RESPONSES TO QUESTIONS FROM OMB 03/19/2009
Information Program on Clinical Trials: Maintaining a Registry and Results Databank (NLM) (0925-0586).

1. Page 11: Keeping in mind the statutory requirements to "provide information to help ensure that information in the results database does not mislead patients [42 USC 402(j)(3)(B)(iv)] and enhances patient understanding of the results of clinical trials [42 USC 402(j)(3)(D)(i)]," please provide a rationale for loss to follow-up data being optional rather than mandatory.

We have attempted to limit the required information to information that is specifically required in the statute or directly follows from it. The statute does not require information about the reasons subjects did not complete the study, only about the number started and the number completed. By providing an optional capability to report more detailed information (in this and other categories), we aim to encourage provision of information that will enhance understanding of the results of clinical trials. It is possible that such information could be made mandatory via rulemaking, but currently the only requirement we impose is that if a data submitter volunteers to provide information about the reasons subjects did not complete a trial, they must account for all subjects that did not complete the study, not just a selected subset of those subjects. This requirement is aimed at preventing incomplete and/or misleading reporting.

2. Page 11: Is there a list of suggested optional demographic characteristics? If race/ethnicity are options, please ensure that reference to standard OMB categories is provided.

The data element definitions document suggests some optional demographic characteristics, including race, ethnicity, and region of enrollment. The system contains default tables and data entry shells for entering race and ethnicity information. These tables use the OMB classifications as their default settings, but respondents are permitted to customize the categories if necessary to match the data analysis or conduct of the study.

3. Page 12: What is the status of the rulemaking mentioned near the bottom of Page 12? If default provisions are expected to be in effect as described, are there standard table formats provided by NIH for the tables that are required to be submitted on adverse events? If default provisions of the FDAAA are put in effect, on what date would this occur? In what way is this communicated to respondents? Are the categories listed as "optional" on page 16 then "mandatory" under the default?

It does not appear that the adverse event reporting requirements will be implemented via rulemaking; rather the default provisions will be adopted. This requirement would take effect at the statutory deadline of September 27, 2009 (2 years after enactment of FDAAA). ClinicalTrials.gov contains an adverse event reporting module that is based on the default provisions in the law, but submission of adverse event information is currently optional. Respondents who voluntarily report adverse event information must, however, provide certain specified data fields (to prevent selective reporting). Mandatory reporting of adverse event information (starting on September 27, 2009) is expected to adhere to the same information

collection requirements that are currently voluntary. We are working with FDA and DHHS to develop formal communications regarding our intentions for adverse event reporting to ensure that data submitters have ample advance notice that the module will become required in September.

4. Please describe the process for validating registration data as provided.

Our quality assurance activities for registration data consist primarily in ensuring that entries are meaningful, internally consistent, and have apparent validity. The agency has developed various materials to assist data submitters in preparing their information for submission (much of this information is available on http://prsinfo.clinicaltrials.gov/fdaaa.html]

5. What mechanism exists for interested parties (members of the public, researchers, policy makers, etc) to keep up with the activities of the registry (e.g. is there a listserve or other alert system in place that people can sign up for)?

A listserv has been established to provide updates on activities related to the data bank. The link to the listserv is available at http://prsinfo.clinicaltrials.gov/fdaaa.html , which is a new Web page that was created to provide the public with information about the expanded registry and results databank and the requirements of FDAAA. NLM and NIH staff also participate in a number of meetings with interested parties to update them on implementation.

6. Page 18: It sounds like at least some of the collection is duplicative with FDA's efforts. Is there any way that FDA could extract that info from the registry instead of burdening the public with reporting twice?

The NIH and FDA data collections are similar but not duplicative. In general, the information collected by FDA is much more detailed than the summary data submitted to ClinicalTrials.gov, is not aimed at the broad set of users of ClinicalTrials.gov, and is considered confidential, limiting FDA's ability to release it publicly. Indeed, these differences were among the primary motivations behind the statutes that required the establishment and expansion of ClinicalTrials.gov. NIH also collects information about clinical trials that are not submitted as part of an application to FDA. NIH continues to work very closely with FDA to improve linkages between NIH and FDA information about clinical trials to assist users in finding related information.

7. Page 18: "Recent research indicates that negative or inconclusive trials are particularly underrepresented in the literature

This comment was truncated in the original communication, but may have been requesting citations to recent research. Two of the most recent (and widely cited) are listed below:

Turner, et al, "Selective publication of antidepressant trials and its influence on apparent efficacy," N Engl J Med. 2008 Jan 17;358(3):252-60. PMID: 18199864

Kirby Lee, Peter Bacchetti, Ida Sim (2008), "Publication of Clinical Trials Supporting Successful New Drug Applications: A Literature Analysis", PLoS Medicine, Sep 23;5(9)

FOLLOW-UP QUESTIONS FROM OMB 04/01/2009:

Coincidently, I see from last week's Federal Register that NIH is planning to have a public meeting on April 20, 2009 to discuss "*the development of regulations to expand clinical trial registration and results reporting through ClinicalTrials.gov*." Can we set up a call to discuss the decision to move forward with rulemaking and what that timeframe may look like?

The development of regulations is required by statute, as is the public meeting on April 20. FDAAA specifies that the Secretary issue regulations for a "expanded registry and results databank" within three years of enactment (which would be Sept 27, 2010). The regulations are supposed to address several topics identified in the statute. The Secretary is also required to convene a public meeting "to provide an opportunity for input from interested parties with regard to the regulations". That is the meeting we have scheduled for April 20.

Following on from that, Supporting Statement A (page 12) reads, "*In order to test different methods for collecting information on serious and adverse events, the data collection permits respondents to submit such information in a form consistent with the default provisions of the law and to provide information about the method by which such information is collected and the threshold for reporting an event (e.g., the threshold frequency above which events are reported).*" What testing of methods is being done to determine the best method for collecting information on adverse events? From the perspective of the Paperwork Reduction Act, and taking into account Congress' view that the current method of collection may not be the "best" - we encourage Program to develop a plan to come up with an optimal way to collect this information. This will likely flow into the rulemaking conversation so we can discuss more on the phone.

The statute lays out a set of default provisions for reporting serious and frequent adverse events. The provisions take effect 2 yrs after enactment (Sept 27, 2009) if the Secretary doesn't issue regulations for adverse event reporting within 18 months of enactment. We built into the system the capability to voluntary provide the information in a manner consistent w/ the default provisions, but enabled data submitters to modify the data submission tables (e.g., to use a threshold other than 5% for reporting frequent adverse events) as a means of testing whether there were better ways of reporting the information. To date, the current approach seems optimal, but could have some discussion of the topic at the April 20 meeting.

Finally, 2 items that were discussed in the Supporting Statement appear to request information, and thereby impose burden on the public, but I do not see a collection instrument for either of them and just want to make sure that the burden is accounted for in the overall calculations:

Page 16: *The submission of a certification is being integrated into the data entry system, allowing the submitter to verify (or update as needed) the FDA approval status of the product(s) involved in the study and to indicate that they are certifying that they are seeking either initial approval or approval for a new use of the product. As a temporary measure (until that feature is*

integrated into the system) responsible parties wishing to submit a certification are asked to submit via email the following information to NIH

Page 17:

For extension requests, respondents will be required to submit to NIH the following information:

- *ClinicalTrials.gov identifier (NCT number) of the applicable clinical trial to which the request for extension applies*
- *Unique Protocol ID (to verify that the NCT number refers to the correct trial)*
- *Explanation that demonstrates good cause for the extension*
- *An estimated date on which results information will be submitted*
- *Name and contact information of the responsible party*

The burden estimate for results reporting includes a separate line for certifications and extensions, which contribute 1,625 hours to the burden. As noted in the SS, we plan to implement the certifications and extension requests in the existing information collection instrument (which will make the process even simpler), but are currently requesting the information via email submission, as outlined above.

Table 12-3 Estimated Burden Related to Submission of Basic Results Information

Type of Product	**Responses**	**Frequency**	**Average Time per Response**	**Annual Hour Burden**
Results for drugs & biologics	1,645	1 initial	10 hrs	16,450
		2 updates	5 hrs	16,450
Results for devices	375	1 initial	10 hrs	3,750
		2 updates	5 hrs	3,750
Certifications & Extensions	1,625	1 per year (1 per trial)	1 hr	1,625
Total	4,365			42,025

Thanks again for the responses both to OMB and public comments. We look forward to setting up a call to discuss next steps.