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ASCO SPECIAL ARTICLE

Addressing Administrative and Regulatory Burden in Cancer Clinical Trials: Summary of a Stakeholder Survey and Workshop Hosted by the American Society of Clinical Oncology and the Association of American Cancer Institutes

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INTRODUCTION

Cancer clinical trials are responsible for many of the recent advances in oncology care, including declining mortality rates and increased survivorship; better supportive care; and clinicians' improved understanding of cancer risk, prevention, and screening. This research has also led to exciting new types of cancer treatments, such as molecularly targeted therapies and immunotherapies.

Cancer clinical trials, however, have become more and more challenging to conduct. Research programs must comply with federal and state legal and regulatory requirements that can be inefficient and costly to implement. In addition, institutions and sponsors often interpret these requirements conservatively and thereby add to the complexity and perceived (but often highly theoretical) risk of conducting clinical trials. Elements of the existing requirements are important for protecting trial participants' safety, for promoting the scientific integrity of research, and for ensuring that trial conduct is efficient and adequately resourced. Such elements are important to preserve. However, taken as a whole, the requirements do not fulfill these goals and, in fact, hinder research and slow patients' access to safe and effective treatments.

To address the problem of administrative and regulatory burden on cancer clinical trials, ASCO partnered with the Association of American Cancer Institutes (AACI) on the Best Practices in Cancer Clinical Trials Initiative (hereafter referred to as the Initiative). ASCO is the leading professional organization to represent oncologists and other health care professionals who care for people with cancer and conduct research to improve cancer treatment. With > 40,000 members, ASCO is committed to the improvement of cancer care through scientific meetings, educational programs, defining and measuring the quality of cancer care, and publishing peer-reviewed journals. AACI represents 95 leading cancer research centers in North America. Its mission is to assist cancer centers in keeping pace with the changing landscape of science, technology, and health care through the dissemination of best practices, creation of member forums, and development of policy recommendations and educational material.

The purpose of the Initiative was to promote practical solutions to meet existing regulatory and administrative requirements on research. Both ASCO and AACI have previously explored various strategies to streamline the conduct of clinical trials, such as the development of supportive tools and templates, networking sessions, and common guidelines and standards. The Initiative was an opportunity to expand on their current work in this area.

A multidisciplinary working group of hematologists/oncologists, research nurses, administrators, and managers as well as industry representatives oversaw the Initiative. Officials from the Food and Drug Administration (FDA) and the National Cancer Institute (NCI), contract research organization (CRO) staff, and patient advocates provided input to the project. The main elements of the project included a stakeholder survey to identify the most pressing issues in clinical trials that could be addressed by the Initiative, assess staff and resources for conducting and managing trials, and gather data on usage of existing tools and resources; an invitational workshop that convened many leading oncology professionals and policymakers to identify potential solutions for improving the efficiency and conduct of cancer clinical trials; dissemination of the recommendations from the workshop through publication and ASCO and AACI annual meetings; and the development of practical resources, toolkits, and follow-up

projects with relevant organizations and individuals. This article summarizes the stakeholder survey and workshop.

OVERVIEW OF STAKEHOLDER SURVEY

ASCO and AACI conducted a survey in the fall of 2015 to identify the most pressing issues in cancer clinical trials that could be addressed by the Initiative. The survey asked about administrative and regulatory burdens associated with conducting and managing clinical trials at various stages in the trial process (ie, getting trials up and running, conducting trials, and post-trial activities and follow-up).

The survey included a list of the common requirements for cancer clinical trials (Data Supplement). For each stage of trial conduct and management, respondents were asked to indicate to what extent a particular requirement was burdensome for their research program on a five-point Likert scale (not at all burdensome, slightly burdensome, somewhat burdensome, moderately burdensome, and extremely burdensome). They were then asked to rank the three components they considered the most burdensome. The survey also gathered data on respondents' use of existing tools and resources for conducting clinical trials. A copy of the actual survey and detailed data tables are provided in the Data Supplement.

Survey Distribution

The survey was distributed in the fall of 2015 to approximately 1,200 physician-investigators, research staff, and administrators in academic and community-based research settings. ASCO distributed the survey to > 700 contacts in the ASCO Research Community Forum (formerly called the Community Research Forum) e-mail list as well as to principal investigators and administrators of the NCI Community Oncology Research Program (NCORP) and the National Clinical Trials Network (NCTN). ASCO also publicized the survey through its member communication venues (ie, Cancer in the News, ASCO Express, Oncology Practice Insider). AACI distributed the survey to > 500 contacts on its Clinical Research Initiative e-mail list, including clinical trial directors; clinical trial administrators; research program managers; and budgeting, contracting, and regulatory managers. The survey was also disseminated to members of the Oncology Nursing Society's Clinical Trial Nurses and Advanced Research Nursing Special Interest Groups, relevant staff at US Oncology, and principal investigators from the Multiple Myeloma Research Foundation.

Survey Respondents

There were 338 survey responses in total, and 310 were included in the analyses (28 cases were excluded because they were duplicates). On the basis of the 1,200 contacts enumerated in the ASCO Research Community Forum and AACI Clinical Research Initiative e-mail lists, this represents a 26% response rate. The true response rate cannot be calculated, however, because of the additional distribution channels and duplicate recipients between the e-mail lists. Of the 310 responses, 84 had incomplete data. Where possible, the analyses included the completed questions from these respondents.

Twenty-six percent of respondents were physicians, and 74% were other research staff, such as nurses, administrators, and managers. Respondents were from a range of types and sizes of research programs. Almost 60% of respondents were from academic-based research programs (NCI-Designated Cancer Centers, universities), and the remainder were primarily from community-based research sites (hospitals, research networks, NCORP programs, private practices). Most of the sites had 100 to 500 patients enrolled each year in clinical trials and approximately one half of sites had > 100 trials open to accrual at the time of the survey (Data Supplement).

Survey Findings

Survey respondents identified many administrative and regulatory requirements for getting trials up and running, conducting trials, and after completion of trials as highly burdensome to research sites from the given list of options as well as wrote in additional items. Their top-three burdens associated with getting trials up and running were most frequently contract negotiations with sponsors, contract negotiations with CROs, and compliance with industry or CRO requirements. Respondents identified site monitoring visits, management of regulatory documents, and external adverse event and serious adverse event reporting most frequently as the top-three most burdensome aspects of conducting clinical trials. Similarly, respondents identified the top-three most burdensome requirements after completion of clinical trials as sponsor queries of databases and access to records, sponsor-required closeout activities, and long-term follow-up (Data Supplement).

The survey asked respondents about the adequacy of their research staff. Fifty-eight percent (n = 127) indicated that they did not have adequate staffing to handle regulatory burden, and 41% (n = 93) did not have adequate staffing to monitor regulatory compliance.

In addition, the survey identified variability in respondents' awareness and usage of various tools for supporting cancer clinical trials, which have been developed by ASCO, AACI, NCI, and other organizations (ie, the Office for Human Research Protections, Clinical Trials Transformation Initiative, Society for Clinical Research Sites, TransCelerate). Few respondents had ever heard of most of the existing tools and resources (Data Supplement).

THE WORKSHOP

ASCO and AACI hosted an invitational workshop on March 8, 2016, at ASCO headquarters in Alexandria, Virginia. The > 60 attendees were representatives from leading cancer research organizations, community oncology practices, patient advocacy groups, government, industry, and CROs. The primary meeting objective was to identify as many tangible solutions as possible to the administrative and regulatory burdens related to the conduct of cancer clinical trials.

The meeting was led by a professional facilitator with expertise in strategic and transformational design.[1] Participants spent the

majority of the day in breakout sessions and small group discussions. The results of the stakeholder survey were used to identify three aspects of clinical trial conduct to be the focus of the small group discussions: overcoming challenges to clinical trial contracts, improving clinical trial coverage analyses and budgeting, and complying with training and regulatory requirements. Three subtopics within each overarching topic (for a total of nine) were also addressed in the breakout group discussions and are discussed in detail herein

The working group developed problem statements for each of the nine subtopics and shared them with the workshop participants in advance of the meeting. The breakout groups were charged with generating solutions to the challenges identified in the problem statements for each topic area. The facilitator led the groups through an iterative process of identifying gaps in the problem statements, brainstorming on solutions, and prioritizing and refining potential solutions. At the end of the day, each small group presented a concept poster to the participants from the other breakout groups that outlined its most promising solutions. The other breakout groups had an opportunity to comment and ask questions on the basis of these presentations.

The workshop also included a presentation from Vice President Joseph Biden's staff on the National Cancer Moonshot Initiative, which was launched by the White House in 2016 to accelerate progress in cancer research, prevention, diagnosis, and treatment and to improve patient access to therapies.[2] This provided the workshop participants with an opportunity to explore how the ASCO/AACI Initiative could inform the National Cancer Moonshot Initiative. The remainder of this section provides an overview of the problem statements and solutions generated at the workshop.

Overcoming Challenges With Clinical Trial Contracts

Research programs have reported that the contract and budget negotiation process is time consuming and creates a barrier to their participation in clinical trials. Frequently reported barriers in the process include sponsors' underestimation of the cost of conducting trials, lack of flexibility with the contract language, and excessive delays in finalizing the contract language.[3] Moreover, many aspects of cancer clinical trial contracts among research programs, CROs, and sponsors must be renegotiated at the beginning of each trial for every participating research site. These impediments and inefficiencies slow trial startup and affect patient access to therapies in development. Similar inefficiencies exist in research programs' negotiations of interinstitutional contracts and subcontracting.

Separate breakout groups at the workshop discussed the following aspects of clinical trial contracting and focused on generating potential solutions to these specific problems:

- The negotiation process: Research sites have reported that negotiating with CROs and/or sponsors can be time consuming and inefficient and can result in master agreements between sponsors and institutions being overlooked.[3]
- Specific contract clauses: Specific clauses of research contracts are particularly challenging for research programs and sponsors/CROs to reach agreement (eg, liability and indemnification, intellectual property).[3]
- Interinstitutional contracts and subcontracting. Ancillary departments (eg, laboratories, imaging) provide necessary services for clinical trials. However, they are outside the control of the research program and the principal investigator. Thus, all parties must decide on the terms of the agreement before the trial can be launched. The trial's funding source can have an impact on the complexity of arranging these subcontracts, with federal grants having many more restrictions than private funding sources. In addition, interinstitutional contracting and budgeting between hospitals and universities represent a difficult process.

The workshop participants identified the preselection process as another major barrier to research programs' participation in research. Before deciding whether to open a trial and engage in the clinical trial contract negotiation process, research sites are required to go through sponsors' preselection processes, which include items such as site evaluation visits, feasibility questionnaires, and the signing of confidential disclosure agreements. These additional processes are burdensome and can lead research sites to decline participation in clinical trials.

Table 1 summarizes the potential solutions workshop participants identified in the clinical trial contracts discussion. In general, the participants recognized that multiple efforts have been made to create contract templates for clinical trials.[4-6] The challenge now is to encourage research sites and sponsors to use these templates rather than to renegotiate the same clauses repeatedly. Many of the recommendations the breakout groups identified relate to the compilation of existing resources into a central location, the education of stakeholders about the existence of tools and resources, and the creation of incentives and metrics around their use. These recommendations are similar to the suggestions made by the ASCO Research Community Forum based on results of a survey of community-based research sites. The forum's key recommendations were to standardize the contract and negotiation processes, improve sponsor processes to minimize the burden on sites, create and promote the use of contract templates and best practices, and provide education and consultation.[3]

The challenges surrounding preselection and interinstitutional contracting and subcontracting have not been the focus of as many previous efforts. Thus, the potential solutions identified by the workshop participants in these categories were related to the development of standardized templates, tools, and resources as well as to having professional societies take the lead in convening the relevant stakeholders for educational purposes and for reaching consensus on best practices.

Improving Clinical Trial Coverage Analyses and Budgeting

Many clinical research sites complete an insurance coverage analysis before opening a trial to identify routine costs that can be billed to insurers, ensure that the trial is consistent with care standards, identify potential barriers to accrual early, prevent financial risk for patients from clinical trial participation, and meet budget needs. The trial coverage analysis process, however, is costly and inefficient and includes many redundancies. Coverage analyses are completed by a myriad of research team members with various levels of knowledge, skill, and expertise in the arena of clinical trials

Table 1. Overcoming Challenges With Clinical Trial Contracts

Topic	The Problem	Potential Solutions
The preselection process	Needless bureaucracy exists with regard to confidentiality and evaluation of institutions as potential research sites, which results in inefficiencies, burdens on resources, and excessive delays.	Develop master agreements between sites and sponsors to cover agreements that do not vary across trials (eg, confidentiality agreements). Certify research programs or register sites on a common platform.
The negotiation process	The research contract negotiation process is time consuming, resource intensive, inefficient, and inconsistent. Specific clauses of research contracts provide a particular challenge to reaching an agreement. These inefficiencies result in excessive burdens and delays in study startup.	Develop a centralized repository of templates and tips for negotiating contracts. Educate legal staff about real-world risks and existing templates. Lawyers currently negotiate over very rare events (eg, few clinical trials result in patentable inventions, few cases of liability occur from clinical trial participation). Develop metrics for comparing and reporting legal staff/organization performance. Identify incentives to promote the use of existing templates. Repeated negotiations over the same contract clauses have little impact on the final contract language.
Inter- and intrainstitutional contracts	Nononcology services often are buried in the protocol (laboratories, imaging, etc), and the involvement of multiple parties (research sites, investigators, ancillary departments, CROs, sponsors, etc) adds complexity to the agreements and negotiation process. More transparency is needed about nononcology services as well as a decrease in the complexity of agreements and negotiation processes.	Engage stakeholders (sites, principal investigators, and sponsors) to create a worksheet that identifies all nononcology services for each specific trial. Identify best practices around subcontracting and strategies for engaging external departments and independent providers. Identify a value proposition for external providers (ie, why they should support clinical trials). Educate all stakeholders to ensure that they have the same information/understanding about trials/ancillary services. Address the cultural disconnect among lawyers, researchers, and sponsors.

Abbreviation: CRO, contract research organization.

coding and billing. In addition, the same or similar analyses are done at multiple sites for multisite trials, so costs are accrued at each participating site. An ASCO Research Community Forum working group found that a conservative estimate of the financial impact associated with each site preparing a separate coverage analysis is approximately $650,000 for new trials opened nationally in the NCORP and NCTN programs.

Separate breakout groups at the workshop discussed the following elements and challenges associated with coverage analyses and budgeting:

- Coverage analyses of funded trials. Various levels of policy guide what gets covered in clinical trials (eg, Medicare coverage policy, National Coverage Determinations, the Patient Protection and Affordable Care Act, local coverage determination policies, third-party payers). Research programs need to be clear on what is and is not eligible for insurance coverage before opening a trial.
- Billing and coverage of procedures. Research programs' billing departments are challenged when there is uncertainty about what qualifies as routine patient care in clinical trials as well as about other reimbursement rules. For example, third-party payers often do not cover the cost of standard procedures (eg, electrocardiogram, computerized tomography scans) that are conducted more frequently than patients receive outside of clinical trials. Disagreement exists about whether the increased frequency of these tests are clinically appropriate monitoring of the effects of the study drug or intervention (or the prevention of complications) or a test for research purposes only.
- Budgeting for infrastructure and research aspects of trials. Research programs need to know that the effort required to open and run a trial matches the trial reimbursement, whereas trial sponsors want to ensure that the trial budgets are in line with fair market costs. Specific issues include costs outside the study budget, such as fees of ancillary departments not under the control of the trial site or the principal investigator; hidden trial costs not clearly identified in the trial protocol; and other fees that research programs may accrue over the duration of a trial.

Table 2 summarizes the potential solutions identified by the breakout groups. In general, the recommendations acknowledge the need to make coverage analyses more efficient either through a software application or a centralized process. Participants also agreed that the cancer clinical trial community needs common language and clinical standards for describing routine patient care and research-related procedures. In addition, they identified the need for training in this area, improved access to clinical trial management systems, and clarity and transparency upfront about the costs of various aspects of conducting clinical trials.

These recommendations align with existing initiatives. For example, the ASCO Research Community Forum collaborated with NCI to conduct a training symposium on centralized coverage analyses.[7] Since, NCI has begun to pilot test centralized coverage analyses of select NCI trials to distribute to NCTN groups and NCORP research bases.[8] NCI expects that this program will result in dramatic cost savings for sites. However, the program is still in the early stages, and coverage analysis issues still need to be addressed for non–federally sponsored trials.

Table 2. Improving Clinical Trial Coverage Analyses and Budgeting

Topic	The Problem	Potential Solutions
Coverage analysis of funded trials	The trial coverage analysis process is costly, inefficient, and includes many redundancies, and sites need clarity about what is eligible for insurance coverage before opening a trial.	Develop an application that allows sites to conduct coverage analyses quickly and effectively (eg, TurboTax [Intuit, Mountain View, CA] software that provides standardization as well as customization). Create common language and clinical standards that account for differences across regions/states and providers (various payment schemes, laws, and standards of care). Provide training to sites on how to conduct coverage analyses.
Billing and coverage of procedures	Uncertainty exists about what qualifies as routine patient care *v* research procedures in clinical trials as well as other reimbursement rules.	Conduct universal coverage analyses (eg, the sponsors do the analyses and feed to sites). Develop guidelines around what constitutes routine patient care *v* research. Purchase in bulk one or more clinical trial management systems to minimize the cost to sites of purchasing this software. This would facilitate tracking patients through electronic health records and billing. Develop an article that illustrates several coverage analyses case studies from completed trials.
Budgeting for infrastructure and research aspects of trials	Some costs and fees associated with clinical trials are not factored into budgets and contracts or are insufficiently reimbursed (eg, costs outside of per-patient budget, ancillary department fee schedules, hidden trial costs not clearly identified in trial protocol). Increased transparency around costs is needed to prevent underfunded trials at research sites.	Create a common language for research-related costs. Develop a list of the items that need to be included in the budget (certification of equipment, radiology, etc). Research sites could then determine the costs for each item on the list.

Complying With Regulatory and Training Requirements

Clinical trials must comply with many regulatory and sponsor-specific requirements that can be inefficient and costly for research programs to implement and often are interpreted conservatively by institutions and practices, CROs, and sponsors. Although the intent of these requirements is to protect trial participants and manage future patients' risk/benefit ratio, they may also delay research and slow patients' access to therapies in development. This is especially true when the parties involved err on the side of over-reporting, given the perceived risk of penalty.

Separate breakout groups at the workshop discussed the following elements and challenges associated with regulatory and training compliance:

- Training requirements. Investigators are required to comply with multiple training requirements for each clinical trial that they enroll patients into (eg, Good Clinical Practice, electronic data capture system, individual sponsor and CRO training). Much of the content of these training programs is similar across trials; however, an investigator may be required to retake the training for each individual trial.
- Adverse events/serious adverse events documentation and reporting. Many sponsors misinterpret the FDA's requirements[9-11] for adverse events/serious adverse events reporting and send all adverse events captured to every research site that conducts a trial that uses that agent, regardless of the relevance of the event.[12] The guidance is clear, however, that not all adverse events should be reported; only those that are serious and unexpected. The result of over-reporting is that investigators are overwhelmed by the number of adverse event/serious adverse event notices they receive without context and struggle to determine which information is relevant to their patients.[13]
- Auditing/monitoring site visits, trial queries, and documentation. Research sites devote significant time, effort, and expense in preparing for sponsor and CRO audits, monitoring visits, queries, and documentation. The FDA finalized a guidance document in 2013 that encouraged study sponsors to implement centralized monitoring in lieu of 100% site visits.[14] However, on the basis of the results of the stakeholder survey, whether sponsors use this process is unclear. Modification of the CRO payment system to an all-inclusive model may help to modulate the need for such overinterpretation and redundancy.

Table 3 summarizes the potential solutions identified by the breakout groups. To address the redundant training requirements, workshop participants recommended harmonization of existing training programs and creation of a centralized database or repository to record, manage, and monitor investigators' training status. Ideally, this database could also deliver the clinical trial training.

The recommendations on adverse events reporting and auditing, monitoring, queries, and documentation focused on the need to convene the relevant stakeholders for focused meetings aimed at understanding why the FDA guidance[9-11,14] has not had a larger impact on easing regulatory burdens in these areas. Workshop participants were also enthusiastic about the potential to create a certification or registration program for research sites, which could be done through an online common platform. Centralized documentation of site resources and metrics could significantly minimize effort from both sites and sponsors to repeatedly provide and seek the same information numerous times.

In the move forward, ASCO and AACI need to support existing and ongoing initiatives that address training and

Table 3. Complying With Regulatory and Training Requirements

Topic	The Problem	Potential Solutions
Training requirements	Investigators are required to comply with multiple training requirements for every clinical trial that enrolls patients.	Inventory existing initiatives and resources that could be leveraged in future efforts. Identify and harmonize all training requirements (ie, core principles [fundamentals of trials, good clinical practice]; cancer-specific electronic data capture systems; protocol-specific, sponsor-specific add-on training). Provide more effective training to reduce frequency and ensure retention (eg, a common platform built on modern principles of training [technology and adult learning]). Develop a system or tool that centralizes training (centralized database/repository to record, manage, and monitor status and, ideally, to deliver the training and provide a one-stop shop for training).
AE/SAE documentation and reporting	Sponsors over-report AE/SAEs. Thus, research sites are overwhelmed by the number of notices they receive and are left having to figure out which information is relevant to their patients.	Organize a meeting with ASCO and AACI leadership, CTTI, FDA, and other sponsors to discuss strategies for increasing compliance with the FDA guidance.
Auditing, monitoring site visits, trial queries, and documentation	Research sites devote significant time, effort, and expense in preparing for sponsor and CRO audits, monitoring visits, queries, and documentation. The requirement of only data relevant and important to define the safety profile of the experimental agent would reduce the amount of burden on research sites.	Convene stakeholders. Review FDA guidelines (risk-based monitoring, selective safety data collection, and protocol design guidelines) and examine why there has been a failure to adopt. Discuss how the protocol design drives what data are collected. Establish clarity about regulatory requirements to address concerns and fears about meeting regulatory requirements, which lead to overcollection of data. Use common data elements and a single electronic data capture system (ie, collect data the same way to allow for better meta-analyses). Certify research programs or register sites.

Abbreviations: AACI, Association of American Cancer Institutes; AE, adverse event; CRO, contract research organization; CTTI, Clinical Trials Transformation Initiative; FDA, Food and Drug Administration; SAE, serious adverse event.

regulatory requirements rather than to be duplicative. For example, TransCelerate has launched the Shared Investigator Platform and the Investigator Registry, which may help to resolve some of the problems associated with documentation.[15,16] Similarly, the Clinical Trials Transformation Initiative has addressed the need to improve adverse events reporting.[17,18] Guidance and ongoing initiatives to simplify training requirements also exist.[19-23]

In conclusion, the Initiative's stakeholder survey and workshop are good first steps toward identifying major inefficiencies and potential solutions for alleviating regulatory and administrative burdens on cancer clinical trials. ASCO and AACI continue to review the list of potential recommendations generated by workshop participants to determine ways that they can leverage ongoing efforts and develop new strategies to effectively and swiftly improve the conduct and management of cancer research. The National Cancer Moonshot Initiative[2] may provide a rare opportunity to effect change given that it is one of the Obama Administration's national priorities. The standard for evaluating the reasonableness of existing requirements should be whether these requirements are essential for protecting trial participants' safety, promoting the scientific integrity of research, and ensuring efficient trial conduct and adequate resources. Any requirements that do not fulfill these goals should be streamlined so that researchers can efficiently conduct trials and ensure that patients' have timely access to safe and effective treatments.

The lack of community awareness and uptake of many previous initiatives demonstrates the critical importance of involving multiple stakeholder groups in future efforts in this area to ensure the community's support and buy-in as well as to improve the dissemination of resources and tools. The workshop was effective at bringing together multiple stakeholder groups to brainstorm about feasible and effective solutions. This community involvement will be important in the move forward. In addition, a review of the earlier initiatives that have resulted in toolkits, standardized forms, and so forth would be helpful to understand why these resources have not been fully used or adopted and to ensure that future efforts do not suffer similar limitations.

ASCO and AACI plan to conduct a number of follow-on activities to the Initiative. The priority topics for implementation are adverse event reporting, site qualification, and insurance coverage analysis. The approach to implementation will likely vary for each topic. For adverse events reporting, stakeholders need to identify strategies to ensure more widespread adoption of FDA guidance.[9-11] Development of a centralized repository of site qualifications (eg, training, investigation pharmacy) that is well used by all sectors of the cancer research community would improve the recording, management, and monitoring of sites' research capabilities and help to match sites to sponsors' open clinical trials. In addition, educational efforts are needed to clarify routine patient care and research-related services for insurance coverage purposes.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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