National Library of Medicine

Board of Regents Working Group on Clinical Trials

Meeting Minutes

February 9, 2009

The meeting of the Working Group on Clinical Trials of the National Library of Medicine's Board of Regents was convened on Monday, February 9, 2009, at 9:00 a.m. in the NLM Board Room, Building 38, National Library of Medicine (NLM), National Institutes of Health (NIH), Bethesda, Maryland. The meeting was open to the public.[1]

WORKING GROUP MEMBERS PRESENT:
Dr. Thomas Bradley, Maine Office of the Surgeon General
Dr. Sherrilynne Fuller, University of Washington
Dr. Brian Haynes, McMaster University
Dr. Donald Kennedy, Stanford University
Dr. Richard Kuntz, Medtronic, Inc
Dr. Barbara McNeil, Harvard Medical School
Dr. Cynthia Morton [Chair], Brigham and Women's Hospital
Dr. James Powell, National Medical Association
Dr. Frank Rockhold, GlaxoSmithKline
Dr. Louis Rossiter, The College of William and Mary
Ms. Myrl Weindberg, National Health Council, Inc.
Dr. Alastair Wood, Symphony Capital

FEDERAL EMPLOYEES PRESENT:
Ms. Annice Bergens, National Library of Medicine, NIH
Ms. Gemma Flamberg, Office of the Director, NIH
Mr. Nick Ide, National Library of Medicine, NIH
Ms. Christine Ireland, National Library of Medicine, NIH
Ms. Gwynne Jenkins, Office of the Director, NIH
Dr. Tony Tse, National Library of Medicine, NIH
Dr. Rebecca Williams, National Library of Medicine, NIH
Dr. Deborah Zarin, National Library of Medicine, NIH

[1] See 74 FR 3627 (Wednesday, January 21, 2009) of the Federal Register at http://edocket.access.gpo.gov/2009/pdf/E9-984.pdf.

MEMBERS OF THE PUBLIC PRESENT:
Ms. Ginny Beakes-Read, Genetech, Inc.
Mr. Jeffrey Francer, PHRMA
Ms. Lauren Hetrick, Abbott Laboratories
Ms. Carolyn Jones, Biogen IDEC
Ms. Jessica Kloda, Technical Resources International
Ms. Holly Lynch, Hogan & Hartson
Mr. Chris Markus, King & Spaulding
Ms. Jennifer Martin, Biotechnology Industry Organization
Ms. Katie McCarthy, Biotechnology Industry Organization
Mr. Jeff Schomisch, Guide to Good Council Practice
Ms. Vidya Subramanian, Technical Resources International

I. OPENING REMARKS

Dr. Donald A.B. Lindberg, Director of the National Library of Medicine (NLM), welcomed the participants to the second meeting of the Working Group on Clinical Trials of the NLM Board of Regents. He informed participants that the meeting was open to the public and welcomed the public observers. Dr. Cynthia Morton, Chair of the Working Group and of the NLM Board of Regents, also welcomed the members and invited them to introduce themselves. She reviewed the Charge to the Working Group, which was formed to advise the NLM Board of Regents on how NLM can best respond to new legislative mandates regarding clinical trial information, in particular, those contained in Public Law 110-85, the Food and Drug Administration Amendments Act of 2007 (or FDAAA). The group is asked to assess how well NLM is carrying out these mandates, provide any advice it finds appropriate, and report its conclusions.

II. UPDATE ON CLINICAL TRIAL REGISTRATION

Dr. Deborah Zarin, Director of ClinicalTrials.gov, briefed the Working Group members on registry developments since the working group's meeting on February 11, 2008. Dr. Zarin reported that ClinicalTrials.gov registrations continue to increase steadily, with over a third of registrations representing studies being conducted entirely outside the United States. Many Industry-sponsored trials are conducted outside the US even though they are used to support marketing applications in the US, and many non-US sponsors register at ClinicalTrials.gov to comply with International Committee of Medical Journal Editors (ICMJE) policy, which requires registration before enrollment of the first participant in a clinical trial in order for the results of that trial to be considered for publication. Registrations from the academic and non-profit sectors continue to rise and currently account for 42% of the total. Of the 2,100 device trials registered between the enactment of FDAAA (September 2007) and January 2009, 175 studies will not be displayed to the public until the device has received initial Food and Drug Administration (FDA) clearance or approval, as specified in the law. Dr Zarin concluded her remarks by reviewing the extensive communication, outreach, and education efforts of ClinicalTrials.gov staff. New and revised documentation is posted at http://prsinfo.clinicaltrials.gov/fdaaa.html. Dr. Zarin observed that pharmaceutical and

device companies appear to be more aware of the new clinical trial registration and reporting requirements than academic medical centers, and she asked the Working Group members to serve as “ambassadors” in informing their colleagues in the academic and non-profit research communities about FDAAA.

Working group members discussed the relationship between ClinicalTrials.gov and other international registries, and concerns about duplicate registration. Dr. Haynes expressed concern about the effects of duplicate registration and the burden on data providers. Dr. Zarin said that, while the degree of overlap in trials among registries is not known, there is overlap. Some is intended: for example, a sponsor of a multi-national study may be required to register that study in several registries due to different national policies. However, lack of communication between the sponsor and the investigators may result in unintentional duplicate registrations, which are difficult to detect and remove. Dr. Lindberg noted that it can be a challenge to determine whether several registrations represent a single grant-funded trial or multiple trials funded by different grants. Dr. Rockhold recalled that the World Health Organization (WHO) has discussed the duplication problem and has proposed development of another unique identifier (i.e., UTRN). Dr. Zarin noted that NLM had proposed several models, including data sharing among a limited number of regional databases (e.g., similar to the GenBank model for molecular sequence data) and using ClinicalTrials.gov to “host” and facilitate national or regional registrations (e.g., the Israeli Ministry of Health requires all Israeli-conducted trials to be registered in ClinicalTrials.gov and the French National Institute for Health and Medical Research (INSERM) instructs its researchers to register in ClinicalTrials.gov). Dr. Fuller said that a meeting of registry owners be convened to discuss the problem. Dr. Zarin indicated that NLM has aggressively pursued such an approach in the past.

Dr. Fuller asked for clarification regarding distinguishing between the Intervention Type data element, such as a “medical procedure” versus a “medical device,” as it applies to determining whether a study is an “applicable clinical trial.” Dr. Zarin acknowledged that it is sometimes difficult to categorize Intervention Types. As a rule-of-thumb, if the focus of the outcome measure or statistical analysis involves the use of a drug or device, then we believe the study would be considered to have a drug or device intervention; if the drug or device is used in the same way in all arms of the study, then it would not be considered a trial of a drug or device under FDAAA. Dr. Wood reminded the group that while the distinction is an important one for complying with FDAAA, the ICMJE policy does not distinguish among intervention types and requires all clinical trials to be registered.

Dr. Zarin reminded the working group that the requirements for registering trials would be clarified through rulemaking. Until regulations are promulgated, ClinicalTrials.gov cannot reject a record that doesn’t contain all of the requested data elements, only records that are missing the smaller set of data elements marked as “required”. As a result, some 40% of submitted records are missing some of the data elements that ClinicalTrials.gov is designed to collect. The rulemaking process provides an opportunity for public comment on the proposed data elements, and the resulting

regulations will provide a basis for future enforcement efforts. Dr. Wood highlighted the differences between a determination of "submission sufficiency" and the assessment of penalties. For example, data elements with missing or insufficiently meaningful information could be highlighted in ClinicalTrials.gov to allow the public to easily see which submissions are incomplete. Dr. Zarin pointed out that the "Tabular View" in ClinicalTrials.gov already highlights missing information without assessing penalties, but, as Ms. Humphreys indicated, NLM was advised by the Office of the General Counsel to undertake rulemaking.

Ms. Weinberg asked who would be designated as a responsible party for a trial conducted under formal contractual mechanisms developed by patient advocacy organizations. Dr. Zarin replied that the principal investigator (PI) would likely register such a trial through an account maintained by an organization with which he or she is affiliated. Mr. Sheehan commented that the algorithm for determining the responsible party is in available in the draft "elaborations" document at http://prsinfo.clinicaltrials.gov/fdaaa.html. The elaboration document represents an interpretation of the statute drafted by NLM, NIH, and FDA, on which comments are welcome. They are intended to assist the affected community until such time as regulations are promulgated. Ms. Weinberg observed that document is written in dense language and requested that a plain-language version be made available.

III UPDATE ON RESULTS DATABASE

A. Implementation of the Basic Results Database and Experience to Date

Dr. Zarin informed the working group that an operational version of the web-based results data entry system was launched in September 2008, prior to the statutory deadline of September 28, 2008. The system is a work-in-progress, and improvements continue to be made. As of February 6, 2009 results had been submitted for 410 studies: 293 were submitted by 72 industry data providers and the remaining 117 studies were submitted by 80 government, academic, or non-profit entities. An increasing number of results submissions are anticipated in the coming months based on projections using registration data. (In general, results must be reported within one year of the "primary completion date," although FDAAA provides for delays in submission under specific circumstances). The basic results data elements are clustered into four modules: Participant Flow, Baseline and Demographic Characteristics, Outcome Measures, and Adverse Events. Other results information includes disclosure of sponsor-imposed agreements that restrict the ability of the principal investigator (PI) to discuss or publish study results, limitations and caveats, and a scientific point of contact for more information about the results. Data providers "construct" the required tables by specifying the needed rows and columns (e.g., specific outcome measures and comparison groups) and then insert the corresponding data. Such a format allows the system to accommodate a wide range of study designs and facilitates consistent display, search, and comparisons across studies.

Working group members asked about the experiences of industry, academia, and government in reporting results. Dr. Zarin replied NIH-funded trials are being registered increasingly by grantee institutions. While industry is familiar with regular, large scale results reporting, government and academia still have much to learn. Results have been reported for several NIH extramurally funded trials, but not from intramural trials. Dr. Wood commented that the Certain Agreements data, which documents whether and how sponsors impose restrictions on principal investigators regarding speaking or publishing the study results, could be very useful in understanding clinical research contracts with industry. Currently, data providers may indicate whether limitations restrict their communications for 60 or fewer days, between 60 and 180 days or "other." Dr. Wood said that a more comprehensive set of categories could help structure the nature of industry-academia contracts and indicated that such data be collected during registration (as any such agreements would likely be arranged prior to initiation of the study). Regarding the Outcome Measures module, Dr. Wood asked why Outcome Measures may be reported without statistical analyses. Dr. Zarin explained that FDAAA requires a table of primary and secondary outcomes for each arm, "*including* the results of scientifically appropriate tests of the statistical significance of such outcome measures." ClinicalTrials.gov does not require statistical analyses because it is unclear which tests are "scientifically appropriate" for a particular outcome measure and not all outcome measures are tested for statistical significance.

Dr. Zarin reported that ensuring the quality of posted results submissions has been challenging. Because results are displayed as data tables with minimal descriptive text, data providers need to provide meaningful and precise labels and/or descriptions for the table columns and rows to help users interpret the results. Before the submitted results are posted, the NLM reviews the information to check its apparent validity (when possible), meaningfulness, internal consistency and logic, and formatting. ClinicalTrials.gov quality assurance (QA) staff and the data providers undergo iterative communications to correct serious flaws and ensure that minimal quality standards are reached. An important lesson from experience to-date is that the person entering results data needs to understand the study design and data analysis (e.g., reporting should involve the clinical investigator and/or biostatistician). While organizing and submitting the results data requires traversing a steep learning curve the quality of the submissions from "experienced" data providers is improving substantially. ClinicalTrials.gov staff is attempting to accelerate the process by developing improved tutorial and outreach materials online, presenting information at numerous conferences, and working with some of the over 6,000 data providers.

Dr. Rockhold observed that reporting Outcome Measures is the largest impediment to results reporting, since the data cannot be entered by a medical writer but requires someone with statistical experience and knowledge of the study. Only a statistician and the PI have the necessary knowledge about statistics and the particular study. From GlaxoSmithKline's (GSK's) experience, there is no easy way to centralize this process. Dr. Rockhold concluded that the best time to prepare for results submission is likely to be at the time a manuscript describing the results is being prepared for publication. Ms. Humphreys commented that NLM needs to get the message to data providers that a

statistician needs to be involved in results reporting. Dr. Zarin pointed out that clinical study reports (CSRs) are prepared routinely. Dr. Haynes asked if there is a way to see what pre-specified outcome measures were originally registered and how they might have changed when results data are submitted. Dr. Zarin replied that changes to the ClinicalTrials.gov registry and results database could be tracked through the archive site (http://clinicaltrials.gov/archive/).

With regard to the Adverse Events module, working group members discussed several ways of making the information more understandable to the public and other users of Clinical Trials.gov. Several members noted that the current way of collecting the data did not allow users to determine how many subjects experienced adverse effects – e.g., did a few participants have multiple adverse events or did many participants have a few? Dr. Wood indicated that a user might add the number of adverse events (incorrectly), not realizing that individuals with multiple adverse events may be represented in multiple rows. Dr. Zarin informed the group that adverse events cannot be listed at the study participant level, as it might lead to identifiable data. Mr. Ide noted that the data element "Total Number of Participants Affected" provides a sense of how many patients experienced multiple adverse events, but is not possible to know for certain based on the data elements. Dr. Kuntz expressed concern that the reported results data could be easily misinterpreted or misused and questioned the wisdom of posting results before it is either peer-reviewed or assessed by the FDA. Dr. Zarin responded that NLM is not in a position to discuss whether basic results should be reported since it is required by FDAAA, but noted that NLM and the Working Group are in a position to consider the optimal way in which to present the data for the public good within the context of the law. For example, providing explanatory material to explain the technical concepts to members of the public would be one way to address these concerns. Dr. Rockhold indicated that the GSK results database includes information providing context for adverse events data and provides links to FDA-approved drug labels. Dr. Wood proposed adding disclaimers to the ClinicalTrials.gov database to convey caveats such as "not all reported adverse events are drug induced" and "not all observed differences are significant." Dr. Zarin noted that such caveats would also apply to the outcome measures and statistical analyses module.

Dr. Rockhold questioned whether members of the public would be able to arrive at the appropriate conclusion after viewing the adverse events tables. Dr. Wood observed that while rare events within a population are easily detected from adverse events reporting data, it is more difficult to detect adverse events common to a population because of substantial "background noise." Even if the adverse events data were available, the baseline occurrence of adverse events in the population being studied would be required to make sense of the reported data. Dr. McNeil asked whether *p* values could be calculated on adverse events reported at ClinicalTrials.gov. Dr. Rockhold highlighted the methodological challenges of doing so (e.g., statistical power; multiple comparisons) and indicated that GSK's experience suggests that statistical analyses around adverse events do not help readers. Dr. Haynes noted that it would be difficult for users to distinguish "noise" from statistically significant differences in adverse events between interventions if they had access only to the raw adverse events data and asked whether

ClinicalTrials.gov could require the reporting of statistics in the Adverse Events module to facilitate interpretation. Adverse events may not be caused by the experimental intervention, and people may confuse “association” with “causation”. Dr. Zarin responded that while the law does not require statistics for adverse events, data providers can and do report pre-specified adverse events as outcome measures with statistical analyses. She indicated that language could be added to ClinicalTrials.gov to explain the adverse events table to the lay public. Dr. Haynes saw value in providing a guide to help viewers of the results database interpret and understand the results data, statistical analyses, and reported adverse events. Dr. Rockhold cited a need for basic terms to be defined and Ms. Weinberg emphasized that plain-language experts be consulted. Dr. Zarin responded that developing such a guide is on the list of features to implement and indicated that NLM would seek the input of risk communication experts in doing so.

Ms. Weinberg observed that no major clinical decision should be made based on data from a single study and that results data needs to be placed in the context of other evidence. Dr. Zarin responded one way to provide context would be to link study results to relevant systematic reviews. Dr. McNeil asked what conclusions physicians or patients could logically draw from the displayed results data, even if all data elements were reported. Dr. Wood noted that a data table reporting myocardial infarctions in the 2000 New England Journal of Medicine paper (on the VIGOR trial) looks similar to the ClinicalTrials.gov results display. Even so, knowledgeable people had trouble interpreting these data.

Dr. Zarin commented that data providers are required to indicate whether the adverse events were collected “systematically” (e.g., using a standard check list of adverse events) or through “spontaneous reporting” (e.g., observed during clinical examinations). She asked the Working Group whether data providers should be permitted to submit “pertinent negatives” when using a systematic approach (i.e., anticipated adverse events that are *not* observed). Dr. Wood objected, noting that if the threshold for reporting adverse events were set to any level other than “0 percent,” the reporting of pertinent negatives would potentially be misleading. Dr. Rockhold observed that without a threshold, reporting all adverse events could result in a list that spans 25 or more pages. Based on the discussion, Dr. Zarin agreed that the reporting of pertinent negatives would not be a useful step.

B. Quality Assurance and Technical Issues and Proposed Next Steps

Dr. Zarin discussed common quality concerns with results submissions, drawing on the first four months of operation of the results database. Some of common errors include improper use of terms (e.g., “incidence,” “proportion,” “ratio,” and “frequency”), lack of sufficient detail in describing measures that involve changes and scales, descriptions of complicated outcomes that are difficult to understand, and inconsistencies between results information and registration information (e.g., participant flow numbers and registered enrollment information. ClinicalTrials.gov will not accept submissions that do not meet minimum quality standards. The question staff must ask (and on which

Working Group input is sought) is “Where to draw the quality line?” While the QA process aims to ensure that meaningful and comprehensive results summaries are displayed to public, it also places demands on staffing and time, for both data submitters and NLM. What is the optimal balance? Dr. Zarin described ongoing work to facilitate QA by the in-house contractor staff, such as developing new technical tools to optimize efficiency. Other efforts could include developing and improving training materials and collaborating with academic medical centers (e.g., NIH-sponsored organizations through its Clinical and Translation Science Awards or CTSAs and the Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Centers or EPCs) to conduct high-level reviews of the submissions. The challenge will become more difficult as the number of submitted results records increased. As noted by Dr McNeil, 410 studies with results have been submitted to ClinicalTrials.gov to date, but only 47 had been posted.

The working group discussed several possible ways of increasing the efficiency of the process. Dr. Rockhold commented that greater efficiencies in the QA process could be obtained if only certain data were reviewed. Ms. Weinberg supported the idea of specifying two levels of data: “reviewed” and “not reviewed.” Unreviewed data, could include a disclaimer stating that the information had not undergone quality review. Dr. Wood stated that only reviewed data could be displayed, with links provided to the unreviewed material that would be formatted differently so that it would be distinguishable from the reviewed data. Dr. Haynes commented that the QA review should focus on establishing a high fidelity record of the pre-specified primary and secondary outcome measures for each study. The key is to know what was planned to be done in the study. Otherwise, if the outcome measures in the results database deviate from those in a published paper, ClinicalTrials.gov will have a credibility problem. Ms. Humphreys commented that NLM cannot verify the validity of the reported results because it does not have access to the raw data. Dr. Haynes replied that there are different types of errors, such as mistakes in data entry or typos versus errors that are introduced intentionally. Dr. Zarin observed that, based on comparing submitted study results data with registration data, she estimates that about a third have discrepancies in reported outcome measures and a half do not provide specific information.

The working group also discussed ways of improving processes within data submitting organizations. Dr. Wood observed that medical writers are not the appropriate people to enter results data – data entry needs to be conducted by people who understand the study and are able to construct data tables and specify statistical analyses. Dr. Zarin said that interacting directly with data providers and providing training materials only goes so far, as ClinicalTrials.gov currently has over 6,000 data providers. Dr. Wood commented that it would be interesting to know whether the improvements among industry data providers result from personnel changes or the existing data entry staff learning the new results submission process. Dr. Zarin noted that, based on consultations with journal editors, journals frequently see errors in manuscripts. So even if there is a training program, there is still a need for the QA function. Dr. Wood concurred that ClinicalTrials.gov would need to support both training and a QA process.

He highlighted the possibility of a forum for data providers to share “best practices.” He agreed that “high-level truth” or “best practices” would be useful for other data providers and added that NLM might consider adopting FDA’s “refusal to file” mechanism for results submissions that do not meet basic data quality standards.

Regarding the reporting of sufficient information for describing scales used in assessing outcome measures, Dr. Zarin discussed the notion of a “bank of scales” from which data providers could select standard scales by domain or medical specialty. Dr. McDonald observed that clinical rating scales often change over time. Dr. Wood noted that, as with methods sections in journal articles, data providers could cite published references to a method or scale and describe any changes or modifications they have made. Working Group members believed that requiring the domain of a scale and its best and worst scores would be reasonable approach. Dr. Kuntz added that data providers might also wish to provide normal ranges for reference. Dr. Rockhold responded that encouraging the submission of more details could be a “slippery slope” with regard to increasing the QA load.

Ms. Weinberg saw value in Dr. Zarin’s proposal to contract with academic medical centers with graduate programs in biostatistics or clinical epidemiology and CTSA or EPC organizations to review results submissions. She commented that such organizations would be a good match because they have people with the appropriate background who would be interested in this kind of work. Dr. Wood observed there are generally two “levels” of data providers: (1) high volume, such as pharmaceutical companies, and (2) low volume, such as academic PIs. However, he anticipates that the marketplace could provide a service for the low-volume data providers (e.g., results reporting consultants). Ms. Humphreys replied that while the responsible party is legally responsible for the results data, large, high-volume data providers could act as “service bureaus” for the smaller data providers, analogous to the experience with PubMed Central. Dr. Wood added that that contracted academic medical centers would develop “core competency” in results reporting. Consequently, permanent employees could provide a results reporting service to University-affiliated clinical researchers. After all, the mission of the CTSA program is providing infrastructural support for clinical research.

IV REQUSTS FOR EXTENSIONS AND OTHER SCIENTIFIC ISSUES

Dr. Zarin reviewed provisions in FDAAA that permit responsible parties to extend the results submission deadline by submitting a written request that demonstrates “good cause” for the delay and provides an estimated date for submitting results. She reported that 14 requests for extensions have been filed to date, over half of which request more time so that data analysis can be completed. She proposed that the Working Group itself help develop a set of general principles that the NIH could follow in making individual case-by-case decisions. The working group could identify broad categories requests that are acceptable (e.g., data is still blinded) and unacceptable (e.g., seeking publication) for extending the deadline and propose them to the Board of

Regents. The Working Group agreed to assist in this manner and to set up a separate meeting for preliminary discussions.

Dr. Zarin then outlined some scientific issues for discussion by the working group, such as tracking and displaying changes to the registry and results database. Data providers may update or change ClinicalTrials.gov records at any time; there is no time when the data become "frozen" and changes are prohibited. Currently, the default public view is the most recent entry (i.e., last updates), as discussed at the February 2008 Working Group meeting. To alert users to what they are seeing, the "first received" and "last updated" dates are posted on the record. In addition, an archive site (http://clinicaltrials.gov/archive/) displays all changes made to a record since the initial registration. However, there are concerns that users may not understand what version they are seeing on the public site. In addition, questions arise about policy implications (e.g., Should changes be allowed to the registry even after completion of the study?). Alternatives to the current system of displaying the most recently updated record include showing the initial registration as the default and showing the most recent version to the public up to a certain point (e.g., study completion), then "freezing" the display while allowing changes to be entered and displayed upon request (e.g., a link to the most recently updated version). Dr. Zarin pointed out that (1) not all data elements are expected to change with the same frequency (e.g., sponsor name versus recruitment status); (2) not all changes are equally significant (e.g., correcting a typo versus revising a pre-specified outcome measure); and (3) there are legitimate reasons for making changes, such as in response to the QA process, changes to the database structure (e.g., addition of a new data element), or changes in policy requirements (e.g., new ICMJE required data element). Dr. Wood described one possible approach -- that ClinicalTrials.gov show the originally registered data and provide links to updates, similar to the way PubMed links to Errata and Correspondence. ClinicalTrials.gov needs to display when changes have been made, whether good, bad, or neutral. Ms. Humphreys suggested providing a general statement that some changes may be legitimate. Dr. Zarin showed a mockup of the ClinicalTrials.gov "Tabular View" with new metadata designed to help users track important changes, which Dr. Wood indicted would be useful and address some of the concerns that have been discussed.

Dr. Zarin noted that outcome measures are being reported to the registry with a low level of specificity and precision, for example, "blood pressure at 3 months" and questioned how much specificity is useful, considering that there are multiple audiences Dr. Wood indicated that getting the protocol at registration would be a useful way to determine when changes in the outcome measure deviate from the original research plan. Dr. Zarin noted that the law requires the issue of submitting full protocols with results reporting to be addressed during the three-year rulemaking. Dr. Haynes stated that data providers should be required to submit sample size calculations to support their designation of outcome measures as "primary." Dr. Haynes cautioned that a proliferation of outcome measures leads to data-driven (rather than hypothesis-driven) research. Dr. Zarin indicated that, as far as she knows, none of the existing registration policies require the submission of a pre-specified analytic plan (separate from the outcome measure), and that analytic plans are not always specified in protocols. Dr.

McNeil added that power calculations and analytic plans are likely to be considered proprietary information. Dr. Kuntz confirmed that such is the case for many device clinical trials and proposed making power calculation and analytic plan information available to ClinicalTrials.gov, but not to the public.

Dr. Rockhold asked for clarification on the 2007 ICMJE editorial ("Clinical Trial Registration: Looking Back and Moving Ahead" at http://www.icmje.org/clin_trial07.pdf) and the statement that results reporting "presented in the form of a brief, structured (<500 words) abstract or table" would not be considered prior publication. Dr. Zarin replied that the editorial was published before enactment of FDAAA. ICMJE has since reaffirmed that the 500 words does not include data in tables and that submission of results data to comply with FDAAA is not considered prior publication by the ICMJE.

V. SUMMARY AND NEXT STEPS

Dr. Zarin summarized the statutory requirements for a public meeting to provide interested parties an opportunity to provide input on the issues to be addressed by the three-year rulemaking provision in FDAAA. She announced that the public meeting would be held on April 20, 2009 on the NIH campus. A *Federal Register* notice is being drafted and will be published with complete details. She then described key issues that would be discussed at the meeting, noting that they are related to topics that are required to be considered in developing regulations to expand the ClinicalTrials.gov registry and results database: possible reporting of the results of trials of unapproved products; inclusion of narrative summaries of trials for technical and lay audiences; processes for data quality validation informed by a pilot quality control project; and whether full protocols or extracts "necessary to help evaluate the results" are to be required. Mr. Sheehan replied that, in addition to the *Federal Register* notice, the information about the public meeting will be disseminated through multiple channels including the NIH FDAAA Update Listserv and FDA mailing lists. Ms. Weinberg observed that the audience at the public meeting could benefit from the panel's experience and suggested the National Health Council (NHC) help disseminate information about the meeting to patients, family members, and others stakeholders. The working group agreed to discuss preparations for the Public Meeting during a teleconference to be scheduled in coming weeks.

Dr. Lindberg wrapped up the meeting by reminding the Working Group of the question on which he would most like their feedback: Is the NLM implementation of FDAAA working? He observed that, while it is incredible that NLM was able to build the results database in a year, the data providers are off to a slow start-- the technical portion of developing a results database is relatively straight-forward compared to changing practice within the clinical research community. Dr. Fuller replied that she sees it as "the glass is half full." In her opinion, a considerable amount of work has been accomplished in six months. This is important to note before raising questions about how to make the system better and faster.