols and experts who have provided consultation for individual 46.407 reviews have voiced concern about the process in terms of clarity of IRB responsibilities, length of time from application to Secretary's decision, public and expert input, transparency, and OHRP/FDA harmonization. In enhancing the 46.407 review process, SACHRP sought to recommend modifications that would help ensure that 1) research essential to the welfare of children is not delayed, 2) stakeholders in the 46.407 review process (the IRB community, the prospective subject population and their families, investigators, funders, and the public) are fully informed in a timely manner about studies under 46.407 review, 3) the Secretary will have available the perspectives of the public and a range of expert opinion, and 4) steps and responsibilities of the process are clear to all stakeholders to ensure consistent, informed, and fair protocol evaluations.

In the remainder of this article we summarize SACHRP recommendations that have immediate implications for local IRB review of protocols deemed to be eligible for the 46.407 review process. Transcripts of SACHRP meetings and detailed summaries of these recommendations can be obtained from OHRP's website.

IRB Responsibilities and the OHRP 46.407 Screening Process

IRBs may forward to DHHS only those protocols funded by DHHS or under the jurisdiction of the FDA that are not approvable under 45 CFR 46.404-406 or 21 CFR 50.51-53. To fulfill this responsibility, SACHRP recommended that IRBs must provide separate justification and document why the protocol fails to meet each of the 46.404-406 classifications and a rationale for why the research is ethically valid and possesses sufficient scientific and societal promise to warrant consideration from a wider perspective. When OHRP receives the request for a 46.407 review it will screen the application and materials and then either accept the request for a review or send it back to the IRB with feedback that insufficient detail or materials were provided or that the protocol may fall under 46.404-406 or 21 CFR 50.51-53 classification.

Model for Obtaining Expert Consultation and Public Input

SACHRP recommended the following panel model for protocols accepted for 46.407 review:

- After it has determined that a 46.407 review is appropriate OHRP will select a panel with at least one public member representing family or child population's interests and consultants with expertise in the science and ethics relevant to the specific protocol.
- Prior to the expert panel meeting, a notice will be posted in the Federal Registrar to permit public review of and comment on documents associated with the study.
- The panel will meet in person to review both the application materials and the written public comments. The meeting will be open for the public to attend and provide additional comment.
- The panel members will discuss their views, but a panel consensus document will not be created. Each consultant will write an independent recommendation.
- The consultants' recommendations will be posted on the OHRP website.
- OHRP will develop its own recommendation based on the materials, panel discussions, and public and expert opinions and forward its recommendation to the Secretary for consideration.
- OHRP will communicate to the IRB the Secretary's decision, and at the Secretary's discretion post the decision on the OHRP website.
- As described in regulations the Secretary may approve the protocol as is, approve with stipulations, or disapprove.
- OHRP will provide advice and assistance to the institution on any modifications that may need to be implemented before the research can begin.
- Final approval of the modifications rests with OHRP.

SACHRP Recommendations for 46.407 Review of Multi-Site Research Protocols

SACHRP considered the unique challenges of conducting ethically responsible 45 CFR 46.407 procedures for multiple site studies. Under the National Institutes of Health (NIH) streamlined grant review process, investi-
gators submit proposals to their local IRBs only after scientific peer review and sponsor commitment to funding. Consequently, the timing of participant enrollment will vary across sites. In addition, there is no guarantee that IRBs at the different sites will evaluate the protocol in the same way. This raises the likelihood that for some studies an IRB at one site may conclude that a protocol requires a 46.407 review when IRBs at other sites approved the protocol under 46.404, 46.405, or 46.406. Finally, some sites with IRB approval may have already begun subject enrollment. To address these complicated scenarios SACHRP recommended that:

- OHRP initiate the screening process described above any time a local IRB associated with a multi-site study requests a 46.407 review regardless of whether other centers arrived at a different risk/benefit classification.
- OHRP notify the funding agency and the Principal Investigator of the IRB’s application for a 46.407 review, and when appropriate seek information from other participating site IRBs regarding their Subpart D classification of the protocol.
- OHRP provide feedback to the IRB and determine whether a 46.407 review should be commenced.
- OHRP and the local IRB may use the following criteria to determine whether enrollments should be suspended or terminated pending a 46.407 review: 1) a study approved under 46.406 by the local IRB may pose more than a minor increment over minimal risk, or 2) a study approved under 46.405 may not offer the prospect of direct benefit.
- Participating families should be informed if enrollments are suspended or terminated.
- Information about the 46.407 review should be provided to families if enrollments are not suspended or terminated pending a 46.407 review if it is reasonable to assume that knowledge about such a review being conducted would raise legitimate family concerns about participation in light of a recalculation of risk and prospective benefits.

- At the conclusion of the 46.407 review process the IRB should seek re-consent from families currently enrolled in the study if the Secretary has ruled that 1) the risk-benefit calculus has significantly changed from that described in the original consent protocol, or 2) the study should be terminated, but previously enrolled participants are permitted to continue in the study.
- Families who have completed participation in the study prior to the Secretary’s ruling should be notified about the ruling if the 46.407 review produced new information pertinent to the continued welfare of the child.

Monitoring

SACHRP asked that as these new 46.407 procedures are implemented, OHRP and SACHRP continually evaluate the process to identify aspects that are successful and those that can be improved further.

Disclaimer

The authors are Co-Chairs of the SACHRP Subcommittee on Pediatric Research. The summary of SACHRP recommendations highlighted in this article is the sole responsibility of the authors and does not necessarily represent how they would be summarized by other SACHRP members.

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References
1. 45 CFR 46 Subpart D. Additional DHHS Protections for Children Involved as Subjects in Research.
4. Under federal statute, non-Federal Advisory Committees are not permitted to submit a consensus document. Protocols jointly reviewed by OHRP and FDA may issue a consensus report if reviewed by the FDA Federal Advisory Committee.
Compensation for Research Injuries

BY HAZEL BEH

Under current federal regulations, research institutions are not required to provide compensation for injuries to human subjects, even reimbursement for medical expenses caused by a research injury. Instead, Institutional Review Boards (IRBs) are required only to ensure that in research involving more than minimal risk, human subjects are informed whether any compensation or medical treatment will be available if injury occurs. In addition, human subjects cannot be asked in the informed consent process to waive their legal rights or release institutions, investigators, and sponsors from liability for negligence.

Many believe that these bare requirements fail to meet the ethical obligations of the research community and society to human subjects. In 1976, James Childress made a particularly compelling moral argument to justify compensation for all research injuries, whether regard to human subject consent, assumption of risk, researcher fault, or the therapeutic or nontherapeutic nature of the research. He wrote:

[It] does not matter whether the participant who is injured is a draftee or a volunteer; he still presents a claim on the community that he not be made to bear the whole burden of his injury. His acquiescence in a draft or his voluntary participation in the social activity does not thereby assign the responsibility for the costs to him. The moral principle of fairness creates a societal obligation to this participant, who can claim as his right not merely consideration or damages but compensation at least for major injuries. The obligation is voluntarily incurred by society, through its establishment, endorsement, or mandate of the practice in question and its acceptance of the individual's participation . . . . This obligation is based on the relationship between the parties . . . . not on the fact that society through biomedical research wrongfully injured the participant . . . . It reflects the moral principle of fairness.

In 1973, the Tuskegee Syphilis Study Ad Hoc Advisory Panel recommended the federal government establish a policy on compensation for human subject injury. Since then, many other blue ribbon commissions have echoed those recommendations. These include the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, the Department of Energy's Advisory Committee on Human Radiation Experiments (ACHRE), and the National Bioethics Advisory Commission (NBAC).

Yet the research community collectively has not responded to these calls to develop a national program or policy for compensation for research injuries. The failure to address the issue of compensation leaves it open to criticism and undermines public confidence, as the 1982 President's Commission noted:

The suggestion of compensation for research injuries has been a mainstay of ethical and public-policy discussions of research with human subjects for many years. The time has come to determine the wisdom of those suggestions. The failure to resolve the issue not only exposes subjects of research to a possible wrong, it exposes the entire research enterprise to the public recriminations that could follow from one or a series of serious, uncompensated injuries to subjects.

While some institutions have developed modest compensation programs, they are the exception, not the rule. Establishing a nationwide, comprehensive compensation system has probably not been viewed as pressing because of the perceived infrequency of claims and lawsuits. Scant information exists about the number and extent of research injuries and whether a lack of compensation has actually harmed human subjects. However, the infrequency of claims or lawsuits neither proves there is no need for a compensation system nor justifies ignoring the issue. In addition, regardless of the frequency of injuries or the number of lawsuits filed, the ethical obligation to compensate injured human subjects remains the same. Nevertheless, if litigation increases, as now appears the trend, complacency may be costly. The costs, unpredictability, and unfairness associated with the tort system may finally compel action.

Moral debates aside, the chilling effect of lawsuits on research and fear of liability may finally motivate researchers, sponsors, and the federal government to develop a fair and predictable compensation system.

The Ethical Argument in Favor of Compensation

The view that society should not expect human subjects to shoulder the financial costs of injury has been extensively considered and approved. Justifications for compensation focus on the benefit to society bestowed by human subjects and the unfaithfulness of placing both the risk of injury and the costs of injury on them alone.

While ethical distinctions can be made between nontherapeutic and therapeutic research to justify a different intervention for purely altruistic volunteers, those distinctions are not particularly compelling. After all, even those who participate in therapeutic research may not benefit, due to the inherent uncertainty of research. In addition, even participants in therapeutic research may be motivated by a desire to help society as well. On the other hand, regardless of whether the research benefits a human subject or his or her prime motive is self interest, human subject participation will certainly contribute to scientific knowledge and benefit society. Therefore, even as to therapeutic research, “[c]ompensation is a means of redressing the imbalance between the risks undertaken by research subjects and the benefits that others enjoy as a result.” As Childress noted, “the combination of roles of patient and subject with the joint possibility of benefiting both oneself and others does not cancel society’s obligation.”

Distinctions also can be made between injuries about which individuals were warned during the consent process and of those that were unexpected. Although subjects agree to assume the risks of injuries for which they were warned, they do not necessarily agree to assume the financial costs associated with injury resulting from research participation. To the extent that the justifications for compensation spring from the recognition of the societal benefits of research, distinctions based on the potential benefit to a subject participating in a therapeutic trial or to the subject’s informed consent are not particularly persuasive.

Inadequacy of Tort Litigation as a Compensation System for Research Injury

Currently, compensation for research injury is relegated principally to the tort compensation system. Yet the tort system, particularly in the area of medical malpractice, is notorious for its shortcomings, including unpredictability, its tendency to under-compensate most negligently injured patients, its over-compensation of some, and its high transaction costs. Tort litigation as a principal mode of compensation does not serve the interests of institutions or of human subjects if the goal is to achieve a fair and efficient compensation system.

Tort compensation for research-related injury depends upon proof of fault. Yet, the ethical justifications for compensating human subjects are not premised on the fault of the researcher, but on the sacrifice of the human subject and the benefit to society. By demanding that human subjects prove fault to establish their right to compensation, a tort-based compensation system fails to acknowledge that it is the subject’s volunteerism and the public’s benefit from such that justifies compensation.

In the case of research-related injury, tort litigation makes for the unlikeliest antagonists: an altruistic human subject versus a humanitarian researcher. Fault-based litigation requires plaintiffs to establish that the research was negligently designed, that researchers were negligent, or that the subject did not give informed consent. Yet research, by its nature, involves unknown risks, uncertainty, and innovation. Thus, the tort system’s scrutiny of research with the advantage of 20-20 hindsight can make litigation based on fault appear unfair to the researcher.

Other Solutions

In devising an alternative compensation system, achieving justice should be paramount. In addition, a compensation system should not be so unwieldy or expensive that it overburdens the research enterprise. Moreover, in recognition of the voluntary nature of research participation, a non-tort compensation system should not substantially impair a subject’s rights to vindicate research-related injuries by traditional legal means.

In order to succeed, a compensation system must meet the needs of the research community and of the individuals who participate in clinical trials. It must be sufficiently appealing so that individuals will voluntarily select it over the tort system. It must offer human subjects the opportunity to obtain fair compensation, allow them to present their claims before a neutral arbiter, and be sufficiently efficient that delays and transactional costs do not impede justice. The research community has similar needs, but as repeat players who will pay for the system, they also require that it be affordable, stable, and predictable.

There are worthwhile models to consider, including some modest beginnings within the research community. The University of Washington has operated a self-insured no-fault compensation system since the 1970s with reportedly manageable claims and expenses. Some institutions, for example, the University of California at Los Angeles and Wake Forest University, provide medical care for injuries directly related to research and require sponsors to do the same. The Department of Veterans Affairs pays the cost of medical treatment for research injuries, subject to some limitations. At the very least, by examining these and other efforts,
the research community can begin to understand the scope of the risks and costs involved in establishing a compensation program.

Outside the research community, there are other federal models to examine. Most notable is the National Vaccine Injury Compensation Program (VICP), which was developed in the 1970s as a result of a litigation crisis that threatened the manufacture and supply of vaccines in the United States. Today, this no-fault compensation program is funded by a 75 cent surtax on each vaccine. Importantly, victims of vaccine injuries are not precluded from pursuing tort remedies. Injured claimants are only required to first attempt resolution via the program. The VICP provides compensation beyond mere medical costs, approximating the types of recovery available in tort. While awards for death are capped at $250,000, other injury awards are not, and payouts have been substantial. The VICP has dramatically reduced vaccine litigation and created a climate that promotes continuing research and development.

Admittedly, part of the success of the VICP is based on the predictability of the risks involved. Relatively few vaccines are covered and the types of injuries are largely predictable based on prior experience. In fact, while individuals can make claims for other injuries besides those well-defined injuries on the program's injury table, the burden to prove causation differs when the injury is of an unexpected nature. Since injuries on the vaccine table carry less proof problems, and manufacturers have experience predicting the nature and severity of injuries, once the unpredictability of the tort system was eliminated, it was possible to calculate an appropriate surtax.

Research injury, on the other hand, by its very nature is unpredictable. Moreover, because the type of research conducted varies so much, even if better data about past injuries existed, it would still be challenging to predict future rates of injuries. However, the potential risks of injury posed by a particular protocol can be approximated in advance. Categorizing research by the nature of the risk can also be accomplished before a study begins. An IRB does something like this now when it evaluates relative risks and benefits as required by current regulations. The clinical trials that an IRB identifies as posing a sufficiently high risk of injury could be required to participate in a national compensation plan. Moreover, depending on the nature of the research-related risks, a graduated surtax could be assessed. Risk considerations might include the number of research subjects and the nature of the risks involved. Funds generated by such a surtax might be held and administered federally, as is the case with the VICP.

Other government sponsored victim compensation systems should be studied as well; some of these compensation models cover more unpredictable losses. While the administration of each system is unique, these victim compensation funds typically share some characteristics. Federal compensation programs include the September 11th Victim Compensation Fund (compensating victims of the World Trade Center collapse and hijackings), the National Swine Flu Act (transferring liability for the 1976 Swine Flu immunization program to the federal government and establishing a compensation fund), the Price-Anderson Act (compensating for injuries and damages sustained by the public in the event of a nuclear accident), various state and federal employment based no-fault compensation programs (workers' compensation), the Black Lung Benefits Act (compensating victims and surviving family for lung disease related to mining), and the Agent Orange Fund (compensating Vietnam veterans and families for injuries due to Agent Orange exposure).

These plans share some common features that maximize fairness to victims while containing the costs associated with resolving claims. First, they establish an adequate funding mechanism, such as insurance, a continuing surtax or excise tax, or congressional funding. In order to contain costs, these plans carefully define who is eligible and the nature and amount of compensation that will be allowed. Typically, the funds are designed to compensate for substantial, not trivial, injuries (which might overburden a system with insignificant claims). The funds place an initial burden on the claimant to establish the legitimacy of his or her claim. Although some of the funds place some limits on the amount of or nature of damages (especially for punitive and emotional distress damages), they generally offer adequate compensation for physical injuries and other actual damages. In addition to carefully establishing eligibility, these plans also recognize that adequacy of compensation is essential, both to induce claimants to opt out of the tort system and to fulfill the fund’s purpose.

Second, the plans establish procedures and deadlines for prosecuting claims. In order to reduce costs and facilitate prompt compensation, the funds also provide a streamlined claims process. To reduce the chances of inordinately and inappropriately large awards, determinations are initially made by individuals with experience and expertise, and who are informed by scientific evidence.

Significantly, some programs offer the victim an exclusive remedy (thus foreclosing litigation as an alternative), while others merely offer an opt-in no-fault compensation program in lieu of tort litigation. The latter is most appropriate for research injuries, because it would be unfair to ask volunteers to forego legal rights to sue based on fault.
Some opt-in systems may place some limits on tort litigation as well in order to curb costs. For example, the VICP requires all claimants to first submit the claim to the VICP before pursuing tort litigation. For those victims who opted out of the September 11th Fund, Congress limited the forum for adjudicating their claims and established a two year statute of limitations. The September 11th Fund also offset recovery to the extent the victim had been compensated by "collateral sources" such as insurance. By placing modest restrictions on litigation, Congress was able to increase the incentive to participate in the fund program without substantially impairing victim's legal rights.

Conclusion


tDAC concluded that "because the costs of research injuries should not be borne by the injured participants and because support for a compensation system should be provided by those most likely to profit or derive benefits from it, sponsors and institutions should be assigned responsibility for funding such a system."

The research community and policymakers have the expertise to design a no-fault compensation system for research-related injury. We have compensation models that should be examined carefully. These offer individuals compensation, while protecting them and enterprises from the vagaries of the tort system. These alternative compensation systems have been justified by the broader public interests at stake. Those public interests include protecting vital industries and institutions from burdensome litigation and providing fair and prompt compensation to injured individuals. Certainly, society's vital interest in a healthy medical research community and the ethical obligations we have toward injured research subjects justify a sincere examination of compensation fund possibilities.

References

1. 45 CFR 46.116 (a)(6).
2. 45 CFR 46.116.
8. See ref. 5, President’s Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research 1982.
14. See ref. 13, Committee on Assessing the System on Protecting Human Participants 2004a, p. 188.
17. See ref. 5, Childress 1976.
28. There have been 6,906 post-1988 petitions filed; and 1,736 adjudications resulting

29. See ref. 26, Burke 2002, p. 163.
30. See ref. 27, VICP 2002.
31. 45 CFR 46.121(a)(2).
33. See ref. 32, Mullenix and Stewart 2002.
34. See ref. 32, Mullenix and Stewart 2002.
35. See ref. 32, Mullenix and Stewart 2002.
36. See ref. 32, Mullenix and Stewart 2002.
37. See ref. 32, Mullenix and Stewart 2002.
38. See ref. 7, NBAC 2001, p. 126.

Annotations

Lockwood AH. Ethics in public health research: Human testing of pesticides: Ethical and scientific considerations. American Journal of Public Health 2004;94(11):1908-1916. • The author conducted a review of six human pesticide-dosing studies submitted and approved by the Environmental Protection Agency (EPA) between 1992 and 1999 to determine ethical compliance and scientific validity. All of the studies aimed to determine either a safe level or a "no observable effect level" (NOEL) of pesticides in humans. Lockwood contends that the studies used misleading information to describe the pesticide in use and failed to adequately describe animal or human studies to justify conducting the studies. In addition, he claims that the sample sizes were too small to support the data, that the conclusions reached are not justified by the analysis, and that the studies did not fulfill the goal of making the data generalizable to children due to poor study design. Moreover, none of the studies were published in scientific journals, and all were approved by an IRB within an organization paid by the sponsors to complete the studies. Lockwood contends that it is inappropriate to continue testing pesticides in humans and that more attention to the EPA approval process is needed.

Pentz RD, Khayat AF. The poster child for the need for central review of research protocols: The Children's Oncology Group. Cambridge Quarterly of Healthcare Ethics 2004;13:359-365. • Based upon the experiences of the Children's Oncology Group (COG), the authors argue for the replacement of the current local IRB review system with a pediatric central review board (PCRB) for multisite pediatric studies. They claim that the current local IRB review system is problematic in three areas: 1) time, 2) expertise, and 3) impact. In contrast to local IRBs, a central review board would be better equipped to spend an adequate amount of time reviewing multisite pediatric protocols, provide the necessary expertise to sufficiently review those protocols, and interact with investigators and facilitate communication such that research protocols are substantially improved following review. In addition, the authors contend there is an ethical imperative to restructure the current review process because a central review system will be better able to protect participants in pediatric studies.
Bounty-Hunting and Finder’s Fees

BY JAMES A. CHRISTENSEN AND JAMES P. ORLOWSKI

Researchers recruit individuals to participate in clinical trials in order to advance medical science. Yet other interests, both financial and nonfinancial, may also influence researchers’ recruitment activities, and may rise to the level of a conflict of interest. Nonfinancial interests such as enhancement of academic standing, prestige, and reputation are deeply rooted in clinical research. Of more recent concern are increasingly common financial conflicts of interest, especially with industry playing a larger role in clinical research. Many researchers have equity ownership, stock options, paid positions, or patents with royalties with the companies that fund their studies.

Two other financial conflicts of interest that have not been adequately addressed are what we refer to as bounty-hunting fees and finder’s fees. We define bounty-hunting fees as large sums of money paid by pharmaceutical houses, manufacturers of medical devices, or other sponsors of research studies to clinical researchers on a per capita basis for the purpose of testing their products. Finder’s fees are sums of money paid to a non-researcher (usually house officers, research nurses, other hospital personnel, or other research subjects) who identifies and/or enrolls research subjects for a specific research study. Bounty-hunting and finder’s fees differ not only in the magnitude of the monetary enticement, but also in the level of responsibility of the involved parties. Bounty-hunting fees involve the primary investigator, who shoulders the ultimate responsibility for the conduct of the research and the procurement of informed consent.

Pharmaceutical firms and medical device manufacturers need to enroll a required number of individuals into their sponsored studies to meet statistical significance and to satisfy the Food and Drug Administration (FDA). In order to complete their studies in a reasonable period of time, they often feel it necessary to entice the researcher to enroll individuals in their study by making the study financially attractive to the researcher. There are often multiple competing studies ongoing at the same time for the same class of research subjects, and so a financial incentive may give a research sponsor an edge in completing enrollment quicker and gaining FDA approval sooner for the intervention being tested. When dealing with a new and unique drug or device, six months or a year advantage over competitors can mean tremendous profits and the recoupment of research and development costs.

There has been a tremendous shift in the paradigm of clinical research over the last decade or so. In the remote past, the vast majority of clinical research was conducted in academic medical centers and was funded by the federal government and private philanthropies. In recent years, greater than fifty percent of clinical research is being conducted in non-academic settings, and most of it is funded by private industry, including pharmaceutical firms and durable medical device manufacturers. Moreover, clinical research is increasingly seen as an attractive means of supplementing the income of clinicians whose base income has been dwindling because of cost-cutting measures by the federal government and managed care organizations. For example, an article in a financial journal for physicians recommended clinical research studies as a means of supplementing income and provided examples of private practice and group practice physicians who had doubled or tripled their annual income by taking on such studies.

It is now fairly commonplace for clinical researchers to be offered large sums of money ($5,000 to $10,000) for each individual they enroll in a research study, even where the investment of time and expertise on the part of the researcher is relatively minor. Of even greater concern is clinical researchers offering substantial bonuses ($250 to $500 per individual enrolled) to poorly paid house officers and research nurses to encourage them to enroll patients in research studies. Many house officers and research nurses at major universities and medical centers may be able to double or triple their annual income by enrolling large numbers of patients in research studies at their institutions. Clinical researchers also use patient-subjects as recruiters by offering them financial incentives to entice other patients, family members, or friends to participate in research studies. This reportedly is a common practice, especially in genetic studies.

Ethical Denouement

It seems reasonable to assume that the vast majority of clinical...
Researchers behave according to established ethical norms and place their patients’ welfare as paramount. Nevertheless, the prospects of peer recognition, publication, and financial gain may create pressures that could compromise or appear to compromise the integrity of the research or the researcher. Economic incentives may affect a researcher consciously or subconsciously. The ethically relevant issues involving bounty-hunting and finder’s fees are conflicts of interest, informed choice, and justice.

A conflict of interest is a discrepancy between the personal interests and the professional responsibilities of a person in a position of trust. Conflicts of interest occur when an individual is occupying dual roles which perhaps should not be performed simultaneously. Because of the potential for abuse, performing both roles simultaneously is potentially inappropriate, even if the individual has good intentions, never exploits the conflict, and does not harm anyone. In the case of bounty-hunting and finder’s fees, the dual roles are advocate and protector of the patient-subject and paid bounty hunter or finder for a sponsor of a research study.

The risks are numerous. A physician-researcher may be tempted to propose a research treatment or procedure that is either not needed or is less beneficial than standard treatment in order to earn a bounty fee. Money might also tempt recruiters to enroll ineligible individuals in a trial, which could jeopardize the study’s scientific validity. But most importantly, a financial conflict of interest has the potential to compromise the trust inherent in the physician-patient relationship.

As DeRenzo has pointed out, there is a “concern that pharmaceutical industry money is so enticing as to override the sacred trust the patient must place in the physician’s adherence to first doing no harm. The concern is that the pharmaceutical industry is paying physician-investigators, including those inexperienced in the conduct of human subjects research, so much money to recruit and retain subjects that the interests of vulnerable persons may be trampled.”

Likewise, Lemmens and Miller point out that “At a 2000 NIH conference on conflict of interest, Dr. Thomas Bodenheimer testified that financial pressures bring physicians to ‘stretch the inclusion and exclusion criteria to enroll as many patients as they can, thereby compromising the trial’s validity.’”

Conflicts of interest are conditions, not behaviors. Conflicts of interest can exist without causing adverse effects or any effect at all. Conflicts of interest can be created and exist without impugning the integrity of the professionals involved. Conflicts of interest may vary in terms of not only the likelihood that professional judgment may be influenced by secondary interests or gains, but also by the seriousness of the harm that may result from such influence or its appearance.

An economic incentive introduces a third interest into the doctor-patient relationship. Patients may perceive or suspect an ulterior motive, even when such does not exist. Patients may wonder whether the researcher is more concerned with his or her own financial gain than with their welfare. Public support for medical research rests in no small measure on trust in the integrity of investigators. Conflicts of interest are situations that threaten to undermine the researcher’s objectivity and veracity due the scientific community, and the trust and loyalty owed to research subjects.

The enrollment of ineligible or inappropriate subjects into research studies might seem unlikely, but has in fact been found. Vanderpool and Weiss reported on phase II and phase III trials where large numbers of ineligible individuals had been entered into the studies, necessitating their exclusion when the trials were statistically analyzed. In addition, in its 1998 investigation of research practices at Chicago’s Rush Presbyterian St. Luke’s Medical Center, the federal Office for Protection from Research Risks (OPRR) found evidence that ineligible individuals had been enrolled in clinical trials. Not only do such protocol violations compromise the findings of the clinical trials, but they potentially place research subjects at increased risk and violate the standards of informed consent. Although it is difficult to know whether financial incentives played a role in these recruitment practices, Vanderpool and Weiss contend that “self-interested motives by physicians who desire either academic recognition or financial rewards” is one of the reasons for enrolling ineligible individuals into clinical trials. In their view, enrolling individuals in clinical trials out of self-interest uses others as a means for one’s personal ends and “is clearly reprehensible morally.”

There is nothing intrinsically wrong with researchers or institutions making money. The issue is whether making money for enrolling individuals in clinical trials is a conflict of interest that requires disclosure as part of the informed consent process. At present prospective research subjects are rarely if ever told outright that their physician will be paid by the company sponsoring the research study for entering them into the study. There are some who feel that this direct financial benefit, one not widely appreciated by research subjects, represents an ethically suspect temptation to the investigator to transgress his or her fiduciary obligation to the patient.

In the situation in which the researcher is paid by the sponsoring company or organization on a per capita basis, and in situations in which individuals are paid finder’s fees, there are substantive ethical arguments supporting disclosure. Compared with routine medical
practice, a higher standard of disclosure may be required for research studies and their informed consent process. The California Supreme Court made conflict of interest and breach of fiduciary duty the cornerstone of its opinion in the Moore case, which involved the use of a patient’s splenic tissue for research and the cultivation of a commercially valuable cell line. Moore’s physician sold the cell line to a biotechnology company for $440,000 plus stock options. Yet Moore never gave consent for his tissue to be used for research and commercial development. The court reasoned that a physician who has a research or economic interest in a patient has a conflict of interest, and that because this conflict might affect the physician’s professional judgment, it is a material fact that must be disclosed to the patient-subject.13

California law had already required that research subjects be informed of the source of an investigator’s funding for a study, but not necessarily of the amount or the mechanism of the funding.19 Full disclosure requires they be told about the source of funding as well as about the investigator’s potential conflict of interest in receiving industry funding for enrolling subjects. In addition, the applicable Institutional Review Board (IRB) regulations require that the information be conveyed in a language in which the subject is fluent and in non-technical terms.20

Some commentators have suggested that when a researcher receives capitation payments for enrolling individuals in clinical trials, prospective subjects should be told about this financial arrangement. Spiro contends that subjects “should be told not only that they are part of a study but that their physician is being paid for those studies. If we are really to talk about ‘informed consent,’ such matters should be explicit.”21 Moreno, Caplan, and Wolpe, writing on behalf of the Project on Informed Consent of the Human Research Ethics Group, also adopt his view.11 Moreover, Shimm and Spece assert that “if a patient is dissuaded from enrolling in a study because of concerns about the investigator’s possible bias, this is precisely the sort of decision that the principle of autonomy must respect.”23

Others go a step further and contend that finder’s fees and bounty-hunting fees should be prohibited outright. The American College of Physician’s Ethics Manual states that “Giving finder’s fees to individual physicians for referring patients to a research project raises the issue of conflict of interest and is unethical.”54 The same admonition apparently would extend to finder’s fees to residents, nurses, and the public. Lind equates fee-splitting to finder’s fees, which he says “should not be a part of clinical research.”35 He does not feel that disclosure is a good compromise, because making patients aware of the finder’s fees or bounty-hunting fees would only make them question the validity or worth of the research project. “Such disclosure” says Lind, “would not be likely to push a patient towards enrollment, but could only serve to dissuade him/her from participating by virtue of waving a red flag that warns him or her to be suspicious of the investigator and/or the research.”25 Some commentators have even suggested that finder’s fees may violate the anti-kickback provisions of the Medicare and Medicaid programs and could be interpreted by the Office of Inspector General (OIG) of the DHHS as a violation of federal law at the felony level.27

Of interest, the FDA recently promulgated new rules on Financial Disclosure by Clinical Investigators which went into effect on February 2, 1999.28 These rules require sponsors of any drug, biological product, or medical device seeking FDA approval to submit information concerning compensation and financial interests of the clinical investigators conducting the studies. As the FDA explains, “One potential source of bias in clinical studies is a financial interest of the clinical investigator in the outcome of the study because of the way payment is arranged (e.g., a royalty) or because the investigator has a proprietary interest in the product (e.g., a patent) or because the investigator has an equity interest in the sponsor of the covered study.”39 The FDA defined significant payments made by the sponsor to the investigator or institution as having a monetary value of more than $50,000, exclusive of the costs of conducting the clinical study during the time the investigator is carrying out the study and for one year following the completion of the study.

The last ethical issue to be addressed is justice. According to the principle of justice, the selection of research subjects needs to be scrutinized to determine whether certain categories of persons are being systematically selected because of their ease of availability, their compromised position, or their manipulability, rather than for reasons directly related to the clinical research problem being studied. Likewise, certain categories of individuals may be recruited solely because of compensation paid to researchers or others. Just as IRBs must assess whether payments or incentives to prospective subjects constitute undue inducement or subtle coercion and thereby compromise their decisionmaking, they must also question whether financial arrangements or other incentives between sponsors and physician-researchers may compromise the physician’s judgment in counseling a patient about a study.

Conclusions and Recommendations

Public perception about the existence of bounty-hunting and finder’s fees is an important consideration. A survey by LaPuma et al. of
patients' and physicians' attitudes concerning post-marketing research found that most patients (56%) did not feel a fee was appropriate, while most physicians (64%) thought otherwise. The vast majority of patients (86%) and three-fourths of the physicians (75%) said that physicians should inform patients when they accept fees for enrolling patients in clinical trials. Two-thirds of the physicians and patients felt that some doctors might be influenced to enroll patients just for the fee.\footnote{10}

In all likelihood the public would not be pleased to find out that their physician and other researchers and health care professionals were making large profits on the participation of research subjects in clinical trials, especially when it is almost exclusively the trial participant who carries the risk. Existing recommendations and requirements for disclosure of acceptance of bounty-hunting and finder's fees are not designed to impede clinical research. In many cases participation in a research study may be in an individual's best interest, regardless of the financial interests that researchers and others have in the clinical trial. What is important ethically is that individuals recruited to participate in research be provided with the appropriate information to make an informed choice about participation. However, we contend that some fees should not be paid at all. Thus, we offer the following recommendations:

1. Under no circumstances should house officers, nurses, staff members, or other hospital personnel be offered or accept a monetary “finder’s fee” or other incentives for recruiting subjects or referring them to clinical trials.

2. Researchers must disclose fully to the IRB at the time of submission of a research protocol all financial arrangements and other conflicts of interest and justify all compensation in terms of the time and expertise required for the research study.

3. The IRB may require the disclosure to research subjects of the financial arrangements between the researcher and sponsor as part of the informed consent process and document.

4. The IRB and individual researchers should encourage the use of block payments rather than per capita payments when negotiating research contracts with sponsors.

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17. See ref. 4, Shinn et al. 1991.

18. Moore u. Regents of University of California, 51 Cal 3rd 120, 793 P2d 479,271 California Reporter 146 (S.Ct. Cal. July 9, 1990); Barnes M, Florencio PS. Financial conflicts of interest in human subjects research: The problem of institutional conflicts. \textit{Journal of Law, Medicine, & Ethics} 2002;30:390-402, p. 396. More recently, a Florida court ruled that medical researchers do not have a duty to disclose their economic interests in research to prospective subjects. A key feature in this case was that the physicians were exclusively researchers, not treating physicians who also conducted research. See Greenberg v. Miami Children's Hospital Research Inst., Inc., 264 F. Supp. 2d 1064 (S.D. Fla. 2003).


20. See ref. 19.


22. See ref. 12, Moreno et al. 1998.


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