Meeting Minutes

CDISC-HL7 Stage I-B
July 17, 2008
11:00 am – 12:00 pm (EST)

Attendees / Affiliation

Jay Levine/CDISC (Co-Chair)
Patty Garvey/FDA (Facilitator)
Julie Evans/CDISC
Terry Hardin/IBM
Wayne Kubick/Lincoln Technologies
Mary Lenzen/Octagon
Mitra Rocca/Novartis
Saurin Mehta/Novartis
Diane Wold/GSK

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 continue reviewing the "draft" Subject Data use cases.

Discussion

- The minutes for the May 1, 6 and 22, 2008 meetings were reviewed and approved.
- The following additional toxicology storyboards were reviewed. It was decided that they these storyboards should be included with the other Study Design storyboards.
    - TOXICOLOGY STUDY ONE: Repeat Dose Toxicity study with Reversibility

      To test the potential toxicology of compound X for 90 days of treatment in the study and follow by 30 days of non-treatment to determine if the animal's recover from the toxicity. 30 Males and 30 Female rats will be administered four concentrations of compound X (0-control, 100, 500, and 1000 mg/kg) for 90 days. At the end of the 90 days treatment, 20 Males and 20 Females per concentration will be necropsied and tissue examined for toxicity. The remaining 10 Males and 10 Females per concentration will remain on the non-treatment phase of the study for 30 days and will be necropsied and tissue examined for toxicity and recovery. The following parameters may be collected but not limited to; Bodyweights, Food Consumption, Clinical Observations, Dosing, Clinical Chemistry, Hematology, and Pathology (Macro & Microscopic).

- TOXICOLOGY STUDY TWO: Oncogenicity Study

  To test the potential toxicity and tumorigenicity of compound X for the life time of the animal, typically two years. 60-120 Males and 60- 120 Female rats will be administered four concentrations of compound X (0- control, 100, 500, and 1000 mg/kg) for 2 years. At the end of the 2 years of treatment, all surviving animals will be necropsied and
  tissue examined for toxicity and tumorigenicity. All animals that die or moribund sacrificed through out the conduct of the study will have Pathology examinations and tissues collected. All palpable masses will be assigned a unique identified for that animal and in Pathology each mass or tumors will be identified and collected for examination and evaluation. The following parameters will be collected, but not limited to: Bodyweights, Food Consumption, Clinical Observations, Dosing, Clinical Chemistry, Hematology, and Pathology (Macro & Microscopic).

- REPRO STUDY ONE: Male and Female Fertility and Early Embryonic Development Study

  To test the adverse effects on male and female fertility and early embryonic development, product X will be administered for 2 to 4 weeks prior to mating, through mating, and through Gestation Day 6. Animals will receive either vehicle (control group) or Product X at one of three dose levels, with the high dose producing some evidence of paternal or maternal toxicity (i.e., a maximum tolerated dose). Males will be evaluated for fertility and male reproductive tissue assessment. Females will be evaluated for changes in estrous cycles, fertility, and female reproductive parameters. Embryos will be evaluated for viability.

- REPRO STUDY TWO: Multigenerational Study (Prepostnatal Study)

  To test multigenerational effects of female rats exposed to product X from near the time of implantation through gestation, continuing through 21 days of lactation. Dams (Fogeneration) will be evaluated for maternal care. Neonates (f1) will be evaluated for viability, and may be evaluated for developmental milestones and neurobehavioral effects. Select neonates will be placed in a maturation phase, monitoring growth and development, and potentially neurobehavioral effects. Upon attainment of sexual maturity, F1 rats will be mated and allowed to deliver to assess neonatal survival. This sequence of rearing and mating offspring may be repeated depending upon study requirements. Histopathology, male and female reproductive parameters, and a variety of neurobehavioral assessment will be conducted in paternal and maternal animals.

- Jay indicated that the subject data analysis use cases should capture what happens to the patient. The cases should also focus on how data will be used, what data elements need to be model and how it will be model.

- Wayne stated that we also need general use cases to define what data to send, how it should be sent (i.e. SDTM) and when it should be sent.

- In general, it was said that SDTM would accurately transmit what is on the case report forms but SDTM does not transmit amendments. The trial design message will capture the intervention and assessment where SDTM captures demographic information and contains results. The content captures other things that may be happening in patients' lives (i.e. adverse events). Content will be part of the gap analysis.

- The group understands the data that are being submitted to the FDA does not have the richness the FDA wants. Jay explained that use case should include what data FDA wants because the message will not solve the problem if there are no data. The use case will ensure that there is a place holder for the information even though the information may not have been collected.

Action Item

Jay will draft practical data driven use cases. These will be discussed at the next meeting on July 31, 2008.

Attachment: DRAFT Subject Data Use Cases (Jay Levine)

Drafted: PGarvey/7-31-2008

Subject Data Use Cases

- Case Review
  - Diagnose AE in a subject
  - Evaluate AE for severity
  - Evaluate AE for causality
- Parameter Estimation
  - Estimate mean and variance of subject response in a study cell
  - Estimate survival time for subjects in a study cell
  - Estimate the baseline value of a subject response
  - Construct confidence intervals for estimates
- Hypothesis Testing
  - Analysis of covariance
  - MH Test

Case Review 1

- Diagnose adverse event in a subject
  - An drug that is marketed in Europe is being evaluated for marketing in the US. A consumer group claims that the drug is associated with a specific adverse event. an analyst needs to evaluate patients that were treated with the product, and determine if they have experienced the adverse event. This will require an analyst to evaluate patients that may not have been previously diagnosed as experiencing the adverse event.

Case Review 2

- Evaluate AE for severity
  - A product is known to cause a particular adverse event. Depending upon the severity of the adverse event, the effect of the adverse event on the patient can range from minor discomfort to disability or death. An analyst needs to determine how many patients experienced the more severe manifestations of the adverse event.

Case Review 3

- Evaluate AE for causality
  - A drug that is marketed in Europe is being evaluated for marketing in the US. A consumer group claims that the drug causes a specific adverse event. An analyst needs to evaluate patients that were treated with the product and experienced the adverse event, and determine if these adverse events can be reasonably explained by factors other than the drug, such as high fever, meningitis, treatment with drugs known to cause the adverse event, or pre-existing conditions. In order to determine causality, the analyst plans to use reasoning similar to that described by Austin Bradford Hill in his paper "The Environment and Disease: Association or Causation (*Proceedings of the Royal Society of Medicine*, 58 (1965), 295-300.)

Case Review 4

- Determine if patients met inclusion criteria
  - 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 analyst wants to ensure that only patients who met the inclusion criteria were enrolled in the study.

Parameter Estimation 1

- Estimate mean and variance of subject response in a study cell, and functions of these means and variances.
  - an analyst 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.

Parameter Estimation 2

- Estimate mean survival time for subjects in a study cell
  - An analyst 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 analyst needs to know if the event happened, and if the happened, when the event happened.

Parameter Estimation 3

- Estimate the baseline value of a subject response
  - An analyst want 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.

Hypothesis Testing 1

- 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.

Hypothesis Testing 2

- 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.