Meeting Minutes

CDISC-HL7 Stage I-B
March 31 – April 1, 2009
Rockville, MD

Attendees / Affiliation

Jay Levine/FDA (Co-Chair)
Chris Tolk/CDISC (Co-Chair)
Patty Garvey/FDA (Facilitator)
Julie Evans/CDISC
Bill Figgle/Sanofi Aventis (via phone)
Scott Getzin/Eli Lilly
Joyce Hernandez/Merck
Dave Iberson-Hurst/CDISC
Wayne Kubick/Phase Forward
Mary Lenzen/Octagon
Armando Oliva/FDA
Jason Rock/GlobalSubmit
Diane Wold/GSK
Mina Hohlen/FDA (3/31 via phone)

Background

The Clinical Data Interchange Standards Consortium (CDISC) formed a Stage IB group to develop the requirements for the CDISC - Health Level 7 (HL7) Content to Message Project. It was agreed by FDA and CDISC to conduct a series of regular conference calls for sub-team members as the initial path forward on the CDISC-HL7 IB activities.

The purpose of this meeting is to discuss the draft Subject Data story boards, project time line and defining xml.

Discussion

- The group completed the review of all the story boards.

  Sponsor Planned Data: Data collected in accordance with the plan. The Study Design message conveys (among other things) the plan for data collection, the Study Participation message includes information on the subjects in the study, and thus those two messages imply an expected set of data to be collected. The subject data message needs to be able to convey that data.

  - Story Board 1: Submission of SDTM and ADaM Data
    Study A1234 is complete and Acme Pharmaceuticals now wants to send to the FDA all the observations recorded for each subject during the study as part of their study report submission. Acme uses the CDISC-HL7 subject data message to provide all the recorded observations, as well as all the key derived parameters resulting from those observations, as defined by the CDISC SDTM and ADaM standards. The message contains all important relationships, such as the relationship between an observed and planned assessment (or lack thereof), the relationship between unplanned assessments and other observations (i.e. finding of jaundice led to a bilirubin measurement), and the relationship between the derived parameters and the collected data.

Those observations that were previously reported in a spontaneous adverse event report (ICSR) need to use common identifier, see story board 4

ACTION: ADaM representative attended 2/12/09 meeting and provide recommendation on this story boards.

** Data must be linked to plan (protocol)*
** Convey all the data we do today (e.g. SDTM domains)*
** Be able to conduct a safety review per "Conducting a Clinical Saftey Review of a New Product Application and Preparing a Report on the Review" CDER 2005 document*
** Think about non SDTM data (e.g. analysis, eHR. audit trail)*
** Present as an SDTM view*
** We need to support define.xml (include all metadata held in define)*
** What about the blank CRF (part of define.xml)*
** Extra data entered on the CRF page (e.g. comments at all levels, page and/or variable)*

- ✓ ***ACTION: Jason need to define.xml for the following:***
  ****planned and unplanned observation***
  ****linking***
  ****blank CRF***
  ****extra data entered on the CRF page***
  ****Ensure that RPS has address this***

- Story Board 2: FDA Completeness Check
  The FDA has received the data for Study A1234 and wishes to assess the level of completness of the data submitted by Acme Pharmaceuticals. The reviewer accesses the Janus data warehouse and runs a check to assess if all planned activities were performed. The reviewer should be presented with a report that provides a detailed view of the missing observations.

  This requires access to the plan held within the Study Design message and needs to allow for all paths to be evaluated at a high level of detail definition (sufficient to allow for a machine to perform the check). Note that this is a check of what is missing against the plan and does not consider additonal data that may have been collected."

  The check needs to run at a granular (data point) level but the story boards make no statement on how the results are to be presented"

- Story Board 3: Periodic Submission
  Acme Pharmaceuticals study XYZ123 being conducted and has some potential toxicity issues. The FDA requested that all subject data be submitted quarterly while the trial was ongoing. Subject data was submitted on 5 occasions while the trial was ongoing including updates to previously submitted data points. After the trial concluded, all of the subject data was sent to the FDA as a final transmission.

  - ✓ ***ACTION: Jason needs to address the following questions:***
    1. ***Does the Study Participation/Registration Message include study status information for such things as "finishing early" and "Last message".***
    2. ***Ensure that there are no overlap in the status information between Study Participation and Subject Data.***

Cross Reference to ICSR: Data collected in connection with ICSRs. It should be easy to make connections between data in the ICSR and other data conveyed in the Subject Data message. At minimum, this probably means that the Subject Data message needs to include unique identifiers for ICSRs.

- Story Board 4: Non-duplicative Adverse Event
  ABC Pharmaceuticals is running study 123A. One of their sites PharmaCRO reports an SAE. ABC Pharmaceuticals collects all the relevant information and promptly submits a report via the ICSR to the FDA (referenced by HL7 identifier 2.16.840.2.113883.4.125)

  A year later, ABC pharmaceuticals is preparing their submission for study 123A to the FDA

utilizing the Subject Data message. As part of their submission process, where information has previously been provided via ICSR there is a link in the subject data message which points back to the ICSR. Note the data can also be included in addition to the link.

The message must be able to identify previously submitted data.

- Story Board 5. FDA Initiated Query of Subject healthcare Data from an EHR
  The FDA team is reviewing the Study 123A which was submitted by ABC Pharmaceuticals. Several patients have experienced SAEs for which the study design has pre-defined treatment strategies. FDA reviewers notice a wide disparity in the outcome for patients with similar disease levels.

  The FDA requests to see a complete set of health records for the affected patients from ABC Pharmaceuticals, who in turn makes a request to all of their sites. Both use RPS as the information request and fulfillment mechanism.

  The site constructs an EHR HL7 message containing the requested information and sends it to ABC Pharmaceuticals who in turn forwards the information to the FDA.

  The FDA discovers that some sites have availed themselves of a new treatment procedure available for the treatment for these worrisome SAEs and that use of this procedure correlates back to improved outcomes.

- Story Board 6: Sponsor Initiates Additional Data Collection
  Use Case: Sponsor initiates the collection of additional data from investigators and then provides an update to the FDA. All of the data reported would be in addition to the plan.

  Study A1234 is complete and Acme Pharmaceuticals has provided the data to the FDA using the CDISC-HL7 subject data message to provide all the recorded observations, as well as all the derived parameters resulting from those observations, as defined by the CDISC SDTM and ADaM standards. Acme is aware of the need to collect some additional observations. The sponsor initiates the collection of the data from the sites and provides the new data to the FDA using the Subject Data message. This data needs to be linked to the data already provided to the FDA but is considered additonal to the plan as defined within the Study Design message. In some cases the Study Design Message may need to be updated.

Class 4: Subject Data may be conveyed in multiple stages, rather than as a monolithic data transfer. Therefore, the message must be capable of conveying both new and updated data.

- Story Board 7: Periodic SubjectData messages (blinded) and then data is unblinded
  See the above use cases.
  1. Since Acme Pharmaceuticals study XYZ123 is being conducted in a vulnerable population, FDA requested that subject data be submitted quarterly while the trial was ongoing.
  2. Subject data was submitted on 5 occasions while the trial was ongoing. In data on study drug administration, the name of study drug was given as “Blinded product” and dose was recorded with units of “tablets.”
  3. After the trial completed and was unblinded, data on study drug administration was updated to include all subjects, and to provide actual study drug data (Drug A, Drug B, or Placebo) for all subjects and dose information (20 mg for Drug A, 50 mg for Drug B) for subjects who received active product.

- Story Board 8: Periodic sending of SubjectData messages and Clarification process results in a data point being changed
  1. Since Acme Pharmaceuticals study XYZ123 is being conducted in a vulnerable population, FDA requested that subject data be submitted quarterly while the trial was ongoing.
  2. On the second occasion when data was submitted, lab data included an ALT value of 526 for subject 145 at Visit 3.
  3. This abnormal ALT value triggered a query. The response to the query was that there was a transcription error, and the true value was 256.
  4. In the third submission of periodic data to the FDA, the message included the corrected ALT value of 256 for subject 145 at Visit 3.

Other

- Story Board 9. Determine if patients met inclusion criteria
  The NCI-sponsored Study RTOG 93-09 is a randomized, unblinded, multicenter, two arm parallel design study comparing Chemotherapy + Radiation Therapy (CT+RT) vs. Chemotherapy + Radiation Therapy + Surgery (CT+RT+S) for the treatment of Stage IIIa non-small cell lung cancer. A key inclusion criterion requires the presence at screening of a single, newly diagnosed, primary lung parenchymal lesion of stage IIIA (T1, 2 or 3) with ipsilateral positive mediastinal nodes. The reviewer wants to ensure that only subjects meeting this criterion were enrolled. The Study Design message contains the plan to collect these screening data, and the reviewer is able to locate and analyze the collected screening data for each subject from the Subject Data message to verify that this criterion was met.

  Use Case: A study is conducted in order to determine if a product is safe and effective in a sub-population of patients. The inclusion criteria are constructed so that only patients in the sub-population of interest are enrolled in the study. The reviewer wants to ensure that only patients who met the inclusion criteria were enrolled in the study.

  - ✓ ***ACTION: Does study design allow this kind of connection?***

Audit Trail Use Cases

- Story Board 10. Original CRF Value Changed
  Use Case: Sometimes the original CRF value is changed by the sponsor (could be the investigator in the case of correcting a data entry error). The full audit trail is provided in the subject data message.

  1. ABC Pharmaceuticals has completed Study123A and this study is part of a submission for a drug that lowers blood pressure.
  2. Data was collected via paper CRFs.
  3. Subject data for BOB123 has a first data value for a concomitant medication of "Atenolol" and a last concomitant medication value of "Aspirin". It is highly suspicious since "Atenolol" is a prohibited medication. The reason for the change is "Dose correction" on the last Aspirin medication record.
  4. The reviewer inspects the full audit trail for BOB123 concomitant medications which has 6 modifications for the record of first value of "Atenolol" and last value of "Aspirin".

- Story Board 11. Audit Trail Information
  Study A1234 is complete and FDA wishes to audit the study data collection process. In order to do so, the reviewer reviews the subject data for the following audit trail information about each recorded observation that is associated with the observation and which has been submitted to the agency:

• Who originated or changed the data point (e.g. study coordinator, data entry clerk, investigator, laboratory, imaging facility, biomedical device) for that subject
• Date and time the data point was originated or changed
• Reason for that modification
• Date and time the investigator signed off

Required Association Between Data and Study Design

- Story Board 12: Estimate mean and variance of subject response in a study cell, and functions of these means and variances.

  A reviewer wishes to estimate the mean and variance of a continuous response variable (e.g. blood pressure) at one or more times (e.g. visit) in one or more study cells, and calculate functions of these means and variances.

  Rosie Reviewer is interested in understanding how blood pressure is affected, over time, by the treatment strategies being evaluated in the Acme 9999 study. In order to do this, she must know, for each measurement, the subject's treatment strategy and the length of time on that strategy at the time of the measurement. She must also be able to identify the baseline measurement for that treatment strategy. In order to evaluate the treatment effect at various timepoints relative to the start of treatment, she must select measurements to be included in evaluation of that timepoint. This will involve decisions about which observations are close

enough to the timepoint to be included in the analysis, selecting from among multiple "close enough" observations, and deciding whether and how to impute values for subjects with no "close enough" measurements. Once observations have been identified, she will calculate estimate of relevant statistics (means, variances, changes from baseline, etc.) for each treatment strategy and timepoint and also estimate differences between treatment strategies.

- ✓ ***ACTION: The message needs to identify a baseline***

- Story Board 13: Estimate mean survival time for subjects in a study cell
  A reviewer needs to estimate the mean survival time to an event (e.g. heart transplant) in a study cell. In order to calculate the mean, the reviewer needs to know if the event happened, and if the happened, when the event happened.

  Rosie Reviewer wants to compare the survival times for two treatment strategies intended to delay or avoid the need for heart transplant. The information needed, for each subject, is when the subject had a transplant, or, if they did not have a transplant, when the last contact with the subject occurred (i.e., when they were censored). The time of transplant or of censoring must be expressed as time from the randomization/start of treatment. Once this data has been derived, Rosie estimates survival times for each treatment strategy and tests for a difference in survival between treatment strategies.

- Story Board 14 Estimate the baseline value of a subject response:
  An analyst wants to estimate the pretreatment value of a patient outcome (e.g. blood pressure). Estimation of this value will be based upon one or more values of the attribute in a study cell prior to the study cell containing study treatment, or from patient history data.
  Must be able to link observations to the study design. Should be able to convey historical data.

- Story Board 15
  Test that a function of the data in one or more study cells is equal to, less than, or greater than a constant. Calculate an analysis of covariance for a continuous outcome measure for study cells in the second epoch of the study. The value at visit 3 is the response variable, and the sponsor-defined baseline score is the covariate. Message needs to allow for linking of the data to the study plan.

- Story Board 16
  Test that a function of the data in one or more study cells is equal to, less than, or greater than a constant. Calculate a Mantel-Haenszel test for study cells in the second epoch of the study. The response variable is categorical (e.g. presence or absence of an adverse event, seriousness of an adverse event). Stratification needs to be done by site, age, sex, and race.

- Project Timeline
  - September 2009 - Submit DSTU ballot for the Subject Data
  - Domain Analysis Model (BRIDG) mapping will be led by Stage IB – Stage II will provide support as requested
  - Julie still need to complete the Study Design mapping and request a few people to assist with the mapping for Subject Data

- Jason provided detailed discussion between the relationship of Care Provision event acts to the Clinical Statement. Care Record is a higher event then clinical statement, which is a record.

ACTION ITEMS:

1. Jason to show diagram (linkage) to statement collector.

2. Jason to get bench marks on uploading file for bulk data transfer.

3. Get someone who know the Define to explain how to link.

4. Jason to get link - how to use HL7 and LOINC.
   Jason's follow-up with the following information:
   - The following link is for HL7 and SNOMED: http://www.hl7.org/v3ballot/html/infrastructure/terminfo/terminfo.htm
   - Unable to find the equivalent for LOINC, here is an article about LOICN and HL7: http://www.openclinical.org/dld_loinc.html
   - The following is LOINCS website: http://loinc.org/

5. Julie and Dave I-H to decide when to ballot subject data - September 2009 or January 2010.

Drafted: PGarvey/4-7-2009
Approved: CTolk/6-9-2009