

ClinicalTrials.gov Webinar Series, March 2011

Protocol Registration System (PRS) Information and Data Review Process

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This presentation provides an overview of 2 important aspects of the ClinicalTrials.gov data flow—

Data entry through the Protocol Registration System, or PRS for short, and the data review process by the ClinicalTrials.gov staff.

So what is the Protocol Registration System?

It's a secure Web-based data entry system for providing summary protocol and results information. To be accessed, it requires an organizational account name, a user name, and password information.

The submitted information includes required and optional structured data elements, and these are implemented in the PRS through pull down menus, free-text fields, and other kinds of data entry mechanisms.

In general, the PRS consists of a series of organizational accounts established by sponsors of clinical studies. The account itself is used by different users within the organization to maintain and provide information about studies sponsored by the organization or, called, "records." There are also two roles of users within each account; administrators in general create user accounts, edit and approve records, and serve as a point of contact for ClinicalTrials.gov staff. Users work at the record level by creating, editing, and modifying individual records.

There are two levels of data review in PRS. The first is accomplished by automated business rules. And these are really for basic quality and completeness checks. They result in generally three types of messages. One is the "error" and these will—data elements that have been identified to have "errors" will need to be addressed or the study cannot be released. Those that have been identified by "warning" indicate that a particular data item may be or is required by the FDA Amendments Act and should be addressed in order to fulfill the requirements of this Federal law. And the last type of message, "note," provides helpful hints about particular data elements. The second type of review is conducted by the ClinicalTrials.gov staff once the errors from the automated reviews have all been addressed. I will talk about that in more detail in the second half of this presentation.

So let's first talk about the protocol data entry process.

So users go to the login screen and, after typing in the information, will be presented with a Main Menu from which they can accomplish a number of functions, including creating protocol records, modifying existing records or adding results to existing records, and accessing review comments that have been provided for particular records by the ClinicalTrials.gov staff. Some important documents to review before entering protocol data, as well as to keep on reference while entering data, include the Data Elements Definitions document, which provides a list of all the protocol data elements as well as descriptions of each and, for some, examples. In this document, the required data elements are identified: red asterisks for those required by ClinicalTrials.gov; the green "FDAAA" for those data elements required by the Federal law, and

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FDAAA in parentheses in green for those that may be required and this will be resolved after rulemaking, which is ongoing. Another document that is important to review is the Detailed Review Items document, and this is available at our public Web site.

So here is an example of a PRS form for interactive data entry. On the left is a list of the names of the data elements, and on the right are the data fields, including free text fields, radio buttons, and drop down menus. In order to find the definition of any particular data item you can click on one of these labels and a new window will open with the appropriate definition from the Data Element Definition document. Also on this screen, you can see that the symbols that were discussed before about which data elements are required are also prominently displayed—the red asterisk and the green FDAAA.

So now, let's move into the results data entry. There are similar documents that data providers should review prior to entering data and will probably want for reference while doing results data entry. The first is a similar, parallel data elements definition for the results record. And again, these are annotated with required symbols that show which data elements are required, but there is one difference in the middle: you can see in the blue asterisk with the brackets, these are conditionally required by ClinicalTrials.gov. That means that there is a set of data elements that are essentially optional, but if you do provide information for at least one of them then you have to provide information for the full set of data items. Other review documents that are important to look at before and while entering data include the Detailed Review Items, the Pre-Submission Checklist and Helpful Hints. These are also on our public Web site.

While it is always important to keep the protocol record up to date, it is particularly important to do this before entering results data because, as you can see here, many of the data elements listed in the slide will be copied over to the results record when it is first established in order set up the template. And we actually even recommend—once you have reviewed and updated the protocol record—to first rerelease it before starting data entry for the results record.

So here is a screen shot of the actual data elements from a particular record that will be copied from the protocol into the results record.

So, how are results reported? Well, the results information data are displayed as tables in ClinicalTrials.gov, so the data provider needs to give the parameters for constructing the table in the PRS. That means for arms and groups, these will be displayed as columns, the particular measures will be displayed in rows, and then the cells between them—at first the data provider will need to specify the type of data that goes there, for example, the number of participants or the mean and standard deviation, and then enter the actual values. In developing and implementing the results data entry systems, we have attempted to balance a fixed structure for entering these data for the various tables with considerable flexibility to meet the needs for each individual study and each table.

So here's an example of how the information will finally be displayed in ClinicalTrials.gov.

Now we're going to move to an overview of the ClinicalTrials.gov review process.

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A data provider with a clinical trial can enter information either interactively through the PRS, through the online forms, or upload an XML file. Once the data entry has been completed, the automated business rules may detect some errors. If there are errors, then the data provider needs to correct them first and then review the other types of messages, including notes and warning. In addition, data providers should also take a look to make sure that the data are compatible with the detailed review criteria. Once all of these have been reviewed, and the review has been completed, the PRS administrator will release the record to ClinicalTrials.gov.

Once the record is released, for the data provider at least, the information is locked. That means they can't change any of the information while the ClinicalTrials.gov staff is reviewing the record. In general the review takes 2 to 5 business days for protocol records and up to 30 days for results records, depending on the complexity of the results. Once the review has been completed, email will be sent to the data provider notifying them. And there can be two results of the review. One is that significant errors have been detected and the record will be reset. That means—the record, with comments about the errors, will be sent back to the data provider for review and correction. Otherwise, if no significant errors have been detected, then the record will be posted publicly at ClinicalTrials.gov.

If the record is reset, then the data provider needs to address these issues and then rerelease the record for another round of review by ClinicalTrials.gov staff.

So, what are the review criteria? First and foremost, the data must be clear and informative for both the protocol and results records. The reviews focus on four categories of issues: logic and internal consistency, whether or not there is apparent validity of the data, that the entries are meaningful, and that there is correct formatting. Additional information about the details of these criteria can be found in the public site.

So the protocol detail review items include things such as formatting and spelling and internal consistency between data elements, such as the dates. Other types of review items include: making sure that the outcome measure and time frame provide enough specificity, for example, “efficacy” and “safety” are not acceptable—they're too vague.

Regarding review of the results record, the basic concept is that the tables should convey the design, conduct, and analysis of the data. The table structure should be logical. If scale information is provided, it needs to be complete. The data must appear valid and there needs to be consistency between the modules within the results record as well as between the results record and the protocol record.

So, when a data provider receives review comments, the comments will be accessible through the PRS Main Menu as well as directly through each record. In general, the comments will be located underneath the particular relevant data element and where the issue is identified. And sometimes the comments may either be more boilerplate, or using the comment step, for very common types of errors, or customized for very specific or complex types of issues.

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So here is an example of accessing reviewer comments through the Main Menu. And again, just as a reminder, reviewer comments will also be accessible through the record itself.

Here's an example of some reviewer comments. At the bottom, you can see the comments and they refer to this table from the participant flow module.

And here's a screen shot of the view from the PRS, a ClinicalTrials.gov reviewer screen. And so the reviewer can essentially, for common errors as mentioned before, add a comment stamp which has pre-specified language to describe the error.

If a record is reset, then the review findings must be addressed by the data provider. So once the comments are addressed and modifications are made the record needs to be re-released.

If there are any questions about the comments, we urge the data provider to email us at this address with the question about the comments. The information that needs to be included in this email includes the NCT number, the date of comments, and a description of questions with any supporting information. Then we would like to have a dialogue with the data provider to try and resolve the question and it may also include not just email but a teleconference.

So when a record is posted on ClinicalTrials.gov, it indicates that no major problems were actually detected. That is, the information is internally consistent, there's a logical table structure, and the scale information is complete, and the data appear valid.

However, the data provider is responsible for ensuring that records meet the review criteria. So data providers should always assess their records using the available review criteria on our public Web site prior to releasing the records. And posting does not ensure that all of the right review criteria were met. Sometimes we are not always able to catch every single issue that comes up and so, therefore, we still may ask data providers, provide suggestions for data providers for improvements, or ask them to make revisions even after the record has been posted.

So here are some additional links from Web sites for other information and resources related to what was discussed in this presentation.