

Adaptive Trials and the Impact on STDM Trial Design Model

Thomas Clinch
e-mail: Thomas.Clinch@TheoremClinical.com

Nate Freimark
e-mail: Nate.Freimark@TheoremClinical.com

Theorem Clinical Research
630 Allendale Road
King of Prussia, PA 19406

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 adequate and well-controlled trials intended 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 regimens. 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 the impacts adaptive trial designs have 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, allow 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, and thus describes the complete sequence of Elements in each Arm.
- TE - Trial Elements: describes the Elements used in the trial.
- TV - Trial Visits: describes the planned schedule of Visits.
- TI - Trial Inclusion/Exclusion: displays all the 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 unplanned 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.

Example1

Adaption: 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.TI: Inclusion/Exclusion criteria modified to allow inclusion of younger subjects.
 - 2.TS: Do you modify AGESPAN or add another?

Original Planned:

STUDYID	DOMAIN	IETESTCD	IETEST
STUDYX	TI	INC1	Men or women 18 years of age or older

STUDYID	DOMAIN	TSPARMCD	TSPARM	TSVAL
STUDYX	TS	AGESPAN	Age Span	Adult (>=18)
STUDYX	TS	AGEMIN	Planned Minimum Age of Subjects	18

Modified:

STUDYID	DOMAIN	IETESTCD	IETEST
STUDYX	TI	INC1	Men or women 18 years of age or older
STUDYX	TI	INC1V2	Men or women 14 years of age or older

STUDYID	DOMAIN	TSSEQ	TSPARMCD	TSPARM	TSVAL
STUDYX	TS	1	AGESPAN	Age Span	Adult (>=18)
STUDYX	TS	1	AGEMIN	Planned Minimum Age of Subjects	14

Or:

STUDYID	DOMAIN	TSSEQ	TSPARMCD	TSPARM	TSVAL
STUDYX	TS	1	AGESPAN	Age Span	Adult (>=18)
STUDYX	TS	2	AGESPAN	Age Span	Adult (>=14)
STUDYX	TS	1	AGEMIN	Planned Minimum Age of Subjects	18
STUDYX	TS	2	AGEMIN	Planned Minimum Age of Subjects	14

Example 2

Adaptive 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 updated:
- 1.TI: Inclusion/Exclusion criteria modified for relaxed criteria.
 - 2.TS: Secondary objective of the trial was added.

Original Planned:

STUDYID	DOMAIN	IETESTCD	IETEST
STUDYY	TI	INC4	Subject must be on stable dose of XYZ for at least 6 months.

STUDYID	DOMAIN	TSSEQ	TSPARMCD	TSPARM	TSVAL
STUDYY	TS	1	OBJSEC	Trial Secondary Objective	To evaluate the efficacy of active in inducing clinical remission

Modified:

STUDYID	DOMAIN	IETESTCD	IETEST
STUDYY	TI	INC4	Subject must be on stable dose of XYZ for at least 6 months.
STUDYY	TI	INC4V2	Subject must be on stable dose of XYZ for at least 2 months.

STUDYID	DOMAIN	TSSEQ	TSPARMCD	TSPARM	TSVAL
STUDYY	TS	1	OBJSEC	Trial Secondary Objective	To evaluate the efficacy of drug Z in inducing clinical remission
STUDYY	TS	2	OBJSEC	Trial Secondary Objective	To evaluate the efficacy of drug Z in improving disease-specific health-related quality of life

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 6 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 regimens creates a difficult situation operationally. More subjects have to be added to maintain the blind and additional visits for the new regimen must be added.

- TDM items needing updates:
- 1.TV: Visit structure needs to be updated for new subjects
 - 2.TA: Description of planned arm
 - 3.TS: Dose per administration and dosing frequency
 - 4.TE: Treatment elements modified and new treatment element added

Original Planned:

STUDYID	DOMAIN	VISITINUM	VISIT	ARM
STUDYZ	TV	0	SCREENING	Drug A 50mg
STUDYZ	TV	1	WEEK 1	Drug A 50mg
STUDYZ	TV	4	WEEK 4	Drug A 50mg
STUDYZ	TV	8	WEEK 8	Drug A 50mg

STUDYID	DOMAIN	ARMCD	ARM	ETCD	ELEMENT
STUDYZ	TA	A	Drug A 50mg	SCRN	Screen
STUDYZ	TA	A	Drug A 50mg	TRTA	Drug A

STUDYID	DOMAIN	TSSEQ	TSPARMCD	TSPARM	TSVAL
STUDYZ	TS	1	PLANSUB	Planned Number of Subjects	800
STUDYZ	TS	1	DOSE	Dose per Administration	50
STUDYZ	TS	1	DOSEU	Dose Unit	mg
STUDYZ	TS	1	DOSFRQ	Dosing Frequency	Q4S

Modified:

STUDYID	DOMAIN	VISITINUM	VISIT	ARM
STUDYZ	TV	0	SCREENING	Drug A 50mg
STUDYZ	TV	1	WEEK 1	Drug A 50mg
STUDYZ	TV	4	WEEK 4	Drug A 50mg
STUDYZ	TV	6	WEEK 6	Drug A 50mg
STUDYZ	TV	8	WEEK 8	Drug A 50mg
STUDYZ	TV	12	WEEK 12	Drug A 50mg

STUDYID	DOMAIN	ARMCD	ARM	ETCD	ELEMENT
STUDYZ	TA	A	Drug A 50mg	SCRN	Screen
STUDYZ	TA	A	Drug A 50mg	TRTA4	Drug A Q4S
STUDYZ	TA	A	Drug A 50mg	TRTA6	Drug A Q6S

STUDYID	DOMAIN	TSSEQ	TSPARMCD	TSPARM	TSVAL
STUDYZ	TS	1	PLANSUB	Planned Number of Subjects	1200
STUDYZ	TS	1	DOSE	Dose per Administration	50
STUDYZ	TS	1	DOSEU	Dose Unit	mg
STUDYZ	TS	1	DOSFRQ	Dosing Frequency	Q4S
STUDYZ	TS	2	DOSFRQ	Dosing Frequency	Q6S

Or:

STUDYID	DOMAIN	TSSEQ	TSPARMCD	TSPARM	TSVAL
STUDYZ	TS	1	PLANSUB	Planned Number of Subjects	800
STUDYZ	TS	2	PLANSUB	Planned Number of Subjects	1200
STUDYZ	TS	1	DOSE	Dose per Administration	50
STUDYZ	TS	1	DOSEU	Dose Unit	mg
STUDYZ	TS	1	DOSFRQ	Dosing Frequency	Q4S
STUDYZ	TS	2	DOSFRQ	Dosing Frequency	Q6S

Benefits from traceability through the TDM

The examples above require a clear planned path for each subject enrolled in the trial. Easy determination of a subject’s planned path is important for those trying to interpret the data. It is critical for a subject 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.