

ASCO SPECIAL ARTICLE

American Society of Clinical Oncology Policy Statement: Oversight of Clinical Research

Adopted on November 7, 2002, by the American Society of Clinical Oncology

Executive Summary: Well-publicized lapses in the review or implementation of clinical research studies have raised public questions about the integrity of the clinical research process. Public trust in the integrity of research is critical not only for funding and participation in clinical trials but also for confidence in the treatments that result from the trials. The questions raised by these unfortunate cases pose an important opportunity to reassess the clinical trials oversight system to ensure the integrity of clinical research and the safety of those who enroll in clinical trials.

Since its inception, the American Society of Clinical Oncology (ASCO) has worked for the advancement of cancer treatments through clinical research and to help patients gain prompt access to scientifically excellent and ethically unimpeachable clinical trials. As an extension of its mission, ASCO is affirming with this policy statement the critical importance of a robust review and oversight system to ensure that clinical trials participants give fully informed consent and that their safety is a top priority. Ensuring the integrity of research cannot be stressed enough because of its seminal connection to the advancement of clinical cancer treatment.

The overall goal of this policy is to enhance public trust in the cancer clinical trials process. To achieve this, the following elements are essential:

1. Ensure safety precautions for clinical trial participants and their fully informed consent.
2. Ensure the validity and integrity of scientific research.
3. Enhance the educational training of clinical scientists and research staff to ensure the highest standards of research conduct.
4. Promote accountability and responsibility among all those involved in clinical research (not just those serving on institutional review boards [IRBs], but also institutional officials, researchers, sponsors, and participants) and ensure support for an effective oversight process.
5. Enhance the professional and public understanding of clinical research oversight.
6. Enhance the efficiency and cost-effectiveness of the clinical research oversight system.

This policy statement makes recommendations in several areas that serve as principles to support an improved system of oversight for clinical research. ASCO will work with all parties involved in the clinical research system to develop the steps necessary to implement these recommendations.

- **Centralized Trial Review:** A large percentage of oncology clinical trials are coordinated through the National Cancer Institute's (NCI) system of cooperative groups, which already incorporates centralized scientific review. As such, there is a tremendous opportunity to employ a centralized mechanism to provide ethical review by highly trained IRB members, allowing local IRBs to take advantage of the

financial and time efficiencies that central review provides. Centralized review boards (CRBs) would also contribute consistency and efficiency to the process. Once successfully completed, the review would represent an approval to open the protocol at all of the institutions that have subscribed to the centralized review system. Local IRBs would be able to devote time usually spent on initial review to ongoing monitoring of the trial taking place at their institution.

Considering the enormous size and complexity of the clinical research enterprise, ASCO envisions multiple CRBs, which could be distributed as regional review boards. Central review will use a single protocol and consent form, and monitor and evaluate adverse events (AEs) on a global basis, eliminating many of the time-consuming steps for the local IRB. Global monitoring and assessment of AEs has real potential to enhance trial participants' safety by giving local institutions more information on the overall trial and enabling them to devote more time to ongoing review of the trial onsite. Use of a CRB also has real potential to reduce the costs of clinical trial oversight by allowing local IRBs to eliminate the costs of initial review. These efficiencies will likely lead to institutions redirecting funds toward monitoring ongoing trials. Although a CRB has potential to improve the efficiency of the process, a CRB could also have tremendous ability to delay valuable trials. Checks and balances must be included in the newly devised system to ensure timely review and appeals of CRB actions.

ASCO proposes the advent of a new pilot program for centralizing review of clinical trials. It requires clear engagement of all stakeholders in planning the experiment, clear articulation of the goals, and assurance of federal regulatory protection for institutions choosing to participate. If successful, this CRB pilot project could be expanded to include multi-institutional industry-sponsored research.

- **Education and Training:** Education and training are critical to the ultimate success of an improved oversight system. All members of the research team should receive compre-

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ASCO sincerely appreciates the contributions of the ASCO Task Force on Oversight of Clinical Research, which devoted significant time and effort to this project. The Task Force was chaired by Lowell E. Schnipper, MD (Beth Israel Deaconess Medical Center, Boston, MA). A list of the Task Force members appears in the Appendix at the end of this article.

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hensive education on conducting scientifically and ethically valid clinical research. The curriculum should also include information on the prevailing local and federal regulations that pertain to the clinical trials process. IRB members should also receive ongoing education and training in the review of clinical research protocols. IRB training should pay particular attention to nonscientific members to give them the tools necessary to speak on behalf of research participants. ASCO should develop a curriculum that focuses on the proper conduct of human research and emphasize ethically sound clinical research in the context of its Annual Meeting.

- **Informed Consent:** Investigators and review boards have specific roles to play in ensuring the education of trial participants through the informed consent process, both when they are considering trial enrollment and as they participate in the trial. Review boards and investigators should focus primarily on the informed consent process, rather than the informed consent documents.
- **Federal Oversight:** The federal government has an important role to play in the oversight of clinical research. This role should be expanded to cover all research, not just that which is funded by the federal government or conducted with the oversight of the Food and Drug Administration

(FDA). The Department of Health and Human Services (HHS) Office for Human Research Protections (OHRP) and the FDA should provide clear regulatory support and guidance for local institutions that choose to employ a CRB. In the case of the pilot CRB discussed in this policy statement, it should serve as the preferred option for the cancer cooperative group clinical trials. Ideally, the federal government should unify and streamline its regulations for the oversight of clinical research.

- **Resources Supporting Clinical Research Infrastructure:** An effective oversight process demands the highest quality scientific and ethical review and onsite monitoring of the safety of trial participants. This can only be accomplished by the involvement of an experienced IRB that receives funding, resources, and institutional support enabling it to fulfill its mandate.
- **Conflict of Interest:** Critical to the integrity of research is the absence of bias in the process. ASCO strongly recommends the adoption of standards for the identification, management, and, where appropriate, elimination of conflicts of interests, whether they are actual, potential, or apparent.

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BACKGROUND

Public and policymaker attention to the oversight of clinical research and the safety of research participants increased significantly after the September 1999 death of an asymptomatic teenager enrolled in a University of Pennsylvania gene transfer trial. Subsequent deaths of research participants at major institutions—including the Fred Hutchinson Cancer Research Center and Johns Hopkins University—and questions about the adequacy of federal and institutional oversight have led to increased scrutiny of research activities in institutions throughout the country. These cases also have raised significant questions about the financial interests of researchers and institutions and the adequacy of the informed consent process.

Before these highly publicized cases, major reports from the HHS Office of the Inspector General,¹ the General Accounting Office (GAO),² and the National Institutes of Health (NIH)³ raised questions about the adequacy and effectiveness of the federal human research protection system. The Clinton Administration responded to these reports and to the research deaths by elevating the federal agency with oversight over HHS-funded human research from the NIH to the Office of the HHS Secretary.

With the increased visibility, the OHRP has been more proactive in its compliance and education activities. Institutions have taken more notice of the importance of research oversight as a result of OHRP-imposed restrictions. In some instances, institutions with identified lapses were required to rereview and audit all of their human trials. In some high-profile cases involving major research centers, OHRP has suspended federally funded human trials and directed the institution to make changes to its oversight system.

The growing recognition of lapses in the oversight and conduct of clinical research, increasing federal regulatory activities, and published reports and studies on a number of aspects of the oversight system have brought this issue to the forefront of

the public's attention. That clinical trials have grown in number and complexity since the institutionalization of IRBs by the federal clinical research regulation, the so-called Common Rule,⁴ serves to heighten the magnitude of the problem. Modern IRBs are facing increased demands and expectations as the burden of federal regulatory requirements and the number of clinical trials are increasing. An added complexity is the diversity of sites at which clinical research is performed. As is often the case, the emergence of a challenge provides a genuine opportunity to re-examine the oversight system and identify ways that it can be improved.

IMPORTANCE OF CLINICAL RESEARCH TO CANCER TREATMENT

Clinical trials have helped to improve cancer care and define the standards for optimal cancer treatment. Although not without intrinsic risks, clinical research is absolutely necessary to treatment advances. Many trial participants also depend on high-quality clinical trials when there are no known treatments for their disease or when the investigative treatment is potentially more effective and less toxic than standard treatments. Clinical trials take into account and try to improve on the best available therapies and provide structure and rigor in a treatment plan. Because of the role clinical trials play, oncologists have been and should continue to be at the forefront of ensuring the highest ethical standards for the conduct of clinical research.

ASCO has always placed clinical trials at the center of its mission. Given the questions and concerns raised about the safety of clinical trials, ASCO's Public Issues Committee formed the Task Force on Oversight of Clinical Research in May 2000. The Task Force included academic and community oncologists, cancer survivors, institutional review board chairs and members, and pharmaceutical industry research representatives. The charge was to develop a policy statement on the oversight of

clinical research that reflects realities of the clinical research environment and economic imperatives. The Task Force has focused its efforts on issues related to the structure, function, and workload of IRBs; initial and ongoing review of trials; and conflicts of interest of those involved in the design and operation of clinical trials.

The operational assumptions of the Task Force are that effective review and oversight is much more than an administrative requirement of research. Along with an investigator who adheres to the highest standards of clinical research, research oversight is a critical element to ensuring the scientific and ethical integrity of clinical research and to maintaining the public trust in this crucial enterprise. Public trust is necessary not only for continued public funding, but also for confidence in the treatments that research supports and for enrollment in clinical trials. IRBs play a central role in research oversight, but should not be the only overseers. Researchers, institutions, and trials participants all must play an active role in ensuring the ethical and scientific integrity of clinical research. It is critical to note, however, that these roles are not equal, especially when it comes to trial participants who depend on the expertise and care of the investigator. The role of investigators and all research staff to ensure the ethical and scientific integrity of research cannot be emphasized enough.

DISTINGUISHING FACTORS OF ONCOLOGY CLINICAL RESEARCH

Clinical cancer research has numerous components. Each raises different challenges for proper oversight, and each is crucial for successful advances in cancer prevention and care. Features emphasized in clinical cancer research that must be considered in a policy addressing research oversight are indicated below:

1. Because virtually all trial participants have cancer, often with life-threatening dimensions, or are at high risk of recurrence, considerations of risk are different than those for healthy participants or participants with other diseases.
2. Clinical trials are integrated into the treatment process for cancer patients and placebo-controlled trials are relatively infrequent.
3. The complexity of cancer trials has stimulated many institutions to require a formalized scientific review process before submission for IRB review. In addition, designation as an NCI cancer research center requires scientific review of all protocols before presentation before the IRB.
4. Clinical cancer research is accomplished through a complex array of trials that range from phase I through phase IV. They are often implemented as national trials at multiple institutions, and range from investigator-initiated trials to those sponsored by the NCI-funded National Cancer Cooperative Group system and trials supported by industry.

PRINCIPLES/GOALS OF THE STATEMENT

In generating this policy statement, ASCO is reinforcing the importance of clinical research with human participants as the

only way to make important clinical advances. This type of research must be supported by the medical community, and most importantly, by present and future trial participants and their families. To do so, a number of goals must be achieved. These are to:

1. Ensure safety precautions for clinical trial participants and their fully informed consent.
2. Ensure the validity and integrity of scientific research.
3. Enhance the educational training of clinical scientists and research staff to ensure the highest standards of research conduct.
4. Promote accountability and responsibility among all those involved in clinical research (not just those serving on IRBs, but also institutional officials, researchers, sponsors, and participants) and ensure support for an effective oversight process.
5. Enhance the professional and public understanding of clinical research oversight.
6. Enhance the efficiency and cost-effectiveness of the clinical research oversight system.

RECOMMENDATIONS

Centralized Review

1. *Current System: Emphasis on Local Review of Clinical Trials.*

The existing system for reviewing clinical trials emphasizes the importance of local review. Local IRBs play the pivotal role in oversight of the majority of clinical research in the United States. Since the creation of the federal Common Rule, clinical research has expanded considerably, especially commercially sponsored research, as novel agents requiring more complex development are brought to the clinic for evaluation. In addition, there has also been a shift from single-center studies to multicenter studies. These factors and many more (including the additional work necessitated by the federal Privacy Rule⁵) have caused most IRBs to be overwhelmed by their responsibilities and left with insufficient institutional resources to carry them out.

The spectrum of institutions that host clinical cancer research is very broad. It ranges from physician practices to small community hospitals, regional medical centers, academic medical centers, and federally designated comprehensive cancer centers. In addition, clinical trials are increasingly being conducted in sites outside the United States and Western Europe, where the elements of institutional review vary and additional issues, such as trial participants' access to treatments after the trial, must be considered. This wide array of research settings makes it clear that some institutions will be well equipped with personnel able to perform these tasks, and others may not have the expertise.

Nonetheless, the basic charge to review boards is the same. Their responsibilities include:

- a. Ensuring that risks to research participants are minimized and that risks are reasonable in relation to anticipated benefits.
- b. Ensuring that the research plan makes adequate provision for monitoring the data collected to ensure the safety of research participants, and that there are adequate provisions to protect the privacy of research participants and to maintain the confidentiality of data.
- c. Ensuring that the consent document contains standard elements and that patients give fully informed consent.
- d. Ensuring that research participant selection is equitable and that appropriate protections are in place for vulnerable research participants.
- e. Conducting ongoing assessment of risks, potential benefits, and the adequacy of the consent document, by periodic rereview of the research and assessment of adverse events.
- f. Assessing the competency of investigators to conduct research and the institution's resources for conducting the trial in a safe manner.

2. *Current System: Widely Perceived Problems*

- a. *Duplication of Initial Review:* As mentioned above, cancer clinical trials are often implemented as national trials conducted at multiple institutions. The current system of local review means that initial review of a single trial is duplicated at hundreds of institutions throughout the country. ASCO envisions a centralized system that will avoid duplicative reviews of the same protocol. A single central review would take place, allowing local institutions to accept that initial review. In the ideal situation, the central review would require use of the same CRB application, protocol, and consent form, thereby creating administrative simplification.
- b. *Lack of Review Board Members With Expertise:* Some institutions may lack review board members with the expertise to conduct a thorough review. This is a concern particularly with regard to finding nonscientific, community members who can serve as effective advocates for patients. Using CRBs would ensure the involvement of board members with nationally recognized expertise in scientific and ethical review.
- c. *Analysis of AEs:* The current system involves fractured analysis of AEs across trials sites. Local IRBs wade through reams of AE reports from other trial sites and are often provided with no guidance or evaluation, particularly as it relates to identifying what qualifies as an AE and the relevance of a single AE in the context of the entire trial population. The central review system would monitor the AEs at all the sites and provide an evaluation of AEs for each of the local IRBs. This CRB report will give the local IRBs much-needed information about the number of AEs compared with the overall number of trial

participants, and the significance and relevance of the AEs to the investigational intervention.

3. *Centralization of IRB Review: A Proposal*

ASCO recognizes the considerable workload and insufficient resources currently plaguing local IRBs. The efficiencies of central review have the real potential to reduce time and expense for the local IRB. Central review would free up resources and time currently devoted to initial review, and would allow the local IRB to devote more time to ongoing onsite review and ensuring compliance with the institution's goals and mission.

Collectively, the tasks outlined in item A1 are challenging for a system that is heavily used, requires greater and greater specialized expertise, and is under serious financial pressure.

To address this problem, ASCO proposes centralizing the review of cancer clinical trials in a step-wise fashion. An important first step is to focus on the review of NCI cancer cooperative group trials by CRBs. The NCI cancer cooperative groups are a good starting point for this initiative because their mission is to conduct a single trial at many trial sites. These trials go through a rigorous process of scientific review before submission to any IRB. An ethical review of these trials could also be done at a centralized level. This would ensure consistency in quality of review, avoid duplication, and create cost and time efficiencies in the system.

Central review would also provide greater consistency across trial sites to improve the data gathered through trials and implement more quickly and consistently protocol and informed consent amendments. The CRB would have dedicated and experienced IRB staff. It could also use the top experts in the field to provide improved analysis of scientific and ethical issues. In addition, central review has the real potential to avoid the significant costs in the current oncology cooperative group system incurred by reviewing each trial at hundreds of institutions.

If deemed to be successful, the CRB could next expand its scope to include multi-institution, industry-sponsored trials.

4. *Current CRB Efforts*

Several efforts are underway to centralize trial review, some of which are proprietary and another of which is based at the NCI. The NCI project is to be lauded for its goals, but its implementation has not been an unalloyed success. The CRB initiative that ASCO proposes is not in addition to the NCI pilot CRB, but would be an expansion and improvement of that system. ASCO is proposing a far-reaching pilot project that will include all phases of trials sponsored by the NCI-funded cooperative groups. The ASCO approach to developing the CRB would begin with a detailed evaluation of the NCI pilot project to determine what lessons can be learned. The considerable challenges raised by this type of radical change must first be understood and addressed.

The considerations in item 5 should help avoid some of the pitfalls of other pilot projects.

5. *Enacting the Pilot Program for Centralized Review*

- a. Local IRB chairs and other stakeholders must be involved in the creation of the CRB mechanism to ensure that they will have a sufficient level of trust in the system to effectively use the central review mechanism.
- b. The nation should be divided into regions, each of which would be served by a regional review board. A single regional review board would be designated to review a trial.
- c. Several alternatives are envisioned in establishing such entities. One possibility would be for the federal government to publish a request for applications (RFA) to solicit proposals from organizations that wish to compete for this role.
- d. Of paramount importance is that the OHRP, the NCI, and the FDA sanction the creation and functioning of the CRBs to provide assurance to participating local institutions that the CRB will meet the requirements of the federal regulations. One of the significant factors diminishing local institutions' willingness to participate in a CRB is concern about potential liability that could result from perceived noncompliance with federal regulations. OHRP, NCI, and FDA can provide the assurance that institutions may need to agree to participate.
- e. The CRB should work toward the advent of standard forms for application to the review board, informed consent, and AE reporting. This modification would build efficiency and cost-effectiveness into the system.
- f. Local IRB members from the medical/scientific staff should be educated in the requirements for trial oversight during the implementation phase to oversee whatever mechanism has been elected to monitor trials performance.
- g. An appropriate appeals process must be incorporated into a centralized review system to diminish the likelihood of arbitrary or capricious decisions regarding a potentially important clinical experiment. The advent of regional review boards would facilitate the development of an appeals process and thereby ensure the fairness of this initiative.
- h. The precise division of responsibility between CRBs and local IRBs is a broad topic that requires consensus of the parties involved. As a starting point for this discussion, ASCO offers the suggestions in items 6 and 7.

6. *Responsibilities of CRB*

The CRB would be responsible for:

- a. Conducting initial review of the protocol and consent form.
- b. Evaluating AEs (with the assistance of a data safety monitoring board or data safety monitoring commit-

tee) and promptly distributing AE reports to the participating local IRBs.

- c. Reviewing and recommending changes to the consent form on the basis of evolving information as the trial is conducted.

7. *Responsibilities of Local IRB*

In the context of the CRB pilot, participating local IRBs would be responsible for:

- a. Ensuring ample resources were available at the institution for conducting the clinical trial.
- b. Assessing the competency of the local investigator.
- c. Ensuring proper reporting of adverse events (AEs) to the data safety monitoring board, CRB, trial sponsor, and government authorities.
- d. Ensuring that there is a mechanism for auditing of the onsite trial to ensure investigator and institutional compliance with the highest standards of conduct for clinical research. Essential elements of the audit process include:
 - i. Trial participant eligibility;
 - ii. Informed consent: use of the proper form and process;
 - iii. AE reporting;
 - iv. Protocol compliance;
 - v. Toxicity; and
 - vi. Response confirmation.

The IRB could conduct certain elements of the audit specific to the trial being conducted onsite, but would likely need to use a data safety monitoring board or departmental committee to perform other elements of the audit.

ASCO envisions the proposed pilot system of centralized review as voluntary, allowing an institution to choose whether to use the CRB review or continue its current mode of operations. If an institution chooses to complete its own local review, however, they would still be required to submit any AEs occurring at their trial site to the CRB for review. The centralized analysis of AEs will be most successful if it incorporates review of AEs from all trial sites.

8. *Trial Monitoring*

The use of centralized data safety monitoring boards (DSMBs) or other types of data safety monitoring committees should be mandated for all phases of the cooperative group, multi-institution trials to provide analysis of AEs and determine whether a trial should be discontinued. AEs should be reported to the CRB, the DSMB, and the trial sponsor. The CRB or DSMB would then be responsible for reporting back to the local IRBs, the trial sponsor, and investigators promptly (within 24 hours of notice); providing analysis of the AE; and recommending any changes to the consent form. The local IRB would remain responsible for tracking AEs that occur at their institution.

9. *Evaluation*

The criteria for evaluating the success of the pilot program should be specified through consensus by the convening parties involved in its creation. Widespread implementation after the pilot phase would depend on its thorough evaluation. If deemed to be successful, the CRB could expand its scope to include multi-institution, industry-sponsored trials.

10. *Conclusion*

Success of centralized review depends on its broad implementation. The widest range and largest number of institutions should affirm and adopt centralized review. Achieving the goal of broad implementation requires the collective “buy-in” that will only come with input from local IRB officials, NCI, the cooperative groups, and professional societies, such as ASCO. HHS and its relevant agencies should provide relief from institutional liabilities related to the transition from local to centralized trial review. This is an absolute prerequisite for gaining broad-based acceptance of this concept. Toward these ends, ASCO recommends convening a meeting with participation of these stakeholders to develop a process that addresses the concerns of the many constituencies involved in the clinical trials review process. Consensus development would recognize the need for thoughtful review of optional models and of the design of processes to implement so radical a modification of the oversight process.

In summary, centralized review would provide for greater consistency across the trial sites to enable review boards and investigators to implement more quickly and consistently protocol and informed consent amendments. The CRB would have dedicated and experienced IRB staff. It could also use the top experts in the field to provide improved analysis of scientific and ethical issues. In addition, central review has the real potential to avoid the significant costs in the current oncology cooperative group system incurred by reviewing each trial at hundreds of institutions.

Education and Training

A well-trained clinical investigator must understand all aspects of research oversight. The integrity of the proposed system of overseeing clinical trials depends on this.

Toward this end all participants in the clinical research process should receive comprehensive education and training to ensure that they are aware of the elements and steps necessary to ensure the safety of research participants and the scientific integrity of research. Investigators should be evaluated and continued approval to conduct research should be dependent on demonstrating competency in research oversight. The need for education and training must be stressed at the highest levels of an institution to ensure that all parties are aware of its importance. The federal government has established educational requirements for federal grantees. It is up to institutions, professional

societies, and patient advocacy groups to help those in the research process meet and exceed the requirements.

As ASCO has done in many other clinical education areas, the Society should develop programs and materials on the necessary elements of clinical trials oversight and the conduct of clinical research, taking into account the nationally recognized programs already in existence. These programs and materials should:

1. Address the following major areas: ethical and scientific standards for the conduct of research, protection of human participants, communicating with patients during the informed consent process, and conflicts of interest. Courses can be conducted online, but attendance at lectures and other in-person settings should be encouraged.
2. Encourage education for all people who participate in the clinical trials system, including investigators, research staff, data managers, and IRB members.
3. Encourage further development of patient education materials about participation in clinical trials. The materials should help potential trial participants formulate questions to ask during the informed consent process and provide information on the payments that researchers receive to conduct clinical trials. Education of potential trial participants and information sharing with trial participants during the process is a key element to transforming research “subjects” into research “participants.”
4. Recognize excellence in the conduct of research through awards to the most successful investigators and institutions.

ASCO should work with other organizations engaged in the creation of education programs on clinical research to create guiding principles and core elements for a curriculum on the conduct of clinical research, with particular focus on a research process that is both scientifically and ethically sound. ASCO should continue to expand sessions at its Annual Meeting to provide opportunities for continuing medical education in this area.

Informed Consent

ASCO believes that the nature of the informed consent process needs to be changed to refocus on the primary goal—educating potential participants about trial participation and fully informing them of the risks and benefits of the trial to allow them to make an informed decision about enrolling onto a trial. The informed consent process has real potential to overwhelm patients. This is especially true because the evolving environment of clinical research seems to place emphasis on the informed consent document as a regulatory or legal protection for the institution and investigator. As a result, the language used in informed consent documents is increasingly legal and scientific in nature. Experts agree that the documents are difficult for potential trial participants to comprehend because of this complex, legalistic language. In addition, the information disclosure required by the authorization process contained in the federal Privacy Rule will serve to create more complexity for the patient. With these factors in mind, ASCO believes that the following considerations should govern the informed consent process:

1. Clinical investigators should be responsible for providing clear and appropriate information to fully educate poten-

tial trial participants and their family members, as appropriate, about the risks and benefits of enrolling in clinical research without overwhelming them during the informed consent process.

2. Review boards should place primary review and oversight on the informed consent process, not chiefly on the informed consent document. Review boards can accomplish this by stressing to all research staff the key elements of the informed consent process and then following up with researchers concerning their implementation of these key elements. This information and follow-up would help create an interactive dialogue between review boards and researchers on the importance of informed consent.
3. When a patient's condition and treatment regimen allow, the potential trial participant should have a sufficient and appropriate interval of time between the patient's introduction to the trial and when he or she is asked to give consent for enrollment. This interval should give the patient time to fully review trial documents and confer with other people.
4. Where possible, the consent form should be simplified to optimize comprehensibility and clarity, reduce intimidating language, and place potential benefits and risks in a proper context. ASCO recommends that NCI and the FDA work with the OHRP to simplify the consent form, particularly in light of the authorization requirements of the federal privacy rule.
5. Consent forms should use the terms "drug," "agent," or "device" to describe the intervention, rather than the terms "treatment" and "therapy." These terms should be modified by language indicating that the intervention is investigational. Possible modifiers include "investigational," "unapproved," "study," or "research."
6. Consent forms should describe the way in which the clinical investigator, his or her staff, and the institution are being compensated by the research sponsor for the time and efforts of conducting the trial. Consent forms should also inform the potential trial participant whether the trial is being sponsored by a publicly or privately funded organization, and, if privately funded, whether the sponsor is planning to market the product under investigation. Finally, consent forms should include information about the review of the financial interests of the investigator, his or her staff, and the institution.
7. The informed consent process should reasonably accommodate the cultural and social diversity of potential trial participants.
8. To the greatest extent possible, all documents presented to potential trial participants during the consent process should be uniform in structure and employ a template with standard language and common elements. The NCI has done exceptional work in this area by producing a model consent document.
9. The informed consent process should be a dynamic process that does not end with the trial participant's

signature on the informed consent document. Investigators and research staff should continue to inform trial participants of AEs or other developments that significantly alter the risk-benefit equation presented in the original informed consent documents and process.

10. The informed consent process should use a variety of communications tools to help inform potential trial participants. Alternative means of conveying information as part of the consent process should be explored; for example, video, DVD, CD-ROM, internet-based material, and other electronic media. Public and private research organizations should provide funding to develop new types of communication methods and examine which types of communication work best.

Federal Oversight

The federal government has increased its role in the oversight of clinical research, both by elevating OHRP to the HHS Secretary's office and by creating the FDA Good Clinical Practice Program. Through these efforts, the federal government is playing a greater role in education and proactive compliance. These activities are helpful and should be increased to enhance the ability of human research protection programs to improve their oversight and self-assessment. Additional guidance in specific areas would also enable greater efficiency in the system and promote greater nationwide consistency in the protection of research participants.

The roles and authorities of these two offices and the rules regarding HHS-supported research and research subject to FDA oversight differ in significant ways. These differences make it difficult for IRBs, researchers, and research participants to understand proper procedures. Uniformity of the regulatory approaches would create greater efficiency and consistency in the human research protection system. Ultimately, these efficiencies would allow members of the system to provide greater focus on the ongoing review of trials.

1. *Facilitate Centralized Review:* The Public Health Service (PHS) and FDA regulations should be modified to alter emphasis on local IRB review and allow greater use of CRBs. OHRP should issue guidance helping to immunize local IRBs from potential liability should they choose to use a CRB. Consistent with the recommendations of this policy, HHS, FDA, and NCI should provide specific regulatory authority for a CRB for NCI cooperative group trials.
2. *Promote Research on Human Protection in Clinical Research:* The federal government should work in partnership with stakeholders in clinical research, including academic institutions, professional societies, patient advocacy groups, and trial sponsors, to perform an assessment of the need for outcomes research regarding the current system to protect human research participants. Funding should be made available to study the effectiveness of current PHS and FDA regulations for the oversight of clinical research and what changes would improve the system. NIH should be commended for the \$28.5 million it has made available to institutions to

strengthen oversight of clinical research. This type of activity should be funded on an ongoing basis.

3. *Coordinate and Streamline Regulations:* HHS should streamline and unify PHS and FDA clinical research regulations, particularly to provide uniform expectations and procedures for AE reporting. The regulations should specifically allow for use of a CRB and central DSMB for analysis of AEs and dissemination of AE reports. If HHS is unwilling to streamline the regulations, Congress should pass legislation directing the Department to issue new regulations.
4. *Extend the Common Rule:* Congress should pass legislation to extend the Common Rule protections to all clinical research conducted in the United States and research conducted by U.S. institutions in other countries, regardless of the sponsor of the research.

Although the focus of the above discussion is on the U.S. system, the problems being addressed are universal. Where appropriate outside the United States, similar changes in regulations pertaining to research oversight should be undertaken to promote the protection of trial participants and facilitate the advent of CRBs for multi-institutional, international clinical research.

Resources Supporting Clinical Research Infrastructure

Lack of adequate support for the infrastructure to support clinical research is a critical problem and has been recognized in reports issued by the HHS Inspector General, the GAO, the NIH, and other private organizations. In addition to established requirements of oversight bodies, new regulations often represent unfunded mandates, which, although well meaning, exceed the capacity of even the most dedicated institution. Lack of adequate financial and political support endangers the research oversight process and contributes to crisis situations that damage public trust in, and support of, clinical research. Ultimately, these crisis situations likely result in an institution devoting more resources to repair their human research protection program than they would have devoted initially to maintaining a properly functioning system. Institutions should dedicate sufficient support and resources to their entire research oversight and clinical trials support system to ensure the highest standards of ethical and scientific research conduct.

1. *Funding the Infrastructure:* A robust oversight system requires the dedication of significant resources. Strong consideration should be given to the way that the entire human research protection system is funded both by the federal government and private industry. Whether it be a centralized review process or an institutional review board, adequate financial resources must be allocated in order to assure that research oversight is performed effectively and efficiently.
2. *Incentives for Faculty Service in the Oversight System:* Faculty members or other members encounter a number of disincentives for service in an institution's oversight system, whether on a review board or conflict of interest committee. These may include: (a) lack of salary support; (b) pressure to generate reimbursement and research

dollars for their department; (c) lack of academic validation for oversight work; (d) legal exposure for making research oversight decisions; and (e) political pressure (from colleagues or administration) to facilitate approval of research.

Institutions should provide incentives for faculty members to encourage their service on central or institutional review boards, such as providing continuing medical education (CME) credit or income for service and compensating academic departments for lost time. Promotion and tenure committees should be strongly encouraged to view IRB service favorably when making their decisions. ASCO should explore ways to provide professional acknowledgment for IRB service. ASCO should also encourage the submission of manuscripts related to aspects of ethical review of oncology protocols.

3. *Involvement of Community Members:* Institutions should strongly consider exceeding the federal requirements by having more than one community member serve on their IRB and requiring that at least one community member be present during consideration of protocols and votes. In addition, review boards should provide adequate training for community members who serve on their board.
4. *Institutional Commitment to Independent Review:* Institutions should make it clear to their stakeholders (including faculty, researchers, and administration) that protection of research participants is a prime concern and that, be they central or institutionally based, the independence of review boards must be ensured.
5. *Evaluation of Review Boards:* ASCO encourages institutions to use performance measures to evaluate the operation of their review boards. These measures should involve tools for self-assessment to enable the review board to identify areas of success and opportunities for improvement.

Conflict of Interest

There is no greater threat to the integrity of the clinical research enterprise than the appearance or reality of a conflict of interest—be it financial, academic, or scientific. Out of a desire to establish what it believes should be the standard for clinical research, ASCO has adopted a revised conflict of interest policy. This new policy builds on the principles and requirements set in the policy ASCO adopted in 1996. Those submitting research for ASCO publication or presentation at ASCO events must comply with this new standard on the policy's effective date.

The revised ASCO policy is built, in part, on the following recommendations. In the ideal situation, institutions would adopt uniform conflict of interest policies that contain the following essential features:

1. Uniform requirements for all clinical research, regardless of the trial's sponsor.
2. Disclosure of all financial interests of investigators, research staff, and members of the research oversight system to an appropriate standing committee for review. Disclosures should be made directly to the committee,

rather than through a department chair or other institutional official.

3. A summary conflict of interest report from the review committee should be issued to the central or local review board. A review board should not complete review of a trial until a review has been received from the conflict of interest review committee. Appropriate disclosure of interests should be made to publication editors, to the organizers and audiences of presentations, and to the participants enrolled in the trial.
4. Consent forms should describe the way in which the clinical investigator, his or her staff, and the institution are being compensated by the research sponsor for the time and efforts of conducting the trial. Consent forms should also inform the potential trial participant whether the trial is being sponsored by a publicly or privately funded organization and, if privately funded, whether the sponsor is planning to market the product under investigation. Finally, consent forms should include information about the review of the financial interests of the investigator, his or her staff, and the institution.
5. The conflict of interest review committee and the review board should determine the information that should be disclosed to those considering and those already enrolled in the trial.
6. Clinical investigators should adhere to the standards espoused in the ASCO policy statement on conflicts of interest in research and should attempt to have them adopted by their home institutions.

It has been acknowledged that institutions are also susceptible to conflicts of interest, but that issue is beyond the scope of this policy statement. Analysis of institutional conflicts of interest is strongly encouraged and should be assessed by independent bodies with expertise in this area.

CONCLUSION

Clinical research is an engine of progress. It is the essential mechanism by which scientific advances are translated into new and effective therapies for all human maladies. The explosion of knowledge in cancer biology has created extraordinary opportunities for clinical advances.

To take optimal advantage of these opportunities, a clinical trials process is required that provides ready and open access to all potential trial participants and is organized in a manner that ensures the highest ethical and scientific standards in the conduct of clinical trials and optimal oversight of human protections. This process should be implemented in the most efficient manner possible to maximize resources devoted to clinical research and to speed access to safe and effective cancer therapies.

In this policy statement ASCO has proposed a revision to the clinical trials oversight process that offers more prompt access to clinical trials, more effective oversight of the conduct of trials, avoidance and management of conflicts of interest, and potential cost savings. The change to a system built around centralized review of clinical trials is a departure from the long-held standard of local institutional review. For this reason, ASCO has

emphasized several features of such a system. These include starting with a clinical trials system of unimpeachable integrity; that is, that of the NCI-funded cooperative groups. Should the system be judged a success, it should be expanded to multi-institution trials of all types. In lieu of a focus on initial review, local IRBs can devote a renewed emphasis to overseeing implementation of the trial and the safety of research participants at the local site.

This modified system has the potential to reduce the massive duplication of having the same trial reviewed in hundreds of institutions, ensure uniform scientific review by national experts, streamline the flow of information from the CRB to local sites regarding AEs, and make efficient use of financial resources for trial review. To achieve this degree of change will require the support of the federal bodies overseeing the clinical research enterprise; that is, the FDA, OHRP, and NIH. Ideally, these agencies would coordinate their regulatory approaches to make them as uniform as practicable and provide an unambiguous signal that, for clinical trials meeting certain criteria, review by a central mechanism is preferred.

ASCO and other societies committed to the clinical research enterprise must educate their membership about the principles underlying ethical clinical research and coordinate with advocacy groups to ensure that the clinical trials process meets the needs of the patients whom it is meant to serve.

By intention, this policy statement does not attempt to address implementation of the proposals outlined above. This is a complex and challenging task that demands involvement by all stakeholders in the clinical research process. ASCO anticipates working with all those involved in the clinical research system to take the necessary implementation steps.

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APPENDIX

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REFERENCES

1. Department of Health and Human Services, Office of the Inspector General: Institutional Review Boards: A Time for Reform, June 1998; Institutional Review Boards: The Emergence of Independent Boards, June 1998; Institutional Review Boards: Their Role in Reviewing Approved Research, June 1998; Institutional Review Boards: Promising Approaches, June 1998; Protecting Human Subjects: Status of Recommendations, April 2000; Recruiting Human Subjects: Pressures in Industry-Sponsored Clinical Research, June 2000; FDA Oversight of Clinical Investigators, June 2000; Recruiting Human Subjects: Sample Guidelines for Practice, June 2000. <http://oig.hhs.gov/reports.html>
2. U.S. General Accounting Office: Scientific Research: Continued Vigilance Critical to Protecting Human Subjects. HEHS-96-72, March 1996. <http://www.gao.gov>
3. Bell J, Whiton J, Connelly S: Evaluation of NIH Implementation of Section 491 of the Public Health Service Act, Mandating a Program of Protection for Research Subjects. June 15, 1998. http://ohrp.osophs.dhhs.gov/hsp_report/hsp_final_rpt.pdf
4. U. S. Code of Federal Regulations title 45 part 46. <http://www.access.gpo.gov/nara/cfr/index.html>
5. Federal Register 65:250, 12/28/2000 pp 82462-82829, and Federal Register 67:157, 8/14/2002 pp 53182-53273. http://www.access.gpo.gov/su_docs/aces/aces140.html