

ASCO SPECIAL ARTICLE

American Society of Clinical Oncology: Background for Update of Conflict of Interest Policy

By the American Society of Clinical Oncology*

CONTINUED PROGRESS against cancer depends on the integrity of the clinical research enterprise. If physicians, patients, and the general public are to maintain confidence in the outcomes of clinical cancer research, the highest standards should be required of those conducting the research. It is for this reason that the American Society of Clinical Oncology (ASCO) has undertaken a process of review and reform of its existing conflict-of-interest policy.

Background: Arguments for Stronger Policy

ASCO's current policy on conflicts of interest, adopted in 1996, is a strong one, as discussed below. However, in the ensuing years, clinical research has become increasingly dominated by private rather than public investment, presenting many more opportunities for questions and concerns about the financial interests of the physician investigators conducting the trial. While biomedical research funding through the National Institutes of Health (NIH) has increased substantially during the last decade, the overwhelming majority of NIH-funded research is not clinical, or patient-oriented. During the same time frame, the pharmaceutical and biotechnology industries have invested many billions of dollars in clinical research.

The increase in industry funding may be particularly pronounced in cancer therapies, where the industry trade association now reports more than 400 new products in various stages of development. Thus, industry is necessarily more involved in the clinical cancer research effort than ever before. At the same time, there is heightened awareness among both physicians and patients of the important role played by clinical trials in the comprehensive treatment of many cancer patients. A situation is created in which the influence of industry seems almost unavoidable in the arena of quality cancer care. In such a setting, every effort should be made to ensure the integrity of the research without imposing undue burdens. Therefore, ASCO determined that review of its already stringent policy was timely and necessary, with an intention to make that policy even stronger in the interest of enhancing public confidence in clinical cancer research.

A Multiplicity of Conflicts Policies

In the interim between ASCO's first adoption of a conflict of interest policy in 1996 and the present, a number of different public and private institutions have articulated their own conflicts policies. Unfortunately, these policies are uncoordinated and inconsistent with one another. Although each

institution is expected to establish its own policies, the variety of approaches and stringency is confusing, both to regulated persons and to the public at large, and does little to build public confidence. For example, components of the United States Department of Health and Human Services (HHS), such as the Food and Drug Administration (FDA) and the Public Health Service (PHS), including NIH, have dramatically different requirements for disclosure of financial interests.

As found in research conducted informally by ASCO staff, the range of requirements among different institutions, private and public, is impressive. Among private entities, the threshold for disclosing financial interests can vary from "any amount" no matter how small to substantial amounts, such as \$100,000 at one institution. Governmental regulations include FDA requirements to disclose payments from a sponsor in excess of \$25,000 during a clinical trial and 1 year after, and holdings of more than \$50,000 equity interest in the sponsor, as well as NIH requirements for disclosure of payments in excess of \$10,000 per year or of equity holdings in the sponsor in excess of \$10,000 per year. Aside from these inconsistent requirements, an investigator may be subject to additional variations in mandates from his or her own institution or from regulations imposed by the state in which the research is conducted. Finally, some trade associations and medical societies have developed their own, differing, conflict-of-interest policies.

In the face of this inconsistency and recognizing its special responsibility as the leading medical society for physicians involved in clinical cancer research, ASCO has undertaken development of an enhanced conflict-of-interest policy de-

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signed to meet the needs of oncology in a research environment increasingly oriented toward private sector initiatives.

Emphasis on Disclosure as Governing Principle

ASCO's new policy is dependent on an aggressive disclosure policy to facilitate transparency and accountability in clinical cancer research. The ASCO policy requires disclosure of any financial interest, with the sole exception of de minimus payments totaling less than \$100. This policy cuts through the wide variety of different financial thresholds requiring disclosure in policies enforced by many different government and private research entities, and establishes a principal that *any* financial interest except the most minimal should be disclosed publicly.

Such disclosure will be required in connection with any ASCO activity, including publications, scientific or educational presentations at ASCO-sponsored meetings, and participation in the work of ASCO boards and committees. Through full disclosure of financial interests, ASCO seeks to enhance the ability of ASCO members and others taking advantage of the Society's scientific and educational programs to assess fully the quality of presentations, including the objectivity of those involved. The goal is a more open process designed to facilitate the exchange of information and opinion regarding clinical cancer research.

Prohibitions for Defined Investigators

ASCO recognizes that, in the current clinical research environment, it would be counterproductive to institute a conflict of interest policy that resulted in the routine exclusion of significant numbers of investigators from various research activities. An overly regulatory approach to the management of potential conflicts might discourage participation either in ASCO-sponsored activities or in vital industry-funded research. In general, qualified physician investigators should be permitted to do both. Under both the existing ASCO conflicts policy and the new policy, physician investigators may do so except in very limited circumstances.

Specifically, ASCO believes that certain practices involving financial inducements to particular clinical trial results should be barred. These include finders' fees and bonuses for accrual, making payments contingent on particular results, or suppressing unfavorable results from publication. Such practices are considered inconsistent with the integrity of the clinical trials process and will be precluded under the new policy.

In addition, individuals holding leadership positions—principal investigators (PIs), members of the trial's executive committee, and members of the data safety and monitoring board (DSMB) for the trial—will not be permitted to receive certain specified payments or benefits from the private-sector trial sponsor during the course of the trial and before publication of trial results. Such restrictions are in no way meant to question the ethics of these individuals in leadership roles, but rather are intended to ensure public confidence in

their objectivity as they undertake important management and review functions in the clinical trial. Moreover, the policy anticipates that exceptions to these restrictions may be granted by ASCO's Ethics Committee and Board of Directors in certain defined situations calling for a more flexible approach. For instance, when the inventor of a new technology is translating it into clinical research, establishing a data safety monitoring board that ensures integrity of the data and safety of research participants may be the appropriate safeguard. Similarly, the restrictions on principal investigators or members of a trial's executive committee are not applicable to trials sponsored by the NIH.

Differences Between Old and New Policies

ASCO's first conflict of interest policy in 1996 was an important step forward, implemented at a time when many medical groups had not yet addressed the issue. Like the new policy, the 1996 policy depended primarily on disclosure as a means of managing potential conflicts. It was specific and comprehensive in its disclosure thresholds, requiring disclosure of ownership interest of \$1,000 or more in a publicly traded company, as well as honoraria in excess of \$2,000 per year or \$5,000 over a 5-year period. Disclosure was required of any ownership interest in a privately held company and of any paid expert testimony. The policy recognized, without identifying them specifically, that there might be some financial interests so problematic that disclosure alone might not suffice and disqualification might be required. In those rare undefined circumstances, it was contemplated that the ASCO Board of Directors could take corrective action, but such action was left in the complete discretion of the Board without any articulated standards. Board action was specifically authorized against members failing to make the required disclosures.

The 1996 policy has worked well. Disclosure of financial interests is built into board and committee activities, and is very specifically mandated in connection with ASCO publications and presentations. However, in an era of heightened scrutiny of relations between physician investigators and industry sponsors, the Society determined that the existing disclosure thresholds were too generous and that an argument could be made that virtually *all* financial interests should be disclosed. In addition, the absence of a specific process for identifying situations where disclosure alone was inadequate made enforcement unlikely, and in fact no such situation has been identified under the 1996 policy. To meet these perceived shortfalls, the new policy will require expansive disclosure, and will make clear the circumstances in which disclosure alone will be insufficient and where prohibitions may be imposed.

Process for Development of New Policy

Review and possible revision of ASCO conflict of interest policy was undertaken by a task force under the jurisdiction of

ASCO's Public Issues Committee. Members of the task force, assisted by ASCO staff, considered the current conflicts policies of a variety of entities involved in clinical cancer research, including cooperative groups, major cancer centers, and other academic health centers. Conflicts policies of several medical societies, other professional organizations, and federal government agencies were also reviewed.

With the fairly stringent requirements of the existing 1996 policy as a starting point, the task force drafted a new policy with much greater disclosure requirements and much more specificity as to the rare circumstances in which disqualification rather than mere disclosure will apply. Enforcement mechanisms and an exceptions process were also added. (Table 1 compares the old and new ASCO policies with those of the Association of American Medical Colleges, the FDA, and PHS.)

The draft of the new policy was reviewed on a number of occasions by the Public Issues Committee and in three different meetings of the Board of Directors. The Board of Directors also took the unprecedented step of placing the draft policy on the ASCO Web site to solicit comment from members. After numerous refinements to address concerns of those submitting comments (both the general membership and the Board of Directors), the draft policy was adopted unanimously by the Board.

Scope of New Policy

The new policy applies specifically only to ASCO members, employees, or staff, and those who seek to participate in ASCO activities, such as ASCO scientific or education programs, or submit articles for publication in the *Journal of Clinical Oncology*. Thus, those who fail to comply with the terms of the new policy could be foreclosed from participation in those activities or even from membership in ASCO. The policy specifically recognizes that ASCO has no enforcement authority over the conduct of clinical trials generally, over the process of informed consent for trial participants, or over management within other institutions, such as cancer

centers, of trial-related activities. Nevertheless, the hope is that the new ASCO policy will become a model for adoption of similar policies in other clinical cancer research settings.

Implementation Issues

Some may regard the adoption of the new conflict-of-interest policy as a cause for concern with the potential to disrupt ongoing relationships. It is important to reiterate that the overwhelming majority of actions required under the new policy involve no more than full disclosure of financial interests. Significant disclosure is already required under the current ASCO conflicts policy, and additional disclosure should impose no meaningful new burdens. For those in leadership positions in clinical trials, attention must be given to ensuring that financial interests are divested before the effective date of the new policy.

Recognizing that such adjustments may be required, the new policy provides generous time for implementation. The new policy does not become effective until 12 months after this publication in the *Journal of Clinical Oncology* and will apply only prospectively after the effective date. In addition, restrictions on financial interests held by those in clinical trials leadership positions will apply prospectively only to trials beginning accrual subsequent to the effective date.

CONCLUSION

ASCO takes very seriously its leadership role in clinical cancer research. With the adoption of the new conflict-of-interest policy, ASCO has enhanced its already strong position on conflicts as they may arise in the context of ASCO activities. However, perhaps equally important, ASCO has in effect issued a challenge to all other entities in clinical research to match the rigor and intensity of ASCO's own policy as those organizations issue guidance on issues of disclosure and disqualification. It is hoped that such policies will encourage participation in clinical trials and eventually progress against cancer by bolstering public confidence in the integrity of clinical cancer research.

Table 1. Comparison Chart of Conflict-of-Interest Policies

Issue	ASCO ¹	AAMC ²	PHS ³	FDA ⁴
Covered individuals	<p>Those who:</p> <ol style="list-style-type: none"> Are members of ASCO Are employees or staff of ASCO Seek to make presentations at any ASCO meeting or to submit to any ASCO-sponsored publication, or Participate on the ASCO Board of Directors, committees, and task forces, or in any volunteer activity in an official capacity for the Society <p>A person engaged in the above activities must also make disclosure for the following people:</p> <ol style="list-style-type: none"> Spouse Dependent children Adult children who are employees of the sponsor of the trial Anyone who shares income with person engaged in above activities 	<p>Faculty, faculty agent, staff, student, fellow, trainee, or administrator who conducts research involving human subjects</p> <p>Includes spouse and dependent children and any foundation or entity controlled by the individual or his or her spouse</p>	<p>Recipients of HHS grants</p> <p>The PI and any other person responsible for the design, conduct, or reporting of research</p> <p>Includes spouse or dependent child of investigator</p>	<p>Entity submitting drug or device for FDA approval</p> <p>Investigator or sub-investigator listed on the FDA application who is directly involved in the treatment or evaluation of research subjects</p> <p>In addition, investigators who have made a direct and significant contribution to the data</p> <p>Includes spouse or dependent child of investigator</p>
Interests requiring disclosure	<p><i>Employment or Leadership Position:</i> Any full- or part-time employment or service as an officer or board member for an entity having an investment, licensing, or other commercial interest in the subject matter under consideration must be disclosed</p> <p><i>Advisory Role:</i> Consultant or advisory arrangements with an entity having an investment, licensing, or other commercial interest in the subject matter under consideration must be disclosed if consultation was performed or payments made for such consultation within two years of the activity or subject matter in question</p> <p><i>Stock Ownership:</i> Any ownership interest (except when invested in a diversified fund not controlled by the covered individual) in a start-up company (the stock of which is not publicly traded) or in any publicly traded company must be disclosed if the company is an entity having an investment, licensing, or other commercial interest in the subject matter under consideration</p> <p><i>Honoraria:</i> Disclosure of honoraria is required when paid directly to the covered individual by an entity having an investment, licensing, or other commercial interest in the subject matter under consideration and when provided within 2 years of the activity or subject matter in question</p> <p><i>Research Funding:</i> All payments associated with the conduct of clinical research must be disclosed if provided by the trial sponsor or agents employed by the sponsor</p>	<ol style="list-style-type: none"> Service as an officer, director, or in a fiduciary role for a financially interested company,⁵ whether or not remuneration is received for service Equity interests (or entitlement to the same), including stock options, of any amount in nonpublicly traded entity Equity interests (or entitlement to the same) in publicly traded company that exceeds the de minimis amount listed in the PHS regulations⁶ Royalty income or the right to receive future royalties under patent or copyright where the research is directly related to the licensed technology Any nonroyalty payments (or entitlements to payments) in connection with the research that are not directly related to the reasonable costs of the research (as specified in the research agreement) Payments that in the aggregate in the prior calendar year (or are expected to in the upcoming year) exceed the de minimis amount established in PHS regulations⁷ <p><i>Including:</i> Consulting fees, honoraria (including payments from a third party if the original source is a financially interested company), gifts or other emoluments, or "in kind" compensation (whether for consulting, lecturing, travel,</p>	<p>Salary, royalty, and other payments for services greater than \$10,000 per year (not including salary or payments from public or nonprofit entities)</p> <p>Equity interests that are worth more than \$10,000 per year AND more than a 5% ownership interest in a single entity</p> <p>Patents</p>	<p>Any financial arrangement in which value of compensation could be influenced by outcome of the study.</p> <p>Payments from sponsor (not including research compensation) in excess of \$25,000 during research and for 1 year after</p> <p>Equity interest in sponsor exceeding \$50,000 during time of research and 1 year after for publicly traded and any interest that cannot be quantified in nonpublicly traded company</p> <p>Proprietary interests, including patents, held by the investigator in the investigational item</p> <p>Applicant must also disclose any steps taken to minimize bias</p>

Table 1. Continued

Issue	ASCO ¹	AAMC ²	PHS ³	FDA ⁴
<p><i>Expert Testimony:</i> Provision of expert testimony must be disclosed when the testimony relates to the subject matter under consideration</p> <p><i>Other Remuneration:</i> The value of trips, travel, gifts, or other in-kind payments not directly related to research activities must be disclosed if received from an entity having an investment, licensing, or other commercial interest in the subject matter under consideration and when received within two years of the activity or subject matter in question. De minimis payments totaling less than \$100 are excluded from disclosure requirements. These payments exclude research-related costs and travel</p> <p>Same policy for federal government and privately supported research?</p>	<p><i>Expert Testimony:</i> Provision of expert testimony must be disclosed when the testimony relates to the subject matter under consideration</p> <p><i>Other Remuneration:</i> The value of trips, travel, gifts, or other in-kind payments not directly related to research activities must be disclosed if received from an entity having an investment, licensing, or other commercial interest in the subject matter under consideration and when received within two years of the activity or subject matter in question. De minimis payments totaling less than \$100 are excluded from disclosure requirements. These payments exclude research-related costs and travel</p> <p>Yes</p>	<p>service on an advisory board, or any other purpose not directly related to the reasonable costs of conducting the research, as specified in the research agreement)</p> <p><i>Excluding:</i></p> <ol style="list-style-type: none"> 1. Stock in diversified mutual funds 2. Stock or stock options in publicly traded company worth less than the de minimis amount in the PHS regulations 3. Reasonable research costs (as specified in the research agreement between the sponsor and institution) 4. Salary and other payments for services from the institution <p>Yes</p>	<p>Only applies to PHS-funded research</p>	<p>Only applies to research used to support a product undergoing FDA review</p>
<p>Restrictions</p>	<p>A. For all covered individuals, the following are absolutely prohibited:</p> <ol style="list-style-type: none"> 1. Payment of finders fees for referral or accrual to a trial 2. Bonuses for achieving certain levels of accrual by specified dates 3. Payments contingent on particular research outcomes, or 4. Research contracts in which the sponsor has the ability to override the principal investigator's or executive committee's decision to publish or present trial results <p>B. For the clinical trial's PI (in the case of multi-institution trials, the national PI), Co-PI (in the case of multi-institution trials, the national Co-PI), and members of the trial's executive committee and trial's DSMB, during the trial and prior to publication of a substantial analysis, of the trial's results the following are prohibited:</p> <ol style="list-style-type: none"> 1. Stock or equity interest in the trial sponsor (except when invested in a diversified fund not controlled by the covered individual) 2. Royalties or licensing fees (prospective or realized) from the product or novel treatment under investigation 3. Patents for the product or novel treatment under investigation⁸ 4. Position as officer, board of directors member, or employee of the trial 	<p>A. For all covered individuals, the following are prohibited:</p> <ol style="list-style-type: none"> 1. Payments that are based on particular research result or tied to successful outcomes 2. Payments for referrals or enrollment that are not reasonable, do not reflect fair market value, and are not commensurate with effort <p>B. Establishes "Rebuttable Presumption Against Financial Interests," meaning that the institution will presume that a financially interested individual may not conduct the research in question. A financially interested individual may rebut the presumption by demonstrating facts that, in the opinion of a Col committee, constitute compelling circumstances, which allow the individual to conduct the research</p> <p>C. Institutions should not permit investigators to enter research agreement that permits a sponsor to</p> <ol style="list-style-type: none"> 1. Require more than a reasonable period of prepublication review 2. Interfere with investigator's 	<p>No</p>	<p>No</p>

Table 1. Continued

Issue	ASCO ¹	AAMC ²	PHS ³	FDA ⁴
<p>sponsor (Note: individuals may serve on a trial sponsor's scientific advisory board, so long as the sponsor does not provide any honoraria or other payments for such service.)</p> <p>5. Travel or trips paid by the trial sponsor to attend scientific or educational meetings, <i>not including</i> travel or trips for either</p> <p>a. Widely attended and independently sponsored scientific meetings with the primary purpose of making a presentation on the trial, or</p> <p>b. Investigator meetings related to the conduct of the trial</p> <p>6. Research-related payments substantially exceeding actual research costs from the trial sponsor</p> <p>7. Honoraria or gifts from the trial sponsor, excluding research compensation related to the time and efforts of the researchers and his or her staff</p>		<p>access to data or ability to analyze data independently,¹⁰ or</p> <p>3. Generally place restrictions on the activities of students/trainees or bind students/trainees to nondisclosure provisions</p>		
Enforcement	<p>The ASCO Ethics Committee, in conjunction with the Board of Directors where appropriate, can grant an exception to the above restrictions in the following situations:</p> <p>1. There is limited worldwide expertise and realistically the project could not be done anywhere else</p> <p>2. An inventor of a unique technology or treatment being evaluated in a trial also serves as the leader of that clinical trial. In this situation, there must be a data monitoring and safety board overseeing the gathered information and its analysis</p> <p>3. In acknowledgment of the diversity of usual and customary practices within the international clinical oncology research community, the Ethics Committee, in consultation with the Board, may grant limited exceptions to those submitting materials for presentation or publication if they are deemed to have acted consistently with recognized international standards of ethics in the conduct of clinical research</p> <p>Clinical trials sponsored by the National Institutes of Health (NIH) are not implicated by the restrictions set forth in B above, even if those trials involve products of specific commercial interests, because NIH-sponsored trials feature sufficient safeguards to ensure objectivity and independent review of safety and other data developed in the trials</p> <p>For those who violate this policy, the following penalties could be imposed by the ASCO Ethics Committee and/</p>	<p>Institution's policy should define the range of possible sanctions for noncompliance, up to an including dismissal. The policy should reference the procedures to be followed for sanctioning violations and for appealing adverse determinations</p> <p>The AAMC policy intends to raise the standards of institutional oversight and management of financial conflicts of interest, and make them more uniform across academic medicine. The recommended policy and guidance provide a floor that permits institutions to adopt even more stringent provisions if they wish</p> <p>No mention of AAMC enforcement</p>	<p>PHS will not issue the grant funds until an institution submits certification that it has reviewed an investigator's financial relationships</p> <p>Each institution must establish a Col policy with adequate enforcement mechanisms and provide for sanctions where appropriate</p> <p>The HHS agency awarding the grant funds may suspend funds until an identified conflict is resolved</p> <p>If an investigator completes the study and it is later determined that they did not disclose a Col or the institution did not properly manage a Col, the institution must require the investigator(s) involved to disclose the conflicting interest in each public presentation of results of the research</p>	<p>If the FDA determines that the financial interests of any clinical investigator raise a serious question about the integrity of the data, FDA will take any action it deems necessary, including:</p> <p>1. Agency audits of the data</p> <p>2. Requesting that the applicant submit further analyses of data</p> <p>3. Requesting that the applicant conduct additional independent studies</p> <p>4. Refusing to treat the clinical study as providing data that can be the basis for agency action</p> <p>FDA may refuse to file any marketing application that does not contain Col information or a certification by the applicant that the applicant acted with due diligence to obtain the information but was unable to do so</p>

Table 1. Continued

Issue	ASCO ¹	AAMC ²	PHS ³	FDA ⁴
	the Board of Directors for the duration deemed appropriate:			
	<ol style="list-style-type: none"> 1. Prohibition from presenting at ASCO-sponsored events, including the Annual Meeting 2. Exclusion from publishing in the Journal of Clinical Oncology or other ASCO publications 3. Exclusion from participation in ASCO board, committees, and task forces, or 4. Revocation or prohibition of ASCO membership 			
	<p>This policy will be effective 12 months after its publication in the Journal of Clinical Oncology. It will apply prospectively to all activities initiated subsequent to the effective date. In the case of clinical trials, it will apply prospectively to trials that begin accrual subsequent to the effective date</p>			

Abbreviations: ASCO, American Society of Clinical Oncology; PI, principal investigator; Co-PI, co-principal investigator; Col, conflict of interest.

¹As adopted by ASCO November 1, 2002.

²American Association of Medical Colleges. Protecting Subjects, Preserving Trust, Promoting Progress—Policy and Guidelines for the Oversight of Individual Financial Interests in Human Subjects Research. December 2001. Available at <http://www.aamc.org/members/coif/firstreport.pdf>. Last accessed 4/4/03.

³Department of Health and Human Services, Public Health Service. Code of Federal Regulations Title 42 Part 50 and Code of Federal Regulations Title 45 Part 94.

⁴Department of Health and Human Services, Food and Drug Administration. Code of Federal Regulations Title 21 Part 54.

⁵Financially Interested Company means a commercial entity with financial interest that would reasonably appear to be affected by the conduct or outcome of the research. This term includes companies that compete with the sponsor of the research or the manufacturer of the investigational product, if the covered individual actually knows that the financial interests of such a company would reasonably appear to be affected by the research. This term also includes any entity acting as the agent of a financially interested company (eg, a contract research organization).

⁶Currently \$10,000 in value and 5% ownership interest.

⁷Currently \$10,000.

⁸If the product or treatment is discovered after the trial is underway and the PI wants to file a patent, he or she must relinquish his or her leadership role in the trial.

⁹For sponsored research, a reasonable period of review would be no more than 90 days, unless both parties agree that extenuating circumstances require an extension of time. For National Institutes of Health (NIH)-sponsored research, the NIH has stated that it would consider a 30- to 60-day review period to be reasonable.

¹⁰When research involves more than one institution and numerous investigators (eg, a multicenter trial), the investigators may delegate primary authorship to a subset who will take responsibility for the publication.