Adaptive Trials and the Impact on STDM Trial Design Model

ABSTRACT
With high drug failure rates and the increasing cost of conducting traditional studies, there is growing interest in reducing the time and cost of clinical development. In February 2010 the FDA released an updated guidance on the design of adaptive clinical trials to address the industry’s desire for a more efficient development process. This guidance is primarily focused on adaptive trials, but it is designed to support the marketing of a drug. Basically, an adaptive clinical trial contains pre-planned modifications to the design or conduct of the study. The decision to implement the modifications is generally based on some form of interim analysis. A few trial modification examples are changing the eligibility criteria, changing the planned schedule patient evaluations, and altering the treatment regimes. These examples of clinical trial modifications have a direct impact on the content of Trial Design Model (TDM) domains and clearly the timing of producing these domains.

INTRODUCTION
While there are many types of adaptive trials designs this paper is intended to address adaptive clinical trial designs on the TDM and not the details on the types of adaptive trials designs. The 2010 guidance on adaptive trials defines an adaptive design clinical study as “a study that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from subjects in the study.” On the data side, we have the Study Data Tabulation Model (SDTM) whose role is to provide a standardized structure that is easy to navigate and understand. Contained within SDTM is TDM which provides a standardized way to describe the planned conduct of a clinical trial in data form. The idea behind TDM is to allow reviewers to easily understand the design of a clinical trial and comparison of trial designs across multiple trials, allow researchers to query a data warehouse of trial designs, and compare planned and actual treatments and visits for subjects in a clinical trial. Lastly, the most important point about TDM is the datasets are not subject-level.

The current TDM includes the following datasets:

- **TA**: Trial Arms: describes the sequences of Elements in each Epoch for each Arm.
- **TE**: Treatment Elements: describes the Elements used in the trial.
- **TV**: Trial Visits: describes the planned schedule of Visits.
- **TI**: Trial Inclusion/Exclusion criteria used to screen subjects. This is quite different then the subject-level IE domain which only lists the inclusion/exclusion criteria not met.
- **TS**: Trial Summary: lists key facts (parameters) about the trial that are likely to appear in a registry of clinical trials.

ISSUES
The current TDM does not address the handling of different planned designs of the study. Amendments have very much the same issues as adaptive trials and seem to be handled in various ways. With regards to TDM, there really is no difference between planned (adaptive) and un-planned changes to the protocol because after all they both lead to modifications to the planned study design. Therefore the issues discussed in this paper equally deal with amendments.

The tone of the adaptive trial guidance makes it clear there is concern about the use of adaptive trials due to the introduction of potential bias, Type I and Type II error. The examples below pose a greater statistical concern contributing to the importance of having a clear understanding of what the study looked like at time of enrollment for each subject.

Example 1
Adaptation: Adaptive Trial X expanded minimum age of participants based on results from another recently completed study.

**Issue:** The addition of younger subjects may introduce bias with regards to safety of the product. The additional information used from a recently completed study may influence an investigator and result in a more favorable safety profile of the drug.

**TDM items needing updates:**
1. **TV**: Visit structure needs to be updated for new subjects.
2. **TA**: Description of planned arms.
3. **TE**: Dose per administration and dosing frequency.

**Example 2**
Adaptation: Trial Y altered eligibility criteria based on accumulated baseline subject data. No interim analysis was needed and therefore no unblinding required. It was determined the subject population was tending towards a similar group and the study designers decided to relax some of the eligibility requirements to broaden the desired patient population. At a later date, a schedule interim analysis was conducted and a secondary objective was added.

**Issue:** Several hundred subjects were already enrolled and treated based on original eligibility criteria. From the time the eligibility criteria relaxed another several hundred subjects were enrolled and treated. The statistical concern is does a treatment-subject factor interaction exist.

**TDM items needing updates:**
1. **TV**: Secondary objective of the trial was added.

**Example 3**
Adaptive Trial Z alters treatment interval after interim analysis. After looking at blinded safety data it was determined to add a new treatment dosing 50 mg every 4 weeks. The original planned design was 50 mg every 4 weeks. Additionally, the visit structure had to be modified to accommodate the new treatment regimen.

**Issue:** The augmentation of treatment regimes creates a difficult situation operationally. More subjects have to be added to maintain the blind and additional visits for new subjects must be added.

**TDM items needing updates:**
1. **TV**: Visit structure needs to be updated for new subjects.
2. **TA**: Description of planned arms.
3. **TE**: Dose per administration and dosing frequency.

Benefits from traceability through the TDM

The examples above require a clear planned path for each subject enrolled in the trial. Early determination of a subject’s planned path is important for those trying to interpret the data. It is critical for a study to be clearly identified as to what the study looked like at the time of enrollment to aid in any exploratory analysis required to look at the concerns addressed in the 2010 Adaptive Trial Guidance. One possible solution is to provide a link on the subject-level data set(s) (perhaps DM) tying it to the correct path in the TDM. This approach would maintain the subject-level integrity of the SDTM and the protocol-level integrity of the TDM. The biggest benefit from some sort of link would be in the comparison of planned and actual treatments and visits for subjects in a clinical trial.

Conclusion
Adaptive clinical trials create an interesting challenge in reducing the amount of time to explore the data. The traditional clinical trial model is more sequential allowing additional time to explore the data before or during the final adequate and well controlled trial is conducted. The goal of adaptive clinical trials is to produce more efficient clinical trials resulting in a shorter time to submission and a cost reduction by not studying unnecessary dose groups or stopping a study for futility. One must be careful in the interpretation of the data and it is the job of the SDTM submission to clearly define the planned path of each subject. The future implementation guide with regard to TDM will have to address the best ways to deal with the multiple “planned” elements of the study and make clear the individual paths of subjects.