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[by email to dzarin@mail.nih.gov and ccmorton@bics.bwh.harvard.edu]

Re: BIO Comments Regarding Expansion of the ClinicalTrials.gov Database

Dear Dr. Zarin and Dr. Morton:

The Biotechnology Industry Organization (BIO) welcomes the opportunity to submit comments to the Working Group on Clinical Trials of the National Library of Medicine's (NLM) Board of Regents regarding implementation of Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA).

BIO represents more than 1,200 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products.

BIO and its member companies are committed to helping assure that patients and healthcare providers are informed of the availability of clinical trials and have access to relevant information about the medicines we discover so that our products can be used safely and effectively. The importance that BIO assigns to clinical trial transparency is exemplified by its adoption of a position statement on Clinical Trial Registries and Dissemination of Clinical Trial Results, available on our website at http://bio.org/bioethics/background/20050621.asp.

BIO appreciates the National Institutes of Health's (NIH's) work toward and commitment to improving the transparency of clinical trials through the ClinicalTrials.gov website and we recognize the tremendous amount of effort required to implement Title VIII of FDAAA. To facilitate the ongoing implementation of Title VIII, BIO would like to note some remaining issues with respect to key provisions in the new law.

BIO welcomes the opportunity to present our issues and recommendations to the NLM Board of Regents Working Group on Clinical Trials.

Open Issues Regarding Implementation of FDAAA Title VIII

Below we have provided a list of current key issues and recommendations with respect to implementation of Title VIII of FDAAA.

- **Process:** Since passage of FDAAA in September, NIH has updated its definitions and instructions on several occasions requiring approximately 28 new required fields and making changes to approximately 6 fields. Companies have updated registration information for hundreds of trials to collect the additional information required by ClinicalTrials.gov. The unpredictability of changes in ClinicalTrials.gov definitions and programming for publishing study information can have significant impact on sponsor companies' standard operating procedures (SOPs) and resources. Therefore, we urge NLM to adhere to a preset schedule (i.e. every 6 months) and ensure version control, similar to MedDRA. We also recommend that NLM allow sponsors a reasonable amount of time, *i.e.*, at least 3 months, between when the finalized schema is released by the NLM and the new information is required to be posted, so that sponsors are able to update SOPs, validate any modifications to their systems to account for the new information, and upload the new information.

- **Public Input:** Transparency and stakeholder input is critical to ensure that patients and others involved in clinical studies appreciate and understand the scope and limits of ClinicalTrials.gov database.

  On May 21st, NIH provided the opportunity for comments on the early mock-up of the interactive Web-based ClinicalTrials.gov results registration system. We appreciate the opportunity to provide comment on basic results materials as they

become available[1] and appreciate the effort to issue rule making and guidance within a compressed time frame on how industry can comply with the new clinical trial results requirements. However, we urge NIH to elaborate on the process for proposed comments being accepted and incorporated into the database. We recommend that comments submitted on the public website http://prsinfo.clinicaltrials.gov/fdaaa.html are publicly available for other stakeholders.

- **Communication Plan**: We recommend that NIH provide a mechanism for sponsors to consult directly, by telephone, with NIH staff when questions arise. The current system, which relies on email communication, does not allow for timely discussion of issues, problems, and ambiguities in what is being sought for some of the fields required for registration. If there is a great deal of overlap among sponsors regarding question type and content, it would be helpful for NIH to summarize these issues and distribute a response via email or letter to the community as a whole.

- **FDAAA Definition of Completion Date:** In consideration of FDAAA Sec. 801. Expanded Clinical Trial Registry Data Bank (1) Definitions; Requirement. - (A) (v.) Completion Date, BIO recommends revising the FDAAA Completed Date definition to last patient, last visit based on a pre-specified trial endpoint (date or event) in the trial protocol; this is a widely used, industry-accepted definition that will achieve final results disclosure in a consistent manner.

  FDAAA definition: "The term 'completion date' means, with respect to an applicable clinical trial, the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated."

  This request is supported by the current definition's exclusion of secondary outcome data for an applicable clinical trial. In addition, a revision to the existing definition would help clarify the actual date of completion for one (1) year results submission time frame. Please consider the following points regarding the current Completion Date definition:

  Multiple results postings will be necessary to account for both primary and secondary results data for a single clinical trial; this may lead to confusion.

  The FDAAA definition specifies last patient, last visit at final data collection at *primary outcome* however; clinical studies with secondary outcome data are included in the overall final trial results at actual trial

[1] Federal Register: May 21, 2008 (Volume 73, Number 99) Page 29525-29526

completion. Primary outcome completion dates therefore will differ from actual trial completion dates resulting in two or more sets of results data to disclose for a single trial. In addition, there may also be different demographic data for primary and secondary outcome groups to post.

Increased risk for breaking the trial blind, increasing risk for bias.

If primary outcome results are due *prior* to the actual trial completion date, an interim data analysis would be required in order to disclose results, which equates to breaking the trial blind.

Poor resource utilization.

Posting multiple results for a single clinical trial will result in significant resource and cost constraints for both the industry and government. Industry will be required to 1) track different completion dates (primary, secondary, actual, estimated, expected, etc.) and 2) enter multiple results postings for a single clinical trial in order to meet the requirements set forth in the current FDAAA definition.

Potentially misleading results.

Section 801, FDAAA requires that results posted are not to be false and misleading. By posting multiple results for a single trial it may appear now that industry is 'cherry-picking' data at certain trial time points and posting these data *without the trial actually being completed* when in reality, all industry is trying to do is to meet the current definition in FDAAA.

- **<u>Basic Results Database Requirements:</u>**

1. We believe that the basic results data entry mockup exceeds the scope of the information requirements described in Section 801 of Public Law 110-85. Further, we note that data element requirements are defined in part C (Basic Results) of the topic "Expansion of the Registry Data Bank to Include Results of Clinical Trials". More specifically, we highlight the following points:
    a. Section 801 does not require that the results point of contact be identified by name, official title or organization, or that a specific phone number or e-mail address be provided. Rather, it requires only that there be a "point of contact for scientific information about the clinical trial results." Thus, we would like to see an option to include a general, centralized email address or phone number to satisfy this requirement. This option would protect individual privacy rights, allow companies to direct questions to the appropriate recipient, and eliminate the need and concomitant burden of having to update this field when a designated individual changes positions, is out on leave, leaves the company, or is otherwise unavailable.

b. We recommend adding a free form text box to the "Certain Agreement" field if the response chosen is "other." This provides the sponsor the ability to explain its policy.
c. We are unsure of the purpose or the issue being addressed by the "Limitations and Caveats" data entry field on the Edit Results Record mock-up screen.
d. We recommend a clear distinction between individual data entry fields that are to be considered as "required" or "optional" fields. Further, we recommend that only specific data elements that are identified in Title VIII of Public Law 110-85 be designated as "required".

2. We believe that the general design of the data entry mock-up makes it difficult to envision the results table as the information is being entered and, therefore, will result in inefficient data entry and create the potential for data entry errors.
   a. Design and group structure has to be defined and tailored for each basic result section separately, which is rather cumbersome. It would be helpful to get a pre-populated table structure either from the Protocol Registry System or to define the table structure only once in the participants flow section. For the Baseline Characteristics and the Outcome section the structure could then be repeated (pre-populated).
   b. If an XML-based upload capability is not immediately available when the basic results database is implemented, we recommend a supporting verification report that mirrors the online representation of the results table and allows for data verification prior to formal publishing of a results record.
   c. Related to point "b" above, the current mock-up lacks a data staging area to enable the review of entered data and the results table representation prior to the formal creation of a results record.
      i. The data staging area should provide a capability that requires a specific action on the part of the sponsor in order to post a formal results record.
      ii. Appropriate protections and agreements must be in place such that use of the staging area to input and review data before formal posting of a results record would not jeopardize intellectual property rights, or ownership of trade secret and other confidential information.
      iii. Once posted as a formal results record, it is expected that NIH will track changes to formally released results records.
3. We recommend that consideration should be given to data tables and other results information posted on the ClinicalTrials.gov website that could be subject to copyright protection, and how sponsors can advise the public so that protected information is not used unless proper authorization and permission is obtained.
4. We request clarification regarding what information is expected for the data entry field "Other" related to the entry of gender information in the baseline measures data entry screen represented on page 8 of the Data Entry Mock-up Guided Tour.

5. We request clarification and consistency regarding whether data values will be rounded or stored exactly as entered (e.g. primary measure, mean std. deviation) in fields requiring a numerical entry.
6. We request clarification of when XML upload will be available for providing basic results data in addition to the data entry system. The Data Entry Mock-up Guided Tour notes that there will "eventually" be two methods of data entry, including a batch upload of results data.
7. We believe the pre-specified categories of reasons of discontinuation of study in the participant flow section are rather limited and would not cover all the withdrawal criteria. We recommend allowing additional entry of reasons.
8. We recommend allowing the sponsor to modify the table header in the total column for the baseline characteristics section. We also request a definition of 'total'.
9. We request clarification of the use of a total column in the primary and secondary outcomes. The Results Registration System (RRS) should not pre-populate a total column and it should allow deletion of a pre-populated total column.
10. We recommend the inclusion of a separate field for entry of percentages when frequencies are entered. In the data entry mock shell, sponsors are able to add the percentage of absolute number of subjects in parentheses directly after the absolute frequencies, so the system must handle these entry fields as character fields. We recommend separate numeric fields for absolute frequencies and the corresponding percentages to help ensure a standardized format, and that standard edit checks be in place..

Conclusion

BIO is committed to posting transparent clinical trial information so the public will have greater access to information about clinical trials. We support the implementation of the clinical trial registry and results databank in a manner that is consistent with FDAAA. BIO looks forward to working with the NLM on issues associated with the expansion of Clinicaltrials.gov and the addition of a results database.

We thank you for consideration of these comments and would be pleased to provide further input or clarification as needed.

Sincerely,

/s/

Sara Radcliffe
Vice President, Science and Regulatory Affairs
Biotechnology Industry Organization