Meeting Minutes

CDISC-HL7 Stage I-B
January 14 - 15, 2009
9:00 am – 12:30 pm (EST)
HL7 Orlando, FL

Attendees / Affiliation

ATTENDEES	COMPANY	1/14 – Q1	1/14 – Q2	1/15 – Q1	1/15 – Q2
Jay Levine (co-chair)	FDA	X	X	X	X
Dave Iberson-Hurst (co-chair)	CDISC			X	X
Patty Garvey (Facilitator)	FDA	X	X	X	X
Doug Del Prete	IBM	X	X		
Isabelle de Zegher		X	X		
Julie Evans	CDISC		X	X	X
Bill Friggle	Sanofi-Aventis	X			
Scott Getzin	Eli Lilly	X	X		
Joyce Hernandez	Merck	X	X	X	X
Linda King	Eli Lilly	X	X		X
Daisuke Koide	Univ of Tokyo			X	X
Wayne Kubick	Phase Forward	X	X	X	X
Pierre-Yves Lastic	Sanofi-Aventis	X	X	X	X
Mary Lenzen	Octagon	X	X	X	X
Mitra Rocca	Novartis	X	X		
Jason Rock	GlobalSubmit			X	X
Chris Tolk	CDISC	X	X	X	X
Diane Wold	GSK	X	X	X	X

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 review and discuss the draft Subject Data story boards.

Discussion

January 14, 2009

- Julie Evans provided an update on the BRIDG domain analysis model. She is currently harmonizing the Study Design RMIM with BRIDG. She anticipates completing this in February and that it will be ready for the May 2009 ballot.

- The Subject Data story boards were reviewed and discussed.

- 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), and the relationship between unplanned assessments and other observations (i.e. finding of jaundice led to a bilirubin measurement).

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

  - Scope question: Do we want ADaM in here for the first version? How should we define “Key derived parameters"?
  - ACTION: Chris Tolk to follow-up with John Troxell (ADaM Team Lead) to address the group concerns.
  - * Data must be linked to plan (protocol)
    * Convey all the data we do today (e.g. SDTM domains)
    * Think about non SDTM data
    * Present as an SDTM view
    * We need to support define.xml (include all metadata held in define)
    * What about the blank CRF
    * Extra data entered on the CRF page

- Story Board 2: FDA Completeness Check

  The FDA has received the data for Study A1234 and wishes to assess the level of completeness 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 additional 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.

  - The following questions should be addressed:
    1. We are seeing a need for an update facility (transactional mechanism). We do we send all of the data again at the end?
       - ✓ YES
    2. Do we need status information for such things as "finishing early", "Last message"
       - ✓ ACTION: check that this is in Study Participation
    3. How does Subject Data in this use case relate to the use of Study Participation and the status info carried there?
       - ✓ ACTION: Make sure there is no overlap between Study Participation and Subject Data
  - Protocol amendments were discussed but the group concluded that this should be deferred to a later release.

- 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.

  Note: Request is from FDA -> Sponsor -> Site.

  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.

- It was noted that the care plan live in the study design and that there are 2 kinds of care plan. There was a question whether the care plan is capable of describing subject data from the clinical trial. For example, would it be able to express the message that it is a second visit. If it doesn't, is there another mechanism?
- This story board was discussed but it was concluded that this should be deferred to a later release.

- Story Board 15: Audit Trail

  Study A1234 is complete and FDA wishes to audit the study data collection process. In order to do so, the following audit trail information about each initially recorded observation is associated with the observation and submitted to the agency:
  - *The origin of the observation (e.g. investigator, laboratory, imaging facility, biomedical device)*
  - *Date and time the observation was recorded*
  - *Subject # (unique study subject identification number)*

  If the result was modified at any time after the initial recording, then the following additional information should be captured and submitted using the subject data message:
  - *The author/observer of the modification*
  - *Date and time the observation was modified*
  - *Subject #*
  - *Reason for the modification*

  The following are specific examples:

Observation	***Result***	***Audit Trail***
Patient ID	*AB0012*	***Origin:*** *randomization algorithm in central computer* ***Date:*** *2008-06-01T15:00* ***Subject #****:AB0012*
Sex	*Male*	***Origin:*** *Dr. R. Smith* ***Date:*** *2008-06-01T11:00* ***Subject #:*** *AB0012*
Hemoglobin	*15.3 g/L* *15.5 g/L (modification)*	***Origin:*** *Co-op Labs* ***Date:*** *2008-06-02T12:00* ***Subject #****:AB0012* ***Origin:*** *Dr. B. Green* ***Date:*** *2008-07-02T14:00* ***Subject #****: AB0012* ***Reason:*** *Lab error reported by Co-op Labs due to standardization problem; sample retested*
Chest X-ray	*Right Upper Lobe Consolidation*	***Origin:*** *Dr. P Brown* ***Date:*** *2008-06-01T16:00* ***Subject #****: AB0012*
Blood Pressure	*124/88*	***Origin:*** *Cardiodiagnostics serial #7834* ***Date:*** *2008-06-01T11:00* ***Subject #****: AB0012*
Concomitant	*Lasix*	***Origin:*** *Dr. R. Smith*

Medication		***Date:** 2008-06-01T11:00* ***Subject #:**AB0012*

- These are implementation issues that should be considered:
    1. The RIM may not currently support submission of an audit trail.
    2. The distinction of important versus unimportant data may be challenging to indentify considering the volume of data.
    3. Recommend examining ODM specifications to address audit trail.

- Need further discussion on defining "author/observer". Is it the principal investigator and/or data clerk?

January 15, 2009

- The majority of the group will not be attending the HL7 meeting in Japan. It agreed that a face-to-face working meeting should occur in Rockville, MD in place of the working session that would have occurred in Japan.

- The information for the face-to-face working meeting is as followed:

  Dates/Time: Tuesday, March 31, 2009 – 10:00am – 5:00pm
  Wednesday, April 1, 2009 – 9:00am – 3:00pm

  Location: FDA 5600 Fishers Lane, Parklawn Building, Rockville, MD

- The Study Participation and Study Design Messages will be a re-ballot for DSTU in May 2009.

- Patient Care Record hosted a meeting with RCRIM yesterday to describe their Care Record DSTU standards. It was concluded at the meeting that the Subject Data message will leverage the Patient Care Record standards. This project would only ballot the gap (e.g. experimental unit) between Care Record and Subject Data. Patient Care Record indicated that the CDISC HL7 project would not be able to comment on the Patient Care Record if is use in the CDISC HL7 Subject Data ballot.

- For the Individual Case Study Report (ICSR), the group will also need to review the ICSR standards to ensure that it captures this project requirement. The International Conference on Harmonisation (ICH) is currently writing a guidance to match the International Organization for Standardization (ISO) ICSR.

- Discussion on Subject Data story boards continues.

- 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 pharmaceutical is preparing their submission for study 123A to the FDA utilizing the Subject Data message. As part of their submission process, the information previously provided in the ICSR is filtered out and a link is inserted in it's place which points back to the ICSR report.

  - This needs further thought given the possible impact on the sponsor company given the current separation of CDMS-type systems and Safety systems.
  - ACTION: The same data will be passed within ICSR and Subject Data. Sponsors will need to use the same unique identifier in both messages so as to be able to relate.

- 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 "issues, need some more detailed explanation here ..." *that suggests that it would be desirable 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 additional to the plan as defined within the Study Design message*

  "Note: Should these additional observations and the plan for them be noted in an updated Study Design message?"

  - ACTION: Group agreed.
  - ACTION: Need language to provide detailed explanation for Acme's issues.

- Story Board 7: Periodic SubjectData messages (blinded) and then data is unblended

  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.

- No further change is needed for this story board.

- 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.*

    - No further change is needed for this story board.

- Story Board 9: Rolling NDA
    - Issues:
        1. Policy issue, may impact the amount of data to be submitted to the agency. Phase 1 only normally only incorporates the safety data
        2. Coding issue in that the data may be coded in different versions
    - ACTION: Story board to be written by Pierre-Yves Lastic

- 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). When this happens, the message needs to state the first and final data value. Further information (the full audit trail) would be provided in a different message if requested.

    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. *A message has been sent from the FDA back to ABC Pharmaceuticals requesting the full audit trail for all of BOB123 concomitant medication records.*
    5. *ABC sends a message back to the FDA with 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".*

- This story board was moved under the Audit Trail Use Cases section, which includes the story board 15 Audit Trail (see above discussion on January 14, 2008 meeting).
- Further discussion on this story board is needed with Armando Oliva.

- Story Board 16 – New storyboard added by Diane Wold
  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.

- Story Board 17 - New story board drafted by Diane Wold
  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.

ACTION ITEMS:

1. Chris Tolk to follow-up with John Troxell to discuss story board 1 “Submission of SDTM and ADaM Data”.
2. Pierre Yves-Lastic to draft a story board 5 “Rolling NDA”.
3. Add language to story board 6 “Sponsor Initiates Additional Data Collection” to provide detail explanation of the sponsor’s issues.
4. Patty Garvey will announce the face-to-face meeting on March 31 and April 1, 2009.

Drafted: PGarvey/1-10-2009
Approved: 2-12-2009