Findings and Implications of a CTTI Project: Improving the System of Reporting and Interpreting Unexpected Serious Adverse Events to Investigators Conducting Research Under an Investigational New Drug Application

Summary of an Expert Meeting held October 3–4, 2010

Clinical Trials Transformation Initiative

Improving the System of Reporting and Interpreting Unexpected Serious Adverse Events to Investigators Conducting Research under an Investigational New Drug Application

A Project Sponsored by the Clinical Trials Transformation Initiative (CTTI)

Expert Meeting, October 3–4, 2010

Marriott Inn & Conference Center, University of Maryland University College.
Hyattsville, MD

This CTTI project focused on practices associated with the current regulatory framework for reporting and interpreting unexpected serious adverse events (SAEs)[1] associated with study drug to investigators conducting research under an Investigational New Drug Application (IND).

Current IND regulations require that investigators who observe in a study participant an SAE associated with an investigational product (IP) must promptly report the event to the sponsor. The sponsor, in turn, "shall notify FDA and all participating investigators" (21 CFR 312.32). With regard to the sponsor notifying all investigators in a multicenter trial, this regulation has been interpreted to mean that the study sponsor should send expedited written reports of each unexpected SAE associated with an IP to every investigator in the clinical trial in which the SAE occurred. In addition, many have interpreted this regulation to indicate that all individual, unexpected SAEs involving a given drug or biologic product should be sent to all investigators involved in any trial or registry of that product, including trials or registries studying different indications for the product. Furthermore, SAE reports often arise from studies using multiple drugs or from blinded studies in which the research subject could have been on placebo or a standard comparator rather than the experimental agent. Interpretation is challenging in these cases because the investigators have no empirical base from which to place the SAE in context: they do not know the numerators and denominators to deduce whether the event is related to the experimental treatment, they do not know the details of the protocol for the trials in which they are not participating, and they do not even know whether a given event occurred in a subject actually receiving the experimental treatment.

This CTTI project sought to provide empirical evidence about the current system for reporting adverse event information to investigators conducting research under an IND and to consider potential modifications that may achieve more efficient and effective information flow and consequent improvement of human subject protection. On September 29, 2010—just prior to the expert meeting described herein—the FDA issued a new final rule and accompanying draft guidance concerning IND safety reporting (Appendix A). The requirements of the new safety rule, which will go into effect on March 28, 2011, will affect interpretation and implementation of the project findings described below.

[1] Serious adverse events that are unexpected (i.e., not listed in the investigator brochure) and for which there is a reasonable possibility that the event may have been caused by the drug must be reported to the regulatory authorities in an expedited fashion (within 15 calendar days; 7 days if the event was life-threatening or fatal) and subsequently to investigators and IRBs (21CFR 312.32, 312.53).

The specific objectives of this CTTI project were to:

1) Document the current range of practices for safety monitoring and reporting of unexpected SAEs to investigators (**Workstream 1**).
2) Quantify the personnel time required by investigators to receive, analyze, interpret, and communicate information in individual expedited safety reports and the perceived value of this information in updating the risk profile of investigational products (**Workstream 2**).
3) Compare current practices with an alternative approach for notifying investigators of unexpected SAEs (**Workstream 3**).
4) Sample the beliefs and expectations of patients concerning adverse event monitoring and communication during the conduct of a trial; also sample the ways in which adverse event monitoring is presented to subjects via consent forms (**Workstream 4**).
5) Convene a broadly representative group of invited experts to integrate the information generated by this project and to develop a set of recommendations for optimal reporting of unexpected SAEs to investigators that will improve human subject protection (**Workstream 5**).

The meeting described in this document represents Workstream 5 and included presentation of the major findings from the other 4 workstreams. A summary of the Workstream 5 discussion follows the synopses of results from Workstreams 1–4 provided below.

Workstream 1 Findings: Presented by Sundeep Sethi, Amgen

The purpose of this workstream was to document the current range of practices for safety monitoring and reporting of unexpected SAEs to U.S.-based investigators of IND research. A voluntary, web-based survey was distributed to industry sponsors of IND research. The survey was anonymous; respondents were not compensated for their time in completing the 79 questions. The data collection period lasted from October 22, 2009, to January 8, 2010. A slightly modified survey was distributed to a smaller number of government and academic sponsors of clinical research to get a full picture of the range of practices in safety reporting. Only industry responses are summarized here as efforts to solicit responses from government sponsors were ongoing at the time of the meeting.

Survey responses (10 companies; ~20% of the invited industry participants) revealed that industry sponsors communicate safety notifications to investigators using individual expedited case reports. They also have well-developed mechanisms for IND safety data management, including written standard procedures, drug safety units/clinicians, and external bodies to manage and review data. While the sponsors conduct aggregate analyses of their safety data and often report aggregate data to regulatory bodies, they do not typically report aggregate data to clinical investigators. Sponsors reported that investigators have expressed dissatisfaction with the volume (too many) and content (not relevant) of individual IND safety reports. The team leaders of this project recommended encouraging more aggregate safety notifications from sponsors to investigators and reducing investigator burden of unnecessary individual expedited reports.

Workstream 2 Findings: Presented by Howard Greenberg, American College of Clinical Pharmacology

The objective of this workstream was to estimate the resources required from site investigators and their staffs to manage individual expedited safety reports under current regulations, and to gauge investigators' perceptions of the value of this information in updating the risk profile of investigational products. A small sample of 12–15 investigators was sought to collect this detailed information, recognizing that the information would be descriptive but not likely generalizable. Investigators had to be currently engaged in at least 2 clinical trials. Three therapeutic areas (cardiovascular, oncology, and infectious disease) were targeted.

To obtain this sample, a large number of investigators (375) from a mixture of academic and private sites were invited to participate. Although 63 investigators indicated they would participate, only 5 investigators actually returned the data forms that prospectively quantified the number of individual expedited SAE reports they received weekly over an 8-week period and the personnel time spent and level of personnel engaged in receiving, interpreting, documenting, and submitting these to their Institutional Review Board (IRB). Six investigators, 5 of whom also contributed to the prospective survey, returned retrospective reviews of all expedited SAEs they had received over a 3-month period starting 6 months prior to the beginning of this exercise. The retrospective review addressed the following:

- Relevance of these reports to the investigators' overall understanding of the risk and benefits of the IP under study
- Any changes made to consent form or study conduct (e.g., recruiting approach, inclusion/exclusion criteria, protocol, subject monitoring) as a result of the reports
- Impact of the reports on investigator vigilance in safety monitoring
- Any sponsor mechanisms used for aggregating, analyzing, interpreting, and communicating SAEs

Of the 528 SAEs reported during the retrospective survey, none led to a change to the informed consent, the description of the risk profile to patients, or safety monitoring by investigators. A resource estimate indicated that it took a median of 0.25 hours/SAE to process these reports (0.12, 0.37 [25^{th}, 75^{th} percentiles]). Assuming hourly rates of $150 for MDs, $60.00 for other healthcare professionals (HCP), $30.00 for non-HCP, and an additional fringe rate of 30% of salary, the time estimates translated to a median cost of $22/SAE ($10, $33 [$25^{th}$, 75^{th}]) using the reported man-hour proportions of 0.25 MD, 0.2 other HCP, and 0.55 non-HCP. Sensitivity analyses using higher and lower proportions of MD time gave median costs per SAE of $32/SAE and $16/SAE, respectively.

Investigators indicated low perceived value of individual SAE reports due to a lack of context (incidence, relatedness) for events. When they received it, "contextual" information was deemed useful—e.g., Data Monitoring Committee (DMC) reports and notification letters of unanticipated problems (according to FDA's guidance of 1/09 regarding reporting to IRBs). It may help investigators, sponsors, and IRBs better understand any emerging safety issues if they were provided with reports summarizing AE experiences of multiple subjects with accompanying contextual information (e.g., comparison to a control group) and if such reports would apply the principles described in the FDA's guidance regarding reporting to IRBs.

Workstream 3 Findings: Presented by Lynda Szczech, Duke Clinical Research Institute
The primary objective of this workstream was to compare current practices of reporting individual SAEs to investigators in studies conducted under an IND with an alternative approach recently allowed by the European Clinical Trials Directive for notifying investigators of unexpected SAEs in periodic aggregate reports of SAEs that occurred during the reporting period. This study collected self-reported data from each respondent using a 2-page paper survey asking investigators to estimate time and level of staff needed to review, analyze, and communicate to other staff and to the IRB the information contained in either type of report. This study was made possible because 2 U.S. IND programs—one studying sirolimus (Rapamune®, Wyeth) and another studying lapatinib (GSK)—had received waivers from the FDA to use an aggregate reporting system, similar to that which is authorized by the European Commission, instead of the standard approach of reporting individual case events as they occur. Participants in this survey included clinical investigators conducting multi-center trials using either Rapamune® (n=9) or lapatinib (n=9), as well as studies using the traditional reporting scheme of notifying investigators with individual (not aggregate) SAE reports. Each responding investigator was asked to choose a comparator study from among the studies in which they were currently involved that used a traditional reporting scheme. Similar information was collected on this comparator study against which to gauge the values that were provided for the studies using the aggregate reporting system.

For these 2 medications as well as the medications selected by the respondents, only a small proportion of SAEs met the criteria for reportability to the FDA (i.e., serious, related, and unexpected). The respondents reported a similar amount of time to review 1 aggregate report as compared to a report of a single event. Although the small number of respondents and small number of reportable events in this workstream limit conclusions, data suggest a potential time savings afforded to investigators by aggregate reporting of individual events.

Workstream 4 Findings: Presented by Kevin Weinfurt, Duke Clinical Research Institute
This workstream was intended to identify expectations of patients concerning monitoring and communicating safety of an IP during the conduct of a clinical trial. It also sampled different ways in which AE monitoring is conveyed to subjects in consent forms. Four race-stratified focus groups were conducted of roughly equal size (5–8 participants/group). Two groups included only persons with clinical trial experience; the remaining 2 groups included persons with no clinical trial experience. In a separate exercise, consent forms from prospective randomized clinical trials coordinated by the Duke Clinical Research Institute were reviewed to identify and code language about SAE disclosure and to assess readability diagnostics.

Results indicated the following:
- Patients had a hard time grasping implications of multicenter clinical trials with regard to reporting SAEs.
- Patients thought investigators should be told about all SAEs immediately.
- There was wide variability of opinions about whether, when, and how participants should be told about each unexpected SAE.

- Patients expressed serious concerns about financial conflicts of interest in monitoring and reporting SAEs (not just concerns about industry, but also concerns about investigators and staff).

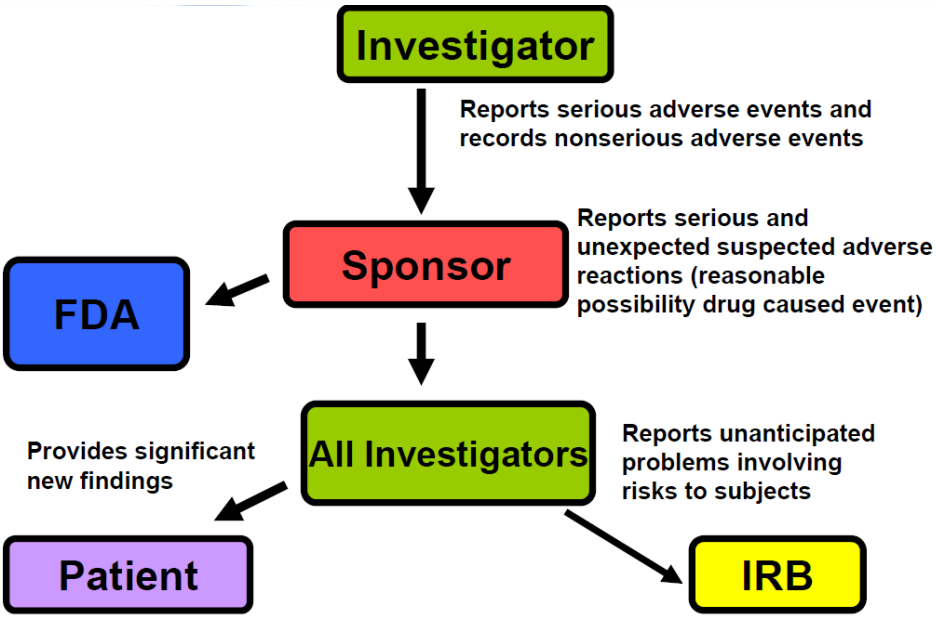
The following recommendations were made by workstream leaders:

- Patients' understanding about clinical trials and how risks are managed should be enhanced—in particular, patients lacked understanding about the nature and logistics of multi-site, multi-national trials.
- Language used in consent forms should reflect the realities of clinical trial logistics and data analysis. Also, terms like "important findings" should be better defined—important to whom exactly?
- The issue of conflicts of interest needs to be addressed to restore/maintain patient trust in the research process; specifically, patients were concerned that investigators might withhold SAE information to prolong the trials that pay their salaries.

Workstream 5: Expert meeting (participants listed in Appendix B)

The CTTI workstreams described above provide documentation that single-case SAE reports rarely have an impact on patients; however, the effort required to manage the current volume of single-case SAE reports is consuming a substantial amount of healthcare provider time. With these findings as a backdrop, the expert meeting began with an observation from facilitator Robert Califf, MD, of the Duke Translational Medicine Institute that the SAE reporting system (as configured prior to the new FDA rule) is not fit for its purpose, which should be to provide investigators with information needed to assess the balance of risk and benefit of a study drug. He further reflected that the massive bureaucracy that has sprung up around existing reporting mechanisms is contributing to the decline of the clinical trial in the United States and elsewhere, with research studies increasingly being exported to other countries. Dr. Califf commented that it should be possible to streamline operations and protect patients, and that the purpose of this expert meeting was to integrate the workstream findings with the FDA's new IND safety reporting rule to accomplish these goals.

Janet Norden, MSN, RN, of the FDA's Center for Drug Evaluation and Research then provided an overview of the IND safety reporting final rule recently issued by the FDA. (See the figure below for a high-level visual representation of the flow of AE information.) As she explained, the rule codifies the FDA's expectations for timely review, evaluation, and submission of relevant and useful safety information; implements internationally harmonized definitions and reporting standards; and clarifies confusing terminology in existing regulations. As such, it should improve the utility of premarket safety reports, thereby enhancing human subject protection.



Ms. Norden highlighted some new definitions included in the rule. The expedited reporting requirement—*Serious and Unexpected Suspected Adverse Reaction*—concerns any suspected adverse reaction that is both serious and unexpected. An *adverse event* is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related; a *suspected adverse reaction* is any adverse event for which there is a reasonable possibility that the drug caused the adverse event. ("Reasonable possibility" means that there is evidence to suggest a causal relationship between the drug and the adverse event.) Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by the drug. *Unexpected* means that the event is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or is mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation. *Serious* means that the event results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Ms. Norden clarified that serious and unexpected events should be reported by the sponsor to the FDA and all investigators *only* if there is evidence to suggest a causal relationship between the drug and the adverse event.

The new regulation also specifies the following: 1) study end points that are serious adverse events (i.e., mortality or major morbidity) must be reported per the protocol and <u>not</u> be submitted as an IND safety report unless there is evidence suggesting a causal relationship with the drug; 2) a sponsor must report any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure; 3) other findings that suggest a significant human risk must be reported (e.g., epidemiologic data, animal

studies). Of note, there are new safety reporting requirements for IND-exempt bioequivalence and bioavailability studies. A key component of the new rule is that causality of the event (i.e., determination of whether it was possibly drug-related) is to be decided by the sponsor, not the investigator.

In light of this presentation, several meeting participants posed questions regarding the rule's impact on when and what events are reported to the FDA. Some wondered about the logistical implications of the new rule for reporting timeframes when information in an initial report of a serious event to a sponsor is incomplete and inadequate to determine causality. One participant assumed the 15-day requirement for reporting to the Agency started when any information was received, even if incomplete. An FDA representative responded that the report should be submitted within 15 days of when the sponsor has adequate information to determine whether the event meets the rule's reporting requirements, including an assessment of whether there is evidence to suggest causality.

As for the nature of the events reported, it was reiterated that both the investigator and the sponsor will classify an event with regard to its seriousness, but only the sponsor will determine whether it is a suspected adverse reaction (that is, possibly drug-related). Bob Temple, MD, of the FDA also explained that investigators must distinguish between SAEs and study effectiveness or safety end points (which should be accounted for in the protocol and are therefore not considered reportable in an IND safety report). It was suggested by a meeting participant that the protocol should explicitly state which end points will be monitored by an independent DMC.

The issue of liability was raised by some participants. The potential legal ramifications of a sponsor's decision to classify an event as a suspected adverse reaction (or not) could raise concerns as the rule goes into effect. However, Ms. Norden provided assurance that the new rule offers more specificity about what should be reported than do current regulations. One participant suggested that sponsors would be wise to carefully document the decision-making process they use in determining causality. A patient representative commented that reliance on the sponsor to determine causality could generate concerns among patients, who may question the impartiality of these judgments. On the other hand, many were concerned that risk-averse lawyers within sponsor companies might encourage (or instruct) company employees to call most serious adverse events "suspected adverse reactions" to avoid later accusations that they hid adverse events of significance.

This latter observation spurred a discussion about the possibility of enlisting an unbiased third party to oversee this decision-making process, the thought being that such a move might dispel worries about potential conflicts of interest inherent to sponsor oversight. One participant suggested that the NIH might be a suitable candidate for this role. Another participant wondered whether there is such a thing as a "trusted" intermediary; every person can be subject to accusations of bias, regardless of his or her commercial interests. It was also observed that the sheer volume of SAEs at any moment in time would complicate review by a central body and that the review process is best kept in the hands of the sponsor, who has more intimate knowledge of the IP.

Steven Hirschfield, MD, PhD, of the National Institute of Child Health and Human Development (NICHD) relayed an example of his organization's attempts to dissipate concerns about judgment and described a policy document first issued in 2007 that provided guidance on this issue (http://www.nichd.nih.gov/funding/policies/upload/Final_NICHD_Clinical_Research_Monitoring_Policy.pdf). As described by Dr. Hirschfield, the purpose of the document is to bring more focus to event reporting and causality determination by relying more on protocol specificity and less on subjective judgment calls. For example, the NICHD advises that expectations regarding the product under study and the underlying condition(s) be enumerated in the protocol, thus using institutional knowledge to inform subsequent decision-making should an adverse event occur. Dr. Temple agreed with the concept as discussed and also encouraged investigators and sponsors to talk with the FDA if questions arise as to whether an event meets the criteria for reporting.

Other meeting participants noted that oversight committees, such as DMCs, are essential safeguards for patient protection (although it was observed that patient distrust can extend to such committees when members are paid by trial sponsors). It was also observed that smaller trials often lack the resources to avail themselves of the services that DMCs provide. The limited number of qualified biostatisticians to serve on DMCs was also raised as a concern.

Regardless of the oversight body/bodies used, there was general consensus that widespread education about the new rule will be needed to ensure its successful adoption. Dr. Califf proposed the creation of use cases to supply examples of what does and does not meet the reporting requirements. It was suggested that CTTI is well-positioned to develop these "best practice" models and to post them to the Internet for widespread reference. It was also remarked that training of site investigators, sponsor monitors, and FDA auditors, among others, should be emphasized to ensure complete understanding of the new rule by those charged with its enforcement.

Another issue of major concern was harmonization of the FDA rule with those of international regulatory bodies. Trial sponsors already struggle to meet varying requirements for drug approval around the world, often opting to adhere to the lowest common denominator in terms of reporting requirements. Implementation of the new rule in the United States may further complicate matters because the European requirements specify that both investigators and sponsors make a determination of causality, while under the new U.S. rule, this will be the purview of the sponsors alone.

A major finding of the workstreams concerned the use of aggregate reporting to convey information about SAEs to investigators. While most meeting participants agreed that this may be an improvement by giving a more synthesized description of events that have occurred, some concerns were expressed regarding the content, format, and interpretability of these aggregate analyses. One participant expressed worry that the aggregated format might create a distorted impression among report recipients by emphasizing only risks without discussing counterbalancing benefits of a study drug. Complications presented by multiple studies of the same drug being conducted by different sponsors were also mentioned—how will these data be incorporated and evaluated? It readily became clear that effort must be put towards generating

best practices for the creation of these aggregate reports to make them as user-friendly and reliable as possible.

As the meeting drew to a close, a number of recommendations were offered for possible next steps in the assimilation of the FDA's IND safety reporting rule into reporting mechanisms. These recommendations are listed below according to general topic.

Recommendations for reports to and communications with investigators

- It is expected that, by requiring some evidence of a causal association for reportable events, the FDA's new premarket safety rule will decrease the number of individual expedited reports of serious events. There was general agreement that supplying investigators with additional aggregate reports would improve investigators' understanding of a drug's safety profile.
- Aggregate reports would best be compiled by a dedicated body within a trial's sponsor organization.
- Best practice for development and presentation of periodic aggregate reports should be developed.
- Aggregate datasets should be set in context for generalizability and applicability to various populations (that is, reports should present the counterbalancing benefits of a study drug). Specific analyses based on at-risk phenotypes and genotypes may be informative.
- Communication with investigators should become paperless, with tracking for follow-through and compliance. Messages to investigators could provide both line-level data and context.

Recommendations for harmonization of regulations

- Outreach to the European Medicines Agency, Canadian regulatory authorities, and other global regulatory bodies should be vigorously pursued to promote harmonization in light of the new FDA rule. Such international efforts should include, in addition to regulators, relevant program officers from the World Health Organization (WHO).
- Coding terminology should be harmonized internationally and aligned with HL-7 for electronic health records.

Recommendations for possible CTTI activities

- Play a role in developing the aforementioned use cases/case studies, seeking agreement on best practice and putting the cases in a public forum for comment. Such cases could be used in a standard educational program targeted to investigators, their staff, and inspectors.
- Create a computer-based training module that explains the new expedited reporting criteria under the IND safety reporting rule. Provide examples of what investigators should report to sponsors and what sponsors should report to FDA and investigators.
- Consider conducting a before/after study regarding the implementation of the FDA's IND safety reporting rule.
- Create a password-protected, virtual venue in which people engaged in clinical research can share bad reporting experiences and lessons learned.
- Convene international regulators to work together to develop consistent reporting requirements. It is recommended that the WHO be invited to such a meeting.

In summarizing the meeting, Dr. Califf remarked that the new FDA rule marks a major step forward in recognizing that little knowledge can be gained from an individual event. Participants agreed that inundating investigators with such data is inefficient and ineffective and that the FDA rule and guidance hold promise for helping to eliminate this burden on investigators. As the discussion revealed, however, implementation of the rule could pose challenges that may only be resolved through the concerted educational efforts and harmonization within the clinical research community, both in the United States and abroad.

APPENDIX A

To view the FDA's final rule on Investigational New Drug Safety Reporting Requirements or Human Drug and Biological Products and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies in Humans, please click on this link:

http://edocket.access.gpo.gov/2010/pdf/2010-24296.pdf.

The rule may also be found in the *Federal Register* (2010;75[188]:59935–59963. 21 CFR Parts 312 and 320.).

Link to the draft guidance:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf

APPENDIX B

Improving the System of Reporting and Interpreting Unexpected Serious Adverse Events to Investigators Conducting Research under an Investigational New Drug Application

Expert Meeting, October 3–4, 2010

Participant List

NAME	ORGANIZATION
Jeff Abrams	National Cancer Institute, NIH
Priscilla Adler	Medstar Health Research Institute
John Alexander	Duke Clinical Research Institute
Leslie Ball	Food and Drug Administration, CDER
Rachel Behrman	Food and Drug Administration, CDER
Fred Bloom	Centers for Disease Control and Prevention
M. Luisa Bonura	Pfizer, Inc.
Grendel Burrell	Duke Translational Medicine Institute
Kelly Cahill	National Institute of Allergy and Infectious Diseases, NIH
Robert Califf	Duke Translational Medicine Institute
Kay Dickersin	Johns Hopkins University
Susan Ellenberg	University of Pennsylvania
Kathryn Flynn	Duke Clinical Research Institute
Bridget Foltz	Food and Drug Administration, Office of Good Clinical Practice
John Fredenburg	Eli Lilly and Co.
Suzanne Gagnon	ICON
Cheryl Grandinetti	Food and Drug Administration, CDER
Christopher Granger	Duke Clinical Research Institute
Howard Greenberg	American College of Clinical Pharmacology (ACCP)

Steve Hirschfeld	National Institute of Child Health and Human Development
Patricia Holobaugh	Food and Drug Administration, CBER
Peter Honig	AstraZeneca
Grant Huang	US Department of Veterans Affairs
Percy Ivy	National Cancer Institute, NIH
Cheri Janning	Duke Translational Medicine Institute
Jonathan Kagan	National Institute of Allergy and Infectious Diseases, NIH
MaryAnn Karolchyk	Novartis
Judith Kramer	Duke Translational Medicine Institute
Mike Lauer	National Heart Lung and Blood Institute, NIH
Michael Lincoff	The Cleveland Clinic Foundation
Diane Maloney	Food and Drug Administration, CBER
Amanda McMillan	Duke Clinical Research Institute
Ann Meeker-O'Connell	Food and Drug Administration, CDER
Margaret Mooney	National Cancer Institute, NIH
Van Moore	US Department of Veterans Affairs
Jean Mulinde	Food and Drug Administration, CDER
Greg Nadzan	Amgen
Janet Norden	Food and Drug Administration, CDER
Nancy Roach	Colorectal Cancer Coalition
Fabienne Santel	Food and Drug Administration, CDRH
Sundeep Sethi	Amgen
Lynda Szczech	Duke Clinical Research Institute
Barbara Tardiff	Parexel
Robert Temple	Food and Drug Administration, CDER
Kathleen Uhl	Food and Drug Administration, CDER
Jose Vega	Amgen
David Vock	Duke University
Kevin Weinfurt	Duke Clinical Research Institute

Janet Woodcock	Food and Drug Administration, CDER
Salim Yusuf	Population Health Research Institute, McMaster University
Deborah Zarin	National Library of Medicine, NIH