

National Library of Medicine
Board of Regents Working Group on Clinical Trials

Meeting Minutes

February 11, 2008

The first meeting of the Working Group on Clinical Trials of the National Library of Medicine's Board of Regents was convened on Monday, February 11, 2008, 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 (Appendix A):

Dr. Cynthia Morton (*Chair*)
Mr. Thomas Bradley
Dr. Jordan Cohen
Dr. Sherrilynne Fuller
Dr. R. Brian Haynes (by teleconference)
Dr. Donald Kennedy
Dr. Barbara McNeil (by teleconference)
Dr. James Powell
Dr. Frank Rockhold
Dr. Louis Rossiter
Ms. Myrl Weinberg
Dr. Alastair Wood.

WORKING GROUP MEMBERS ABSENT:

Dr. Rob Califf

SPEAKERS:

Dr. Deborah A. Zarin, Director, ClinicalTrials.gov, NLM
Mr. Jerry Sheehan, Assistant Director for Policy Development, NLM
Mr. Todd Danielson, Executive Officer, NLM
Dr. Clement McDonald, Director, Lister Hill National Center for Biomedical Communications (LHNCBC), NLM

¹ See 73 FR 3473 for the Federal Register Notice.

MEMBERS OF THE PUBLIC PRESENT:

Mr. Hugues Barbier, CRNS
Ms. Tracy Beck, Eli Lilly and Co.
Ms. Inbal Bentzuitzchori, TRI
Ms. Jonca Bull, Genentech
Mr. Dane Christiansen, MLA-AAHSL
Mr. Jeffrey Francer, PhRMA
Ms. Rosemary Ganz, Medtronic, Inc.
Ms. Barbara Godlew, The FAIRE Co.
Dr. Alan Goldhammer, PhRMA
Ms. Jennifer Hobin, FASEB
Ms. Kerstin Mikalbrown, BIO
Mr. Daniel Molina, TRI
Ms. Jen Pollakusky, Elizabeth Glaser Pediatric AIDS Foundation
Mr. John Powers, SAIC (contractor to NIAID)
Mr. Jeffrey Schomisch, Guide to Good Clinical Practice
Ms. Gail Shearer, Consumers Union
Ms. Alexis Walker, AAAS
Ms. Rita Warfield, Wilmer Hale, LLC

FEDERAL EMPLOYEES PRESENT:

Ms. Annice Bergeris, LHCBC, NLM
Ms. Valerie Bonham, Office of the General Council, NIH
Ms. Kathy Cravedi, Director, Office of Communications and Public Liaison, NLM
Mr. Todd Danielson, Executive Officer, NLM
Ms. Gemma Flamberg, Office of Legislative Policy and Analysis, NIH
Ms. Pam Gilden, Office of Extramural Research, NIH
Ms. Lakshmi Grama, National Cancer Institute (NCI)
Dr. William Harlan, LHCBC (Contractor), NLM
Ms. Betsy L. Humphreys, Deputy Director, NLM
Mr. Nick Ide, LHCBC (Contractor), NLM
Ms. Christine Ireland, Division of Extramural Programs, NLM
Mr. Robert Lanman, Office of Science Policy (Contractor), NIH
Dr. Donald A.B. Lindberg, Director, NLM
Dr. Clement McDonald, Director, LHCBC, NLM
Ms. Margarita Ossorio, NCI
Ms. Alison Robbins, LHCBC, NLM
Mr. Jerry Sheehan, Assistant Director for Policy Development, NLM
Ms. Terry Toigo, Food and Drug Administration (FDA)
Dr. Tony Tse, LHCBC, NLM
Dr. Rebecca J. Williams, LHCBC, NLM
Dr. Deborah A. Zarin, Assistant Director for Clinical Research Projects & Director,
ClinicalTrials.gov, LHCBC, NLM

I. OPENING REMARKS

Dr. Donald A.B. Lindberg, Director of the National Library of Medicine, welcomed the participants to the first meeting of the Working Group on Clinical Trials of the Board of Regents. He informed participants that the meeting was open to the public and indicated that any written materials submitted to the Working Group would be distributed for their consideration after the meeting. 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 best the NLM can respond to new legislative mandates regarding clinical trial information, in particular those contained in Public Law 110-85. In particular, the group is asked to determine if NLM is doing the best job possible in carrying out these new mandates, provide whatever advice it finds appropriate, and report its conclusions.

II. BACKGROUND AND LEGISLATIVE REQUIREMENTS

Dr. Deborah Zarin, Director of ClinicalTrials.gov, reviewed the ethical and scientific rationales for increasing clinical trial transparency via prospective, public registration of clinical trial information. She then summarized the history of ClinicalTrials.gov, noting that the registry was originally developed to provide information about effectiveness drug trials to patients with serious or life-threatening diseases and conditions, as mandated by Section 113 of the Food and Drug Administration Modernization Act of 1997 (FDAMA 113). The system has evolved to accommodate a number of domestic (federal and state) and international registration policies, including the registration policy of the International Council of Medical Journal Editors (ICMJE), which went into effect in September 2005. Since that time the number of new registrations and new user accounts has steadily increased. ClinicalTrials.gov is currently the largest clinical trials registry in the world, with information on more than 50,000 interventional and observational studies being conducted in more than 150 countries. Dr. Zarin summarized the current data entry and validation process via the Web-based Protocol Registration System (PRS).

Mr. Jerry Sheehan, NLM's Assistant Director for Policy Development, reviewed the main provisions in Title VIII of Public Law 110-85, also known as Section 801 of the Food and Drug Administration Amendments Act of 2007 (FDAAA 801). The law, which was enacted on 27 September 2007, calls for expanding the ClinicalTrials.gov registry and adding a clinical trial results database. FDAAA 801 sets out a specific timetable for: 1) expanding the existing ClinicalTrials.gov registry to include more trials (e.g., device trials, in addition to trials of drugs and biologics), more information about each trial, and links to existing results information at FDA and NIH (within 90 days of enactment, i.e., by 26 December 2007); 2) adding a basic results database (within one year of enactment, i.e., by 27 September 2008); 3) holding a public meeting, adding a listing of serious and frequent adverse events to the results database, conducting a pilot quality study, and 4) expanding the registry and results database by rulemaking (within three years of enactment, i.e., by 27 September 2010). Mr. Sheehan reviewed key terms defined in FDAAA 801, including "responsible party," (the sponsor of the clinical trial or a designated principal investigator) and "applicable clinical trial" (certain trials of drugs, biologics, and devices regulated by the FDA), as well as the registration data

elements that are explicitly enumerated in the statute and that are needed to implement the registry in compliance with the law. He then explained some of the procedural aspects of the law's provisions, including the timing of submitting and posting clinical trial information, information required for the basic results database, issues to be considered during the three-year rulemaking, and the penalties for non-compliance with FDAAA 801.

Mr. Todd Danielson, NLM's Executive Officer, explained that implementation and operation of the expanded ClinicalTrials.gov registry and results database would require additional resources. In FY 2007, ClinicalTrials.gov had a budget of \$3 million, which supported 16 government and contractor staff engaged in technical development, administration, and quality assurance. Two of those staff members were added during the year in anticipation of the legislation. The budget also supported exploratory work on results reporting. In FY 2008 (which began on 1 October 2007 – only four days after enactment of the law), NLM's budget remains flat in nominal terms, but declines in real terms. Despite this, NLM is reallocating \$700,000 to augment the ClinicalTrials.gov budget and support the implementation of new requirements mandated by FDAAA 801. This funding will support an estimated 6 additional full-time staff. A request has been submitted for additional office space. Once the results database is implemented (near the end of FY 2008), the cost of maintaining the increasing load of registrations and simultaneously processing clinical trial results will require substantially more funding. The law authorizes \$10 million annually for FDAAA 801, but these funds were not included in the FY2008 appropriations, and it is not clear how such funding would be distributed between the NIH and FDA were they to be appropriated.

During the discussion, Dr. Cohen asked if NIH is considered the responsible party for its funded studies. Mr. Sheehan responded that NIH considers itself the responsible party for all intramural clinical studies. For extramural studies for which it holds the IND or IDE, and all studies for which it has provided funding via a contract, NIH is the responsible party, but may transfer that responsibility to the principal investigator as permitted by the law. For other grant-funded research, the grantee institution would be considered the responsible party.

Dr. Wood observed that some terms used in the law are not well-defined (e.g., phase 1, controlled, adverse event), causing confusion among registrants. The definition of adverse event and the way in which it is reported may also affect the ability to detect safety issues (mortality can serve as both an outcome measure and adverse event). Dr. Rockhold mentioned that the World Health Organization avoided the specification of study phases in the scope of trials to be registered due to the inherent ambiguities in this classification scheme. Ms. Humphreys indicated that interpretation of the law is currently under discussion at the Department of Health and Human Services (HHS) and that rulemaking is being considered. Mr. Sheehan reminded the Working Group that the law specifies that both anticipated and unanticipated adverse events observed in a trial are to be reported.

Dr. Fuller requested clarification regarding the trials of drugs or devices that are regulated by FDA. Dr. Zarin explained that the situation is not always straightforward. For example, if a study has at least one study facility in the United States, then it likely falls under FDA's jurisdiction. Studies conducted outside the U.S., but intended for use in an FDA application for marketing approval or clearance, may also need to be registered. Dr. Zarin indicated that ClinicalTrials.gov has requested further clarification of the scope of FDA's authorities and the definition of applicable clinical trials so that it may better guide registrants.

Dr. Haynes suggested that the revised Consolidated Standards of Reporting (CONSORT) statement and its recent extension may serve as a source of standard, consensus definitions of clinical trial terms. Dr. Zarin remarked that the work of the CONSORT Group, including the recent extension on meeting abstracts, informed planning for the basic results database and adverse events tables. However, the requirements in the law are highly specific and not completely consistent with CONSORT.

Dr. Rossiter asked for clarification about rulemaking. Ms. Humphreys replied that HHS, NIH, and FDA would be involved in any rulemaking that may occur. She indicated that rulemaking is explicitly required only for the expanded registry and results database (within 3 years of enactment). It appears that Congress intended NIH to complete the initial expansion of the ClinicalTrials.gov registry without rulemaking. Due to ambiguity in the law, however, it has been suggested that rulemaking may be advisable. HHS is considering this option, and a decision should be made soon. In the meantime, NLM has provided a system in good faith and within the timeframe allowed that enables registrants to comply with the law. Dr. Kennedy agreed that Congress appears to have wanted the expanded registry to be implemented rapidly without rulemaking.

Dr. Rossiter inquired about responsibility for enforcement. Mr. Sheehan replied that details of the enforcement plan are still to be worked out among NIH, FDA and HHS, but that different functions would likely be taken up by different agencies. NIH would be responsible for withholding grant funding from non-compliant grantees (as would other federal funders of applicable clinical trials), and NLM would be required to post notices of noncompliance, but application of civil monetary penalties would be handled elsewhere. Dr. Lindberg stated that the Department of Justice could also be involved in enforcement.

Ms. Weinberg asked about coordination of the various trans-HHS responsibilities in implementing the law. Ms. Humphreys indicated that there is a Department-wide process in place to coordinate implementation of all titles of the new law. While the immediate focus had been on the 90-day requirements, the Department-wide process is now being applied to the full set of statutory requirements. Mr. Sheehan pointed out that several NIH-FDA Working Groups are being established to coordinate implementation of various parts of the law.

Dr. Powell asked whether efforts would be made to explain differences between adverse event information that is submitted to the results database and that is included on FDA product labels. Mr. Sheehan replied that this type of review is not required by the statute, even if the creation of the results database and adverse event reporting system would enable such comparisons.

Dr. Cohen asked how the \$10 million annual authorization for FDAAA 801 would be distributed among agencies (if it were appropriated). Ms. Humphreys said that such funding, if appropriated, would likely be distributed among all relevant agencies. Dr. Lindberg stated that implementing this law is a high priority for NLM. Mr. Danielson reiterated that while the transfer of internal FY08 funds will sustain the design and development activities, implementation of the results database – in addition to managing an increased number of data submissions to the registry – will require more resources.

Dr. Cohen asked for clarification about the required data elements under FDAAA 801. Dr. Zarin responded that ClinicalTrials.gov was modified by 26 December 2007 to enable registrants to comply with the law. Pending HHS's ongoing deliberations, it is not yet possible to identify the data elements that will be required for registration or their specific formats. Nevertheless, NLM's view is that registrants will most likely be in compliance with the law if they provide responses for all of the requested data elements at ClinicalTrials.gov.

Dr. Rockhold stated that the multiple versions of data elements and annotations used in the current data element definitions document for ClinicalTrials.gov are causing confusion. Ms. Humphreys explained that the data elements correspond with the 25 items listed in the law, but that a structured approach has been used to collect and display information about some complex concepts, such as "Study Design," to enhance the usefulness of the registry and improve data quality. Some additional data elements not specifically enumerated in the law have also been included in the registry because they are necessary for complying with the law. For example, knowing whether a trial is an applicable clinical trial is necessary to implement compliance and enforcement provisions. NLM cannot be more explicit about absolute registration requirements until decisions have been made in consultation with HHS.

Dr. Wood suggested distinguishing between data elements that a reasonable person would agree are required by the law and those based on NLM interpretation, including the set of additional data elements that NLM believes are necessary to implement the law. Compliance with the first set of data elements would allow affected parties to fulfill their legal obligation to register without getting bogged down in the ongoing debates over the data elements in the second set.

Dr. Rockhold also commented that the current data elements do not easily accommodate the registration of phase 1 trials, which some registrants, including GSK, submit voluntarily. Dr. Wood emphasized that the registration of phase 1 trials is important. Dr. Zarin reminded the Working Group that the ICMJE policy will require registration of phase 1 trials for all intervention types beginning in July 2008 and welcomed further discussion of appropriate data elements for such trials.

Dr. Lindberg commented that the current disagreement over data elements is not a clear-cut dispute between the federal government and industry. He noted that some companies are not fully complying with the requested data elements, but many are submitting most, if not all, of the requested data elements.

III EXPANDED CLINICAL TRIALS REGISTRY

Dr. Zarin summarized NLM's recent achievements to-date in modifying ClinicalTrials.gov to meet the requirements of FDAAA 801. She informed the group that a modified PRS was launched in November 2007 to allow registrants to comply with the expanded set of registration requirements. In addition, new links were added from ClinicalTrials.gov to the NIH and FDA results resources specified in the law, and NIH prepared and distributed several documents to inform affected communities (e.g., data element definitions, fact sheet, NIH Guide notices, and a FAQ for NIH grantees and contractors). Registrants are actively using the revised system. During the seven-week period from 1 December 2007 to 20

January 2008, the average weekly numbers of new and modified trial registrations more than doubled from their previous levels, and the number of new PRS accounts grew by approximately 65%. Of the more than 500 device trials registered or revised during the seven-week period, just 27 were withheld from public posting, but more than 70% of device registrants did not respond to the question that would put their information in the lock-box.

Dr. Zarin reviewed the data elements collected by ClinicalTrials.gov. She noted that requested data elements have evolved since ClinicalTrials.gov was first established to allow registrants to comply with multiple registration requirements, including applicable federal and state laws and the publication policies of medical journal editors. Doing so ensures that ClinicalTrials.gov remains a comprehensive clinical trials registry while minimizing the reporting burden on registrants. FDAAA enumerates 25 elements of information to be submitted to the ClinicalTrials.gov registry, but implementing the new requirements has been challenging. Ensuring complete entries for some of these items means that several pieces of information must be collected. For example, “study design” is generally recognized (e.g., by the International Conference on Harmonization and FDA) to include information on the intervention model (e.g., parallel vs. cross-over design), masking (e.g., double vs. single blinding and who was masked), and allocation (i.e., randomized vs. non-randomized). In addition, operating the registry in a way that conforms with specific requirements of the law appears to entail the collection of additional information (e.g., knowing whether a listed outcome measure is a safety issue is needed to enable the required ability to search by this criterion). Some registrants claim the law does not authorize the collection of such information, prompting the Department of Health and Human Services to consider various options, including rulemaking, to improve the clarity and enforceability of requested data elements.

In response to a question about the quality assurance process used by ClinicalTrials.gov, Dr. Zarin reported that a number of automated and human checks are made to the data. Both follow algorithms to improve data completeness and validity. Human intervention is especially important for certifying the validity of intervention names (e.g., “new chemical entity” is not an acceptable entry). Quality assurance typically requires 2 to 3 days, but the increasing volume of registrations and updates has slowed the process in recent weeks. Dr. Wood observed that while drug names are fairly well controlled, devices are not easily distinguishable or identifiable, making quality assurance more difficult.

Several Working Group members, including Dr. Haynes, Dr. Cohen, and Dr. Wood, asked for clarification about the role of the Working Group, the criteria it should use in assessing NLM’s efforts, and the types of questions it should address. Dr. Lindberg replied that the role of the Working Group is to evaluate and assess what NLM is doing in its attempt to comply with the law. He added that the Working Group should evaluate the program’s progress over the course of its first meetings, which he proposed to convene prior to meetings of the NLM Board of Regents. Dr. Lindberg agreed that it would be useful for the Working Group to comment on specific issues, such as the importance of the data elements, or make suggestions to pursue certain directions in implementing the required databases.

Dr. Wood inquired about the disposition of information regarding trials of devices that are never cleared or approved by FDA. Dr. Zarin replied that the law does not provide any mechanism for ever releasing this information to the public. Some registrants have requested public posting of their studies of unapproved/uncleared devices, while others have designated

previously registered (and publicly available) studies as eligible for delayed posting under FDAAA 801, thereby withdrawing their records from public view. In some cases, public information about these trials is available on the Internet from the organizations involved in the study. Dr. Cohen asked if records are ever purged from ClinicalTrials.gov. Dr. Zarin responded that they are never removed, but considerable effort is made to prevent and identify duplicate registrations for a single trial. Once identified, copies are suppressed so that only one official record is available to the public.

In terms of data elements, Dr. Wood stated that it is important for ClinicalTrials.gov to collect the full set of data elements that are currently designed into the system. He suggested that mechanisms other than legal enforcement be used to compel users to provide the requested data elements (e.g., journal articles and information highlighting the importance of the registration information). Dr. Rockhold views NLM's work as an important step in defining effective ways of defining a clinical trial and determining what information needs to be provided. He made a distinction between the information elements required by the law and those required to provide a useful description of a trial. Dr. Haynes suggested that "concealment of allocation" be considered as part of the study design data element, in compliance with the CONSORT statement. He noted that such information is especially important for device trials in which blinding may not be possible. Ms. Humphreys reminded the Working Group that NLM will be constrained by what is agreed the system can require and noted that rulemaking might help in this endeavor by providing greater clarity.

Dr. Rockhold viewed the greater challenge as providing registrants with greater certainty about the registration requirements and future modifications to the system. Staff who input data into the registry are not generally authorized to alter information or information formats to comply with changing data collection schemes. Registrants also need time to retool their data systems and to reformat studies retroactively after definitions and registration requirements change. Dr. Wood suggested that advanced notification of changes to the data elements would be helpful. Dr. Zarin explained that while ClinicalTrials.gov strives to provide advance notice to PRS users of changes – and did so successfully in the past – it has been more difficult to do in the current environment. Ms. Humphreys also noted that some of the NIH institutes and centers, including NCI, submit data to ClinicalTrials.gov via automated systems and face similar challenges as industry in reprogramming them to meet the new data element formats.

Ms. Weinberg asked about the intended audience for the ClinicalTrials.gov registry and results database, and Ms. Weinberg asked whether any particular segment of the audience is considered a priority. Dr. Zarin responded that ClinicalTrials.gov consists of two systems that are aimed at different users: the Protocol Registration System (PRS), which is aimed at registrants; and ClinicalTrials.gov, which is aimed at users. Online surveys indicate a heterogeneous audience. Patients, family members, and healthcare professionals are clearly one priority population; another is the set of researchers involved in evidence-based medicine. As a general rule, the more comprehensive ClinicalTrials.gov becomes, the more useful it becomes to a broader set of users. Dr. Wood pointed out that industry is another significant user of ClinicalTrials.gov. Dr. Lindberg observed that NIH institute and center directors also use ClinicalTrials.gov to provide a public view of their funded clinical research portfolios. Dr. Rockhold suggested that identifying intended end-users should be a driving force in determining the type of protocol information sought and displayed. He also noted

that patients in trials run by GlaxoSmithKline infrequently cite ClinicalTrials.gov as the source of their information about the trial.

Dr. Powell inquired about the readability and understandability of ClinicalTrials.gov records for average consumers. Dr. Lindberg stated that many features have been built into ClinicalTrials.gov to help consumers understand technical terms and concepts, such as links to MedlinePlus and other online consumer health resources. Dr. Powell also observed that ClinicalTrials.gov is available only to patients with Internet access. Ms. Humphreys said that NLM has a broader outreach effort for all of its information sources through the National Network of Libraries of Medicine (NN/LM). Dr. Rossiter stated that academic researchers may also benefit from greater outreach to ensure that principal investigators are aware of clinical trial registration requirements. He suggested collaborating with the International Society of Pharmacoeconomics and Outcomes Research (ISPOR). Dr. Zarin agreed and noted that providing information to academic medical centers through organizations such as the AAMC has been useful in informing academic clinical researchers of changing policies involving ClinicalTrials.gov.

IV. RESULTS REPORTING

FDAAA 801 requires that NIH/NLM establish a basic results database by 27 September 2008 to collect specified results information for trials of approved drugs and cleared/approved devices. Dr. Zarin reviewed activities to date to meet this requirement. She noted that several earlier activities helped prepare NLM for designing and operating a results database, including a 2004 Trans-NIH Working Group on Clinical Trials Reporting, two NLM-sponsored expert workshops in 2006 and 2007, and a commissioned review of existing results databases. The law specifies that collection of tables of results information (rather than a structured narrative) and describes specific content to be submitted and displayed: demographic and baseline characteristics, overall and by arm; participant flow data; and values for primary and secondary outcomes, by arm, including scientifically appropriate tests of statistical significance. The challenge for NLM is to develop a data entry system to allow for the submission of structured data for heterogeneous variable types among a heterogeneous set of trial types and designs.

NLM's current approach for meeting the basic results reporting requirements is to ask registrants to provide data in two steps: 1) specify information about the trial and variables measured (e.g., outcome measure data type), and 2) enter values for the data. As with the registry, the results database will support manual data submission through a Web-based system and automated uploading of data using XML files. NLM plans to provide the public with opportunities to review and comment on the data entry and presentation prototypes before the system is launched on 27 September 2008. Dr. Zarin presented mockups of the screens of the data entry system and compared them with the types of tables and figures that appear in published medical articles. Dr. Zarin raised several issues to be considered, including ways to provide sufficient context for users to understand results of individual studies, the inclusion of links to relevant, complementary resources such as systematic reviews, ways to determine when results data are minimally acceptable, and whether and how to include post-hoc analyses in the results database.

Dr. Clement McDonald, Director of NLM's Lister Hill National Center for Biomedical Communications, reviewed the underlying technology and process for storing results data. The goal is to represent summary patient and clinical data in a generalized, but structured format while minimizing data entry burden and accommodating heterogeneous study designs. He enumerated the three parts of the problem: 1) defining variables used in a study (e.g., name, description, data time); 2) defining a variety of study designs and data analyses (e.g., number of arms, statistical tests); and 3) defining the underlying data structure (e.g., storing values in cells of a table with variables represented in rows and study design, in columns; or XML structured data format for data submission). Dr. McDonald concluded by emphasizing that while a relational database is a fundamental tool for storing results data, the problem of designing the database is not trivial because of the need to accommodate current and future variables and designs used in clinical research.

Ms. Weinberg commented that a national phone survey on risk communication found that consumers: 1) do not have a good understanding of how to balance risks and benefits, and 2) are unlikely to find tables and numbers alone to be useful. Dr. Zarin explained that it is important to put clinical research results into an appropriate context to help people understand the relevant risks and benefits.

Dr. Rockhold asked whether NLM would require data submission in compliance with health informatics standards such as CDISC and HL7. He noted that WHO is trying to take advantage of existing standards in its clinical trial database work. Dr. McDonald noted that NLM is engaged with relevant standards groups to ensure that NLM works in harmony with their efforts. He added that such standards are currently designed for describing data at the individual patient level and may not be appropriate to summary data, however.

Dr. Lindberg asked the Working Group if they knew of any existing results reporting systems similar to the one being proposed by NLM. None were identified. Dr. Zarin noted that the GSK Clinical Trial Register has many similar features, but that the format of the reports can be standardized more easily because the data are provided by GSK, and not by a heterogeneous set of data providers. Dr. Rockhold indicated that the GSK site was being redesigned to provide improved search features. The original GSK site, which was developed in 2004, required 40 full-time employees to coordinate posting data from earlier studies. The site currently contains over 3,800 results records.

Regarding post-hoc analyses, Dr. Wood proposed that they be considered separate from results reports based on pre-specified variables. He thought it advantageous to link post-hoc analyses to the original protocol entry via the NCT number, even though not all end users might understand the distinction between pre-specified and post-hoc analyses. Dr. Wood also suggested that registration records be locked after study completion to prevent them from being edited subsequently, and he proposed freezing specific data elements, such as outcome measure, once the study has started. At minimum, he suggested that post-hoc modifications be discouraged. Dr. Rockhold observed that even if data elements are changed after trial completion, such changes are tracked publicly at the ClinicalTrials.gov archive site (<http://clinicaltrials.gov/archive/>). Dr. Zarin pointed out the distinction between the pre-specified outcome measure and the pre-specified analytic plan, and explained that analytic plans are not mentioned in any trial registration policy and are not included in the registry.

Ms. Humphreys asked how corrected data analyses and results should be handled in the results database. Dr. Wood suggested that amendments to the originally reported data be allowed to correct statistical errors and omitted data. He did not think that it was necessarily better to display the corrected data first. Dr. Rockhold emphasized that, regardless of how the original and corrected data are presented, the order of display should not imply any value judgment regarding the data. Mr. Bradley highlighted the importance of ensuring that only the responsible party be able to modify results information. Dr. Zarin confirmed that this would be the case, just as it is with the registry.

Dr. Fuller asked about results reporting for studies that are terminated prematurely. It was widely agreed that it is important that information from such studies be included in the database. Dr. Zarin confirmed that results reporting would be required for prematurely terminated studies.

V. ADVERSE EVENT REPORTING

Dr. Zarin reminded the Working Group that the requirement for submitting information about the adverse events observed in a trial is dependent on rulemaking by HHS. If no rules are promulgated within 18 months of enactment, default provisions of the law take effect 24 months after enactment and require submission of tables of information about serious and frequent adverse events. Key issues to consider include: 1) definitions of adverse event and serious adverse event, which are not specified in FDAAA 801; 2) characteristics of adverse events, such as frequency, attribution to the intervention(s), statistical significance across arms, and how events are collected and assessed (e.g., systematic ascertainment vs. spontaneous reporting); and 3) different ways to count and present adverse events (e.g., split into many different specific categories or lumped into fewer broader categories).

Dr. Zarin proposed implementing a set of default adverse event tables in the basic results database as a pilot test. Submission of information for the tables would be voluntary, but experience gained would be used to inform subsequent rulemaking. The pilot study would indicate the kinds of data that responsible parties are willing to report; the ways in which such data can be collected and displayed to serve the needs of various end-users.

Dr. Kennedy supported the idea of pilot testing the adverse event data tables at the time of the launch of the basic results database, prior to deciding whether to conduct rulemaking.

The working group discussed alternative ways of reporting and displaying adverse event information. Dr. Wood suggested that the tables used in the pilot study not have a 5% threshold (i.e., not report only adverse events with a frequency of 5% or more as specified in the law). He advocated the reporting of *all* adverse events, rather than those exceeding an artificial cutoff point, in order to counteract some of the difficulties of aggregation and avoid the loss of information about adverse events that just miss a threshold value. Such shortcomings have delayed the recognition of adverse events associated with some drugs. Dr. Rockhold noted, however, that large studies with many participants can have such large numbers of adverse events to report that the information becomes difficult to summarize and review. GSK began truncating the tables of adverse events in its clinical trial registry at the request of end-users who found comprehensive lists too long and confusing. Dr. Zarin noted

that information on all adverse events could be collected, and the results database could allow users to alter the display of the information dynamically, for example, adjusting the cut-off point to show the level of data they wish to see. Dr. Wood supported this idea, as adverse events that may not be observed frequently in a single study may take on some significance when aggregated over multiple studies.

Dr. Rockhold highlighted the importance of having a standard terminology and consistent coding of adverse events if one intends to compare information across studies. Ms. Humphreys noted that FDA requires that adverse events be coded using controlled terminology in the Medical Dictionary for Regulatory Affairs (MedDRA). It would be useful to know more generally how studies collect and report adverse events.

Dr. Kennedy reiterated his observation that the law appears to be written to allow the implementation of the expanded registry and basic results database without rulemaking and the attendant notice-and-comment period. He expressed concern that additional rulemaking would unnecessarily delay implementation of the law. Mr. Bradley reminded the Working Group of a fundamental legal principle in statutory interpretation: more specific statutes override more general ones. Hence, he argued, the specific provisions of FDAAA 801 might override the requirements of the Administrative Procedures Act, which sets out general rules regarding government regulatory authorities and processes. Dr. Zarin noted that the deadlines set in the statute are aggressive, even without having to undertake rulemaking.

Dr. Rossiter asked whether NIH institutes and centers would be able to comply with the results reporting requirements. Dr. Lindberg said that at a recent meeting, Dr. Zerhouni indicated his interest in ensuring that NIH and its funded grantees comply. Dr. Zarin stated that it is difficult to determine how many summary results will be submitted on 27 September 2008. Regardless, submissions to the registry will not stop once the results database is launched, meaning that the workload – and staffing needs – will undoubtedly increase.

Ms. Weinberg asked that Working Group members be kept informed when decisions are made.

VI. SUMMARY AND NEXT STEPS

Working Group members agreed to schedule future meetings adjacent to meetings of the NLM Board of Regents, if possible. NLM staff will circulate a set of proposed dates for consideration by Working Group members. The Working Group will report to the NLM Board of Regents on February 12, 2008. The meeting was adjourned at 2:55 p.m.

APPENDIX A: Working Group Members

Cynthia Morton, PhD* (*Chair*)
Brigham & Women's Hospital

Thomas Bradley, JD
Attorney General's Office for the State of
Maine

Rob Califf, MD***
Duke University Medical Center

Jordan Cohen, MD**
George Washington University

Sherrilynne Fuller, PhD
University of Washington

R. Brian Haynes, MD
McMaster University

Donald Kennedy, PhD
Stanford University

Barbara McNeil, MD, PhD
Harvard Medical School

James Powell, MD
National Medical Association, (formerly)
Proctor & Gamble

Frank Rockhold, PhD
GlaxoSmithKline

Louis Rossiter, PhD**
The College of William & Mary

Myrl Weinberg
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Scientific Counselors