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Adverse Events Module

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This presentation will be covering the adverse events module within the results database at ClinicalTrials.gov. I will be providing an overview of the module, reviewing the specific data elements that are required to input data as well as the review criteria used by ClinicalTrials.gov staff and provide some examples of common errors that we have encountered in submissions to date.

The purpose of the adverse event module is to summarize data regarding the serious and nonserious adverse events that were collected during the course of the study. The module is not intended to be used for real time or spontaneous adverse event reporting while the study is ongoing and really is just intended to summarize data at the end of the study. It is also important to note that the adverse event module is not intended to dictate how data be collected during the course of the study, but rather just describes the criteria for reporting once the study is done. Generally, only the adverse event data that was collected will be required to be reported within the adverse event module.

The module requirements are driven by the provisions in FDAAA. FDAAA requires two tables of information. The first is a table of anticipated and unanticipated serious adverse events, grouped by organ system, with number and frequency of each event in each arm of the clinical trial. It is important to note that the definition explicitly states that these are both anticipated and unanticipated serious adverse events. It is essentially all serious adverse events that were collected. The second table of information is again, anticipated and unanticipated, but these are adverse events that are not included in the serious adverse event table. The adverse events that are included in this table are those that exceed a frequency of 5 percent within any arm of trial, are also grouped by organ system, again with the number and frequency of each event in each arm of the clinical trial.

You may be familiar with adverse event reporting in a journal article, which is typically a much higher level summary of the adverse event information collected during the course of the study. The ClinicalTrials.gov format is very similar to other modules that you have seen within the database and it includes information on the time frame over which adverse events were collected, any additional description that is necessary to provide context to the tables that are being presented, information on the columns or the arms and groups of the participants that were being evaluated during the course of the trial. You can see here the tabular information that includes a summary of the serious adverse events that were collected per arm and then organized by organ system. This is the other adverse event table that does not include serious adverse events. As you will see on the slide, there is a threshold being reported and it is a threshold of 5 percent meaning that participants in at least one arm of the trial had adverse events occurring at, at least 5 percent.

The data elements for the adverse event module include both optional and required data elements. There is some overall information that is applied to both of the tables within the module. Those are the data elements that you see on this slide and at this time are considered optional. The first is the time frame over which adverse events were collected. Any additional information that needs to be provided about the adverse event data collection. It is possible to specify whether or not a source vocabulary was used. Commonly for adverse event reporting,

dictionaries such as MedDRA are used to report adverse events. If one was used, it is possible to specify that with a data element and then also whether or not the adverse events were considered to be assessed in a systematic way or a nonsystematic way. For each adverse event table, it is important to provide sort of the structure for this table, so providing, again, the information about the arms or groups that are being presented including an informative title and description. Each table will include a summary of the overall number of participants that were affected by the adverse event. In this case, it is by any serious adverse event as well as the total number of participants that were at risk for the serious adverse event meaning sort of who was part of the analysis population for the adverse event module. Then, to complete the rows of the table within the adverse event module, it is necessary to specify the specific adverse event term that is being reported. It is also optional to provide any additional description that maybe necessary to understand that term. As required by FDAAA, the organ system for that adverse event term must be provided and then the number of participants who had that particular adverse event should be reported within the data cell. If the information within the adverse event table is different from the overall data I had on the previous slide then that can also be specified per adverse event term, but in general, many of the overall information will apply to the table itself. The other adverse event table is essentially the same as a serious adverse event table in terms of the data elements that are required to input data. The key difference being the threshold for reporting in that at least a threshold of 5 percent must be used, but it is also possible to specify a threshold that is lower. If a sponsor wanted to, they could report all nonserious adverse events for the study by specifying a threshold of zero percent.

This is just another representation of the information that is required to be inputted into the adverse event table. It is representing the data elements in a tabular format. I have included here some screenshots just showing how the data is entered. As with many of the other information that is entered into the Protocol Registration System, there is free text data elements as you see here and then there are also pulldown menus. After completing each screen, you would of course, click okay to move to the next section.

After some of the basic information is provided for the table, the total number of participants affected by any adverse event can be provided as well as the total number of participants who are considered at risk for that adverse event. This slide is just showing how you actually enter then the specific data for each adverse event term after it has been specified for that row. As you can see here, first sepsis in the first arm of participants, four participants experienced sepsis, and the information for the total number of participants at risk is carried over to that specific adverse event term, so four out of forty-five participants had sepsis.

The review criteria for the adverse events module are initially the same as any of the other scientific modules within the results database. Those are described here on this slide and include expanding abbreviations, monitoring for spelling errors, ensuring that the arms/groups have informative titles as well as informative descriptions. The information within the adverse events module should be consistent with other sections of the record and there should not generally be written results or conclusions. The law requires all of the information to be presented in a tabular format and that holds true for the adverse events module as well.

Some of the specific data elements that will be evaluated during a review at ClinicalTrials.gov include the time frame and additional description, if they were provided. In general, the time frame should be specific and understandable and there is additional information about reporting time frame in the outcome measures presentation that was previously provided. The additional description should include content that is actually relevant to the data element and relevant to the module itself. Looking at the number of participants at risk and consistency with other sections of the results record; we want to insure that the information for the number of participants at risk is consistent with the information provided in participant flow. Generally, the number of participants at risk will be the same as the number of participants who started in the participant flow module. If this isn't the case, the discrepancy between the two sections should be explained.

This is just an example record. You can see that the arm titles and descriptions are quite descriptive and informative. There is information on the time frame, which is quite specific. They specified that the adverse events were collected starting on or after day zero and continuing to day 100. They also provided some additional description about the adverse events that were reported.

You can see here the serious adverse event table. One of the things that would be evaluated is looking at the total number of participants affected and at risk and we would compare that to the participant flow module. As you can see, there is a slight difference actually in the number of participants who are at risk in the adverse events module versus those who started in this participant flow module, but in this case, the sponsor had actually used the comments field to provide some additional context about the number of subjects who were treated. That information also would have been appropriate to display as a milestone and would have allowed for easy cross referencing between the adverse events module and the participant flow module and would have allowed for the numbers to be more easily assessed.

This example shows a different study that had two arms. Here is just an excerpt from the participant flow module and then information from the adverse events module. In the adverse events module, they indicated that there were zero participants who were affected by either a serious adverse event or an other adverse event and that zero participants were at risk. Well, it is not really clear what is meant by zero participants at risk. Does that mean that zero adverse events were collected or that no one was considered to be eligible for an adverse event occurring? It is really not understandable as presented here and we would have expected that the number of participants to be potentially at risk for the adverse event would have been the number started in the participant flow module. The sponsor updated the record and actually further explained in the additional description that adverse events were not actually collected for this study and that was the meaning behind zero participants at risk.

Another thing that we evaluate during the review at ClinicalTrials.gov is consistency with the outcome measures module, if it is relevant. In some cases there may be overlapping information and if there is any obvious discrepancies, that will be noted. This outcome measure was actually reporting on the number of participants who were reporting a serious adverse event. If you go down to the data table itself, it indicated that four participants reported this serious adverse event, but then when reported in the serious adverse events table, there was an indication that six

participants had a serious adverse event. It is not really clear if there is a difference between the way the information was collected or reported or if this is actually an error between the two modules and we would ask the date provider to clarify that information.

There is additional information on the Web sites that you see listed here. If you have any additional questions, you are always welcome to email register@clinicaltrials.gov.