

## The CDISC/FDA Integrated Data Pilot: A Case Study in Implementing CDISC Standards to Support an Integrated Review

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### ABSTRACT

The CDISC/FDA Integrated Data Pilot was initiated in 2008 with the mission of demonstrating that a subject data submission created using the CDISC standards will meet the needs and expectations of FDA reviewers in conducting an integrated review of data from multiple studies and compounds. This paper will provide an overview of the mission and goals of the Pilot, the major findings across the CDISC spectrum to date, and the timeline for finishing and publishing the final report. The session will present a case study of experiences implementing the CDISC models and provide the industry with feedback on the use of standards for data integration.

### INTRODUCTION

At the beginning of 2008, CDISC released a Technical Road Map providing an overview of activities regarding the development and harmonization of current and future CDISC technical products over the next three years. One of the roadmap's key objectives is to "execute pilots with regulatory authorities to gain a better understanding of the needs of regulators and industry". The CDISC/FDA Integrated Data Pilot was initiated in the spring of 2008 with the mission of demonstrating that a subject data submission created using CDISC standards will meet the needs and expectations of FDA reviewers in conducting an integrated review of data from multiple studies and compounds.

The goal of the pilot was to expand on the work of the SDTM/ADaM Pilot conducted from 2005 to 2007 on a single study and test the ability of CDISC standards to review integrated data across several studies with different designs. The objectives of the pilot include the ability to:

- Assess the applicability of the CDISC models to integrate data
- Validate the components of the CDISC models can be effectively used together
- Evaluate and Identify any issues/questions with the most current CDISC models including SDTM, ADaM, Define.xml, and Trial Design
- Support the critical path initiatives around data standards, integrated databases, standard data collection, and studies of special populations

The Team members include over 20 participants from pharmaceutical and biotechnology companies, vendors, NIH and FDA. The Pilot Team is engaged with a number of medical and statistical reviewers across both CDER and CBER to identify efficiencies and explore limitations with using the CDISC standards to review integrated subject data across studies.

During the course of the pilot the Team has addressed a number of challenges with implementing the CDISC standards to review data across studies. This session will provide the following:

- An overview of the Pilot including the mission, goals, and objectives
- A summary of the challenges with implementing SDTM across studies
- A summary of the process and challenges with implementing the new draft ADaM 2.1 model and 1.0 Implementation Guide
- An overview of the draft extensions for define to support value level metadata and analysis metadata results
- A timeline for completion of the pilot and publication of the results

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## PILOT PLAN

### PILOT TEAM STRUCTURE

Due to the breadth and scope of work targeted within this Pilot, the Team is led by three co-leaders. In addition to managing the overall Pilot, each co-leader manages one of the following subgroups.

- Programming group – Responsible for managing the metadata, performing all SDTM and ADaM transformations, and generating the summary tables
- Analysis and Design group – Responsible for writing the analysis plans including table shells, defining the ADaM specification, and summarizing the results within abbreviated clinical study reports
- Packaging group – Responsible for organizing the eCTD, bookmarking the submission, and implementing the define.xml and rendering of the outputs

In addition, a FDA review team was identified consisting of both medical and statistical reviewers who were responsible for providing an ongoing review of the Pilot deliverable and a final semi-formal review of the entire submission.

Managing a team with this much effort is much like running a small company and everyone on the team continues to put forth tremendous effort.

### CDISC MODELS

During the initial planning of the Pilot, the CDISC leadership and Pilot Team leaders had in depth discussions about what models to test given the challenges of the ongoing development of different versions. The Team decided to take on the challenge of testing the most current models, even though they were under development and continuously changing. This included SDTM 3.1.2, ADaM 2.1, and collaborating with the ODM team to define new draft extensions to handle gaps identified in the first pilot. This decision was important for meeting the strategic vision for CDISC; however, it created quite a challenge for the Team as they “Were going where no person had gone before”.

### SOURCE DATA

The data used within the Pilot came from a collection of studies that were standardized as part of a collaboration between the FDA and SAS Institute. As part of this project, safety data from over 25 studies were standardized to a common data model. As part this effort the FDA agreed to provide the data to the CDISC Pilot Team after a rigorous de-identification process that included altering the data.

Due to the high volume of studies, the Pilot Team defined a subset of eight studies that were in ‘better’ shape and provided a robust, but manageable set of data. The studies chosen spanned three different compounds and two different study designs. The study designs included a double blind dose escalation design and an open label pharmacokinetic design. Due to confidentiality reasons, the Pilot was only supplied with the following components:

- One page summary of each study
- SAS transport files for each domain with each study

Since the goal of the original project was to review safety, the domains included supported a safety profile. The following domains were included:

- DM – Demographics
- AE – Adverse Events
- DS – Disposition
- MH – Medical History
- EX – Exposure
- VS – Vital Signs

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- LB – Labs
- CM – Concomitant Medications
- SC – Subject Characteristics
- PC – Pharmacokinetic Concentrations

The drugs studied within the Pilot data were indicated for the treatment of pediatric hypertension. Due to the limited information provided to the Pilot Team, the Team had to make a number of assumptions in working with the data. Some of these assumptions will be described later on.

### TARGET DELIVERABLES

The Team spent a long time discussing what the final deliverables should be for the Pilot. During the planning phase the Team decided on the following deliverables:

- Analysis plans for each study, each integrated compound, and an overall composite integration
- SDTM domains for each study
- ADaM domains for each study, each integrated compound, and an overall composite integration
- Define files for each study, each integrated compound and an overall composite integration
- Clinical study reports for each study, each integrated compound and an overall composite integration

An important decision made early on was that all analyses would be conducted on the ADaM domains and not SDTM. The Team decided to deliver SDTM only for the individual studies and not for any of the integration components. This decision will be evaluated during the FDA review to see if this meets the needs of both the medical and statistical reviewers.

### ANALYSIS

#### ANALYSIS METHODOLOGY

To address the need to demonstrate the feasibility of integrating data within the limits of what was provided, the Team developed an approach that is different from conventional analyses. An integrated efficacy analysis was not possible because the original protocols with eligibility criteria, primary outcome variables, and statistical analytic plan were not available. In addition, the data had been altered. An integrated safety analysis was not possible for similar reasons plus safety cannot be assessed as an absolute, but is always relative to efficacy.

The approach selected was to use the data sets for what they were – a collection of values in different domains – and perform analyses of the general subject experience. The general subject experience means the series of events and observations that occurred for each subject and subject population. Not having baseline values for the particular subject populations, the Team referenced published age calibrated normal values to determine if any given event or value was within or outside the range of normal.

The output is then a series of individual subject profiles that are integrated within a study to provide a descriptive study population profile. Across studies, the population is defined as all enrollees because everyone received at least one dose of study drug. That profile can be parsed on the basis of demographic variables such as gender and age and study specific variables such as epoch within each study, across studies, and across compounds to test exposure to treatment. The rationale for performing an integrated analysis across the compound level is to describe a profile for the entire population of subjects with hypertension. This profile could be used as a reference framework, and future analyses comparing individual compounds or even individual studies to a total disease or condition centric reference frame may be informative.

To summarize, due to various limitations, a conventional analytic approach was not possible. An approach was that would invoke all of the technical requirements and tools to perform an integrated analysis across studies, but would not specifically map to the more conventional and familiar analytic approaches. Consequently, conventional expectations should not be applied to this exercise. Instead, the exercise should be evaluated on its own merits as a

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demonstration of proof of concept for the use of data standards and a structured approach to integrate data and perform analyses.

### ANALYSIS PLAN

Based on the methodology above, the analysis subgroup wrote abbreviated Statistical Analysis Plans for each study, each compound and the composite for all studies.

Some of the specific approaches used were to convert and reconcile all the data fields and values to conform to the most recent version of the CDISC Study Data Tabulation Model (SDTM). Subsequently, ADaM datasets were created using the SDTM datasets as inputs based on the most current draft ADaM Implementation Guide. Due to evolving standards in both SDTM and ADaM, the process involved careful reconciliation and alignment. Once all the nomenclature, logical decisions and structure were agreed upon, some of the variable definitions were quantified.

As part of the exercise paradigm, the Team decided that all clinical events, vital signs and laboratory values that were outside the range of normal would be considered an abnormal event. Recorded adverse events, by virtue of being recorded, were automatically incorporated.

The major variable affecting laboratory values in children is age. Laboratory values were compared to age adjusted reference standards from the National Institutes of Health Clinical Center. Because the values are periodically updated, the normal ranges were selected as of a particular date to normalize all study values.

Pediatric normal vital signs, due to the changing proportions of height, weight, body surface and body volume as a whole and also based on anatomic regions, for example relative head size, are complex to calculate. For each study participant, the age, gender, height and weight were factored into normal distribution curves to determine abnormal events within vital signs. The Team used formulae derived from the Centers for Disease Control to support our programming decisions and logic to make the calculations.

The selection of tables, as exemplified by the table shells in the SAPs, was based on variables that plausibly may be informative such as age, gender, study epoch and exposure to test compound. Other analyses are also plausible and possible, but the Team chose to focus on the selected outcomes because they each demonstrated a different facet of the datasets and together provide a composite proof of concept for the integrated approach. Because a formal statistical analysis could not be performed, the decision was to provide descriptive statistics and an associated summary with no conclusions. It will be the responsibility of the FDA members to perform that assessment.

### METADATA FRAMEWORK

The first step in managing the information across studies was to define a metadata framework to collect and manage the metadata for both SDTM and ADaM. The Team used a framework that was defined as part of the ADaM/SDTM Pilot that allowed the programming group to enter the metadata within Excel spreadsheets in a standard format. This metadata was then processed within the framework and a metadata model was built to support the entire process including the development of SDTM and ADaM domains, the publishing of define.xml, and the validation of both the SDTM and the ADaM data.

In addition to capturing table, column, and codelist information, the metadata framework was extended to include the capability to capture value level metadata. An example of this metadata is below.

table	column	param	paramrel	ptype	plength	pformat	pformatla	pdescription	computation_method
ADLB	PARAMCD	ALB	AVAL	N	8	4.1	1	ADLB_AVAL	Equal to LB.LBSTRESN
ADLB	PARAMCD	ALB	LBCAT	C	20	LBCATBC	2	ADLB_LBCAT	Equal to LB.LBCAT
ADLB	PARAMCD	ALB	PARAM	C	20	LBTALB	2	ADLB_PARAM	Equal to LB.LBTEST Plus units MM

In this example, specific metadata is defined within the ADLB domain where the value of PARAMCD='ALB'. In the first row metadata is defined for the value of AVAL when PARAMCD='ALB' including a length of 8 and a format of 4.1. This metadata is used later during the creation of the define.xml file.

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A detailed discussion of the metadata framework can be found within the paper by Steffens, Fleming (SAS Global Forum, 2009) referenced below.

### **SDTM DEVELOPMENT**

The first step in defining the SDTM specification for the eight studies was to perform a gap analysis of the data to evaluate what additional work would need to be done to conform to the specification and to support the analysis plans. Since the data provided had already been put into a SDTM 'like' format this process was not as complicated as it might be in real world context. The Team divided the original ten domains across multiple team members and performed an analysis looking for gaps.

There were a variety of issues identified during this gap analysis but most can be summarized in one of three categories. The first category is the most common problem working with legacy data – BAD DATA. There were a number of locations where there existed discrepancies in the data. Where possible, the Team made assumptions and 'fixed' the data. The second bucket involved compliance with SDTM. Even though the original data was supposed to be SDTM 'like' there were a number of instances where the input data did not meet the SDTM specification. This is a great example of the challenges with interpreting standards. The final bucket involved issues around what derived data should be included within the SDTM domains. The Team evaluated how much derived data to include and decided to only include it where absolutely necessary, such as calculation of age or baseline flags. Instead the Team planned for this type of data within ADaM.

Below are some of the issues identified and how they were addressed. These are just a few examples as not all the issues could be documented within this paper but will be described in the final Pilot report. Again, due to the limitations on the documentation provided the Team had to make some 'assumptions' regarding the data.

#### **BAD DATA**

##### **Inconsistent Units/Values**

Throughout the Vital Signs and Laboratory data there were a large number of inconsistencies in both the units and values within the data. In some cases the laboratory data had verbatim parameters instead of a standard set of terms and thus lead to confusion over what parameters were actually the same measurements. In addition, the units were inconsistent across sites and the group had to make their best guess at conversion options. In the case of Labs the Team made the decision to drop the Urinalysis data completely since it would be so time-consuming to fix and was not going to be included in the final analysis. The Team also decided to convert all the lab units to a standard unit measure and store the information within the \*STRES\* variables of SDTM.

##### **Controlled Terminology**

Throughout the domains there were differences in the controlled terminology within the values of a variable both across studies and in comparison to SDTM controlled terminology. Where possible the Team used the CDISC controlled terminology and mapped the raw terms or codes to those values. This information was documented as part of the metadata collected within the Pilot.

##### **Mapping Raw Variables to SDTM**

Throughout the raw data there were numerous occasions where the data expected within SDTM either didn't map very well or just didn't exist. For example, within Concomitant Medications instead of having separate raw variables that easily mapped to the dose, frequency and unit, the raw data captured this information within a single text field with no standard structure. This made it nearly impossible to effectively map to the standard SDTM variables and made the domain somewhat useless. In this case the analysis group made the decision to not include this domain since it was not necessary for the final analysis. There were more examples like this which had to be addressed and are common problems with the conversion of legacy data.

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### **SDTM COMPLIANCE**

Another decision made during the development of the SDTM domains was to decide how much of the 3.1.2 model would be implemented. Since the FDA is not yet capable of reviewing this SDTM 3.1.2 the decision created a challenge. The Team finally decided to include as much of the 3.1.2 model as possible that would not 'break' the current 3.1.1 production specification.

#### **Core Variable Category**

During the initial review of the data there was a significant amount of discussion around the core variable category classification within SDTM and the associated raw data. For example, in some cases there were fields required by SDTM that were just not available in the data. In some cases variables like AEDUR were calculated in the raw data but should only be included within SDTM if they are collected. In most cases the Team 'pretended' the data was as expected in SDTM and included it in the final data. In the case of missing data, the Team created data where possible. The Team made a decision early on in the project that the goal was to have SDTM data that could be transformed to ADaM for integration and analysis and decided not to be as concerned about the validity of the data.

#### **Modifying Data Structures**

A number of discussions within the Team revolved around the interpretation of the SDTM specification regarding the structure of specific domains. For example, within the EX domain, one of the notes within the SDTM specification says "This domain should contain one record per constant dosing interval per subject". Within the raw data, dosing information was collected at every visit and the data contained one record per visit even if the dosing remained the same. In addition, there were examples where the dosing ranges overlapped. The Team had long discussions over the interpretation and how to implement the dosing records. In this example, the Team decided to collapse the records based on the consistent dose and to correct the overlapping of records. There were a number of examples like this where the Team made decisions based on 'interpreting' the standards.

### **DERIVED DATA**

A core discussion that always arises when developing SDTM and ADaM domains is how much derived data should be maintained within SDTM domains. This discussion has been ongoing for many years as the SDTM model matured and pieces were added to support the medical review. This discussion continues as the FDA and CDISC try to ensure they are delivering what both the medical and statistical reviewers need to perform a complete review. Within this Pilot, the Team initially made the decision to limit derived data within SDTM as much as possible. However, as the planning continued the Team decided that some derived data had to be present to ensure a complete review. Below are some examples of the issues discussed and addressed.

#### **Definition of Epoch**

Half the studies within the Pilot involved a dose escalation multi phase design. Given this design the Team decided to include Epoch within the domains where applicable and make sure the definition of Epoch was consistent across domains and aligned with the Trial Design domains. In this case, Epoch was included in the Exposure, Laboratory, Vital Signs, and Pharmacokinetic Concentration domains.

#### **Baseline Flags**

The raw data used in this Pilot did not include baseline flags for any of the Findings domains, and the Team did not have access to the documentation for the studies. Given these limitations it was difficult to define a baseline flag. The Team made the decision to use the limited visit information that was provided and use associated windows to determine these flags. Again, the Team felt the goal was to have complete data within scope of the standards instead of clinically 'accurate' data.

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## Normal Ranges

Throughout the data, but primarily within Laboratory, the normal ranges were scarce and there was no documentation provided to give the Team a better understanding how the abnormal flags were defined. The Team made a decision to obtain published standard ranges for both Vital Signs and Laboratory data to ensure consistency within the domains and some level of standardization as data was moved from SDTM to ADaM.

## TRIAL DESIGN

One of the primary objectives of this Pilot was to implement the Trial Design domains, something that had not been done in the previous Pilot. The different trial designs within the Pilot and the complexity of the dose escalation multi phase trials made this an excellent sample to test the creation and use of the Trial Design domains. A team member worked with the CDISC trial design group to review the different study design and developed a robust set of trial design domains. The decisions made during this process were carried over to the development of the other domains (e.g. Epoch) which provided consistency. The use of the Trial Design domains will be evaluated during the FDA review of the Pilot.

## ADAM DEVELOPMENT

After the completion of the SDTM domains the next step was to define the ADaM specifications for each individual study and for the integration of studies both at the compound level and across all the data. The Team used the ADaM implementation guide 1.0 which is currently in draft format. The Team was fortunate enough to have a few team members who also served on the ADaM Team which allowed for an easy flow of questions and information between teams.

The Team started the process of defining ADaM specification by identifying the variables needed to support the analysis within the abbreviated analysis plans. As these discussions continued within the Team and among other groups, the Team realized the objectives of the analysis data sets would go behind the narrowly focused analysis and need to support other efforts. Given this realization, the Team included additional information within the analysis domains.

During the process of defining the ADaM domains, the Team ran into a lot of the same challenges the ADaM team has struggled with in finalizing the ADaM 1.0 Implementation Guide.

## DEFINING ADSL

The first step was to define the ADSL domain. This was the fundamental domain that would be used throughout the analysis and used to define the subset of variables which would be included in the other domains. The definition of the standard variables expected in ADSL (e.g. RACE, AGE, SEX, etc.) was relatively straightforward. After these variables the definition process became a bit more subjective and led to a significant amount of discussion.

## Analysis Subgroups

The first step was to define a complete set of analysis flags and subgroups that would be needed to support all the analyses defined within the analysis plans. This was an iterative process as the Team continued to refine and update the target analysis. Most of the discussion focused on how to capture a complete set of variables for each subgroup including the cumulative dose category, maximum dose category, and age group subgroups. Questions discussed within the Team included:

- What ranges to use for the various subgroups?
- How to name the various subgroup variables?
- Does each subgroup need the actual value, numeric group value, and character group value?

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These questions, in addition to others, led to many different opinions on how to implement these variables. The final decision was to implement two variables for every subgroup analysis, a character variable containing the group and an associated numeric variable for sorting purposes. However, due to the need to have variables that were more descriptive the decision was made to deviate from the implementation guide and truncated the suffix instead of the variable name. The list of subgroup variables included:

- AGEGRP and AGEGRPN – Age Group category variables
- DOSCUMGP and DOSCUMGN – Cumulative dose category variables
- DOSMAXGP and DOSMAXGN – Maximum dose category variables

The detailed algorithms for these variables were collected in the metadata and captured within define.xml.

### Treatment Variables

The Team spent significant time discussing the best way to implement the treatment group variables. Some questions that were raised during this discussion included:

- Does a TRTxP variable need to exist for every phase of a trial or only those of interest in the analysis?
- Should the TRTSEQP variable include a combination of the TRTxP variable or display some other combination of values?

This was another example of the ADaM Implementation Guide not providing a precise definition on how to define these variables. In the Pilot a TRTxP variable was added for every phase whether or not it was used in the analysis. In addition the numeric version (TRTxPN) of the treatment was added and the associated start and stop dates. In the case of the double blind dose escalation studies there were three phases within the study so nine variables were included in ADSL.

There was also discussion of the use of TRTSEQP. The implementation guide indicated it is required when there is a sequence of treatments that are analyzed, and if applicable, is required. There wasn't a clear definition of what should be contained in this variable which leads to it being sponsor defined. The Team defined it as the concatenation of the TRTxP variables. In hindsight, since the analysis didn't use this variable, it probably could have been left out.

### Phases, Visits, and Windows

The Team had a lot of debate over the implementation of phase, visit, and visit windows. The implementation guide does not clearly define how to capture phases of a trial within ADaM. It references the use of EPOCH from SDTM but does not address the need for an ADaM specific phase. Initially the Team defined an APHASE variable to capture this information but after discussion APHASE was removed and replaced with EPOCH from SDTM. After further analysis the Team realized that the Pilot studies had an analysis phase that did not necessarily match the EPOCH from SDTM. After more discussion AEPOCH was defined to capture the required information. The ADaM Team has defined this as an issue and is addressing in the final Implementation Guide.

With regards to visit the Team had a similar discussion regarding the use of visit variables from SDTM. Should copy the visit variables be copied over and used if there are no differences in the algorithms for generating visit or should a new variable be created. The Team decision was to append an 'A' to the visit variables and define the algorithm in the metadata as a 1-1 mapping.

### ANALYSIS FLAGS

#### ADSL Flags

Another challenge the Team faced, which deserves its own section, is the definition and implementation of analysis flags. First, within ADSL specific flags had to be defined for each subject. These flags included:

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Description	Variable
Flag if the subject had at least one serious adverse event	AESERANY
Flag if the subject had at least one adverse event	AEEVNTFL/ AEANY
Flag if the subject had at least one abnormal vital sign event	VSEVNTFL
Flag if the subject had at least one abnormal laboratory event	LBEVNTFL
Flag if the subject had at least one abnormal event (including adverse events, abnormal vital signs, or abnormal laboratory events)	ABEVNTFL

The Team attempted to follow the implementation guide and use the FL suffix to define each of these flags. However, there was no need for the numeric equivalent so FN variables were not included. In addition, the 'ANY' suffix was used for the adverse event flag variable. In this case two flags were defined for 'any adverse event' which meant the same thing. Retrospectively, only one variable should have been included and the FL naming convention should have been used for all flags.

### Record Level Flags

Within the individual domains multiple analysis flags had to be defined. The first flag was the record within a window that should be analyzed. The Pilot Team had the same discussion as the ADaM team regarding whether a record should be flagged based on whether it was analyzed or whether it could be analyzed. At the end of the day the Pilot Team made the decision to flag the record that was analyzed and chose the observation closest to the middle of the window. As per the implementation guide this variable was identified as ANLFL. Another analysis flag had to be defined at the record level within the Laboratory and Vital Signs data sets that flags a specific shift from baseline to that record. This analysis flag, which was named ANL2FL, has a very different definition than the first record level flag.

Two record level flags were identified that were very different in terms of the type of information being collected and the algorithms used for these two variables were captured as part of the metadata. The Team did discuss the use of the \*CRIT\* variables to describe the second analysis flag since it seemed to fit the definition within the implementation guide. The ANLxFL section within the implementation guide seems to refer to ANLxFL flags as flagging records as analyzable whereas the second flag variable defined was more of a criteria. The Team decided to leave the variable as a ANLxFL variable.

### NAMING CONVENTIONS

One of the biggest challenges during the definition of the ADaM specification involved those variables not clearly defined within the IG and the relationship between SDTM and ADaM. The ADaM IG is designed to allow for flexibility; however, this also can lead to challenges in defining variable name and roles and determining the relationship between SDTM and ADaM.

### SDTM to ADaM

Similar to the discussion within the SDTM section regarding derived data and the issues already discussed, the same issue resurfaced during the definition of the ADaM Specifications. Most of the discussion was focused on what variables should be copied from SDTM to ADaM, should the variable names and labels change, and how and when to store imputed records. Within the implementation guide it describes the possible need to copy over SDTM variable for supportive purposes. However, what if the SDTM variables are actually used for analysis? Should they be copied over or should they be renamed or have a prefix of 'A' added?

Some Team members had the opinion that if variables were copied over all attributes should remain the same, while other members thought variables from SDTM should be very limited and analysis variable names should be used even if the values of the variables were just copied with no derivation. In the end, the Team ended up with a mix of both options which they felt met the analysis needs.

### Relative Day Variables

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The ADaM IG gives some general guidelines for defining relative days but can lead to differences based on each person's interpretation. SDTM defines relative day variables as well as ADaM, each of which could have a completely different definition. The question raised by the Team was whether SDTM variables should be copied over as is, or whether new variables should be defined even if the definition of the variable is the same. In addition, the Team struggled to define the appropriate naming conventions given the implementation guide only defines that the variable must have a suffix of \*DY. The Team finally made the decision to not copy over any SDTM relative day variables, and use the naming convention of including an 'A' in front of the relative day to indicate an analysis relative day (e.g. ADY, ASTDY, AENDY).

In addition to the examples above, the Team had to decide how to define additional relative day variables that were based on other milestones independent of the start of study (e.g. EPOCH). This provided another example of an analysis decision not defined within the ADaM IG.

### ADAM INTERPRETATION

As the Team progressed through the specification, a number of analysis concepts were identified that could not be answered by the existing Implementation Guide. Either the concepts were not clearly defined or were not defined at all. The examples provide above give just a flavor of some of the challenges the Team faced when defining the analysis variables.

The primary lessons learned during the development of the ADaM specifications was that the ADaM IG doesn't answer all your questions, has some area of confusion or does not cover all the questions users might have in defining an analysis standard. However, given the overall mission of ADaM and the fact that that Team was using a draft implementation guide some of these challenges can be expected. While the process was tedious it did lead to a very robust and standard set of analysis tables.

## INTEGRATION

### REDEFINING METADATA

After the extensive work defining the detailed ADaM specifications within each study, the Team had to evaluate how well the standards helped define the integration components. In order to address the limited resources, the Team identified a small subset of integration components to address instead of the originally proposed target deliverables. The focus was to redefine the analysis subgroups for the integrated analysis. Most of these changes were due to the differences between trial designs. These differences led to changes in how the subgroups for both the integrated data within a compound and across compounds would be defined.

The Team focused on redefining two subgroups within the integration. Both the Cumulative Dose Group and the Maximum Dose Group were redefined as quartiles based on the integrated data and not the quartiles as originally defined in the individual studies.

### STUDY DESIGN

Within the Pilot data, half the studies were dose escalation studies with three epochs and half the studies were open label Pharmacokinetic studies with one epoch. After significant discussions, the Analysis group made the decision that it didn't make sense to combine studies of different designs and use the same algorithms. Therefore, the studies with similar designs were combined first using algorithms as described above. In the case of combining different designs slightly different algorithm were used.

One of the main analyses included a summary of abnormal events by phase. Since the study designs were different, when the data was combined across those different study designs, the Team could not use the same epoch information. Instead, a simple summary of epoch was developed that only included before treatment and on treatment.

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### ASSESSMENT

While the Team is still working through the intricacies of integrating the data the standards have provided significant benefit in integrating the analysis data. The only caveat to this assessment is that the Team was going through this exercise involving legacy data so making the studies look 'similar' was an easier process than ongoing projects within a company's organization.

Even though the process of moving from individual studies to the integrated component was easier, there were a number of issues that were identified and had to be addressed. Therefore, while the use of standard made the process more efficient the ADaM domains from the individual studies could not just be 'set' together. The Team did have to go through a thought process since the overall analysis changed.

### SUBMISSION DEVELOPMENT

After the development of all the pieces and parts the final steps include the generation of the final reports and the compilation of all the pieces into a eCTD structure for delivery to the FDA. This work involved a number of components including the development of the abbreviated clinical study reports, development of the eCTD structure, and the define.xml.

### ANALYSIS COMPONENTS

The Analysis group worked on developing an abbreviated Clinical Study Report (CSR) which would contain all the required parts but only support the limited analysis pieces. While the content will be limited, the Team wanted to make sure a structure was provided to the FDA that they were familiar with. Each CSR will have the summary tables listed and the appropriate linking between the define file and the CSR.

### ECTD STRUCTURE

Within the first Pilot only one study was submitted and therefore the process of developing the eCTD, defining the appropriate links between components, and creating the final package was fairly straightforward. In this case, this task became much more complicated due to multiple studies and integrated components. Most of the discussion revolved around two general challenges.

The first challenge was to define how to link the Integrated data and associated define files within the individual studies. After much discussion, the Team decided there was not an efficient way of providing this linkage so default standard eCTD rules were used for individual studies.

The second challenge was where to store the define files and associated style sheets. The Team wanted to avoid copying style sheets in every directory and confirmed that a higher level folder did not 'break' any eCTD rules, so they made the decision to create a top level folder containing one set of style sheets. With regards to the define files, the Team decided to store them with the data as expected.

### DEFINE.XML

One of the most critical components of delivering the metadata for this Pilot was to ensure the define.xml provided a clear path of traceability from the SDTM domains for each study to the ADaM domains for each study to the overall integration.

#### Value Level Metadata

One of issues identified in the first Pilot with the FDA was the inability of define.xml to capture value level metadata. The Team worked in collaboration with the CDISC ODM Team to identify a draft specification to handle this additional metadata which was critical for providing a robust set of information about the data. The goal of this extension to define.xml was to provide a machine-readable way of capturing metadata at the value level.

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This draft extension is under review and is being considered for inclusion in the next production release of the define specification. Below is an example of the rendering of the proposed draft specification. This is only **draft** and has not been finalized. An example of the XML will be presented at the conference.

This figure shows the reference to the LBTESTCD variable. Note the dynamic link to LBTESTCD.

Variable	Label	Key	Type	Length	Code List / Controlled Terms	Derivation	Origin	Role
USUBJID	Unique Subject Identifier	1	text	22				Identifier
VISITNUM	Visit Number	2	float	8				Timing
LBDMTC	Date/Time of Specimen Collection	3	text	19				Timing
<a href="#">LBTESTCD</a>	LAB Test or Examination Short Name	4	text	8	<a href="#">LBTESTCD</a>	<a href="#">LB_LBTESTCD</a>		Topic

This link then displays the value level metadata for LBCAT when LBTESTCD='ALB' and has links to an associated virtual code list and derivation.

Parameter Value	Parameter Related Variable	Type	Length	Format	Code List / Controlled Terms	Derivation
Context: In LB where LBTESTCD is ALB	LBCAT	text	20		<a href="#">LBCATBC</a>	<a href="#">LB_LBCAT_PV</a>

Finally, the virtual code list and derivation can also be displayed.

LBCATBC, Reference Name (CODELISTC14)		
<b>Valid Values</b>		
BLOOD CHEMISTRY		

  

LB_LBCAT_PV	Computation	Equal to LBNORMALS.LBCAT merged on LBTESTCD
-------------	-------------	---

As mentioned earlier this is a draft extension with the goal of tracing the metadata down to the value level. It is still being evaluated for inclusion in a final production release.

### Analysis Metadata Results

Within the first pilot, the concept of Analysis Metadata Results was introduced and well received by the FDA reviewers. This includes metadata about the analysis tables which can be included within the define.xml and provides a flow from the summary table to the Clinical Study Report, the input tables, and the associated algorithms. Within the first pilot, this was implemented as a one off extension to the define specification. Based on this prototype the ODM team, in collaboration with the ADaM team, has defined a formal draft specification which the Pilot Team is implementing and testing. The example below contains both the implemented XML and the rendering of the proposed analysis results metadata. This example takes on a more tabular format as defined by the ADaM team. The example below is actually from the first Pilot since the Team is still populating the analysis metadata for this Pilot.

```
<Study OID = "ADaM Results Standard Example1">
  <GlobalVariables>
    <StudyName>Define Analysis Results Metadata Example</StudyName>
    <StudyDescription>Example of ADaM Analysis Results Metadata</StudyDescription>
    <ProtocolName>ADaM Standard</ProtocolName>
  </GlobalVariables>
```

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```

<MetaDataVersion OID = "CDISC.ADAM.MDV1" Name = "ADaM_Standard, Data Definitions"
  Description = "Study ADaM_Standard, Data Definitions"
  crt:DefineVersion="1.0.1" crt:StandardName="CDISC SDTM"
  crt:StandardVersion="3.1.1">
<adamref:AnalysisResults DisplayIdentifier = "Table 14-3.01" DisplayName = "Primary
  Endpoint Analysis:ADAS Cog(11) - Change from Baseine to Week 24 - LOCF"
  ResultIdentifier = "Analysis of dose response" Reason = "Pre-specified in
  Protocol">
  <adamref:Parameter ParamCD = "ACTOT11" Param = "ADAS-Cog (11) Total Score"/>
  <adamref:AnalysisVariable Name = "CHG"/>
  <adamref:AnalysisDataset Name = "ADQSADAS"/>
  <adamref:SelectionCriteria>EFFFL='Y' and ITTRFL='Y' and AVISIT='Week 24' and
    PARAMCD='ACTOT11'</adamref:SelectionCriteria>
  <adamref:Documentation> <TranslatedText xml:lang = "en">SAP_SEC_10.1.1,
  SAP_TEMP_5. Linear model analysis of dose response for the ADAS-Cog(11) total
  score change from baseline at Week 24 - missing values imputed using LOCF,
  Efficacy population. Used PROC GLM in SAS to produce p-value (from Type III SS
  for treatment dose); Independent terms in model are TRTDOSE (randomized dose: 0
  for placebo; 54 for low dose; 81 for high dose) SITEGRP (site group, as a
  class variable) and BASE (baseline ADAS-Cog score).</TranslatedText>
  </adamref:Documentation>
  <adamref:ModelSpecification>PROC MIXED; CLASS USUBJID SITEGRP AWEEK TRT1P;
  MODEL CHG = TRT1P SITEGRP AWEEK TRT1P*AWEEK BASE BASE*AWEEK / OUTP=PRED
  DDFM=KR; REPEATED AWEEK / SUBJECT=USUBJID TYPE=UN; LSMEANS TRT1P / DIFF CL;
  RUN;</adamref:ModelSpecification>
</adamref:AnalysisResults>

```

### Analysis Results

Display Identifier	Display Name	Result Identifier	Param	ParamCD	Analysis Variable	Reason	Dataset	Selection Criteria	Documentation	Model Specification
Table 14-3.01	Primary Endpoint Analysis:ADAS Cog(11) - Change from Baseine to Week 24 - LOCF	Analysis of dose response	ADAS-Cog (11) Total Score	ACTOT11	CHG	Pre-specified in Protocol	ADQSADAS	EFFFL='Y' and ITTRFL='Y' and AVISIT='Week 24' and PARAMCD='ACTOT11'	SAP_SEC_10.1.1, SAP_TEMP_5. Linear model analysis of dose response for the ADAS-Cog(11) total score change from baseline at Week 24 - missing values imputed using LOCF, Efficacy population. Used PROC GLM in SAS to produce p-value (from Type III SS for treatment dose); Independent terms in model are TRTDOSE (randomized dose: 0 for placebo; 54 for low dose; 81 for high dose) SITEGRP (site group, as a class variable) and BASE (baseline ADAS-Cog score).	PROC MIXED; CLASS USUBJID SITEGRP AWEEK TRT1P; MODEL CHG = TRT1P SITEGRP AWEEK TRT1P*AWEEK BASE BASE*AWEEK / OUTP=PRED DDFM=KR; REPEATED AWEEK / SUBJECT=USUBJID TYPE=UN; LSMEANS TRT1P / DIFF CL; RUN;

### Traceability

One gap identified within the first Pilot was the ability to provide traceability from the ADaM data sets to the source data. After a significant amount of discussion within the Pilot Team and in conjunction with the ADaM team no good answer was identified. Without a standard metadata and computational method language this process becomes almost impossible. In the meantime, the Pilot Team documented free form text within the computational method to identify this traceability.

### Location

There has never been a clear recommendation on how to physically store the define files within the eCTD structure.

- Should you have one define file for each study containing all the metadata?
- Should you have separate files for SDTM and ADaM?
- Where should the analysis results metadata be contained?

Within the first pilot a number of issues were identified with placing all the metadata in one file. First, the rendering of the define file became an issue when a certain maximum number of external links was reached. Second, the define file had to be copied and stored with both the SDTM and ADaM data.

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Initially the packaging subgroup decided to create three define files: 1) SDTM metadata 2) ADaM metadata and 3) Analysis Results Metadata. After further discussion, the Team realized the Analysis Results Metadata would have to be linked to the ADaM domains and it would be easier if this information was stored together. The final decision was that a single define file would contain SDTM metadata and be stored with the SDTM domains, and a single define file would contain ADaM metadata and the analysis results metadata.

In addition to the rendering of the define file using style sheets, a PDF rendition was also created to provide an easy to print version. This request came from the reviewers of the first Pilot who indicated they would like a printer friendly version.

### NEXT STEPS

The CDISC/FDA Pilot has been working diligently over the last 18 months to work through a wide range of issues and questions encompassing the implementation of new and ongoing standards. The Team has completed a bulk of the work including the following:

- Creation of SDTM domains and ADaM for each of the eight studies
- Creation of Summary Tables and Clinical Study Reports for the first two studies
- Statistical Analysis Plans for the individual studies, integrated studies at the compound level and integrated studies at the class or total population level
- Creation of integrated ADaM domains for both the first Compound
- Package including the first two studies

The Team has targeted delivery of the first interim package to the FDA for their review at the end of September. This package includes all the components of the first two studies. While this review is ongoing, the Team is currently working on building the integrated package of the first Compound. Due to the volume of work, the co-leaders have decided to reduce the scope of integration to focus on the first Compound which includes four studies.

The goal of the Team is make the entire package available to the public by the end of 2009 and will include an extensive report of our findings. As with any volunteer effort, the ability to deliver in a timely fashion can sometimes be a challenge but the hope is that the information provided will help organizations improve their use of standards and avoid common pitfalls.

### SUMMARY

In 2008 CDISC released the technical roadmap which included an objective to plan and implement pilots to gain a better understanding of the needs of both industry and regulatory groups. This Pilot was initiated to test the latest CDISC models and their ability to facilitate the review process and support the integration of data. While the Pilot is ongoing, it has continued to provide benefit. Internal to CDISC, the pilot has provided a real world environment to test the standards to ensure they are meeting the needs of all customers and has provided invaluable input back to the CDISC teams. With the collaboration between CDISC and the FDA it has provided the FDA an opportunity to assess the capability to use standards to improve the review process.

The adoption of the CDISC standards will continue across the industry and within regulatory bodies to improve the drug development process, and pilots that help these two customers collaborate will only improve the efficiency of drug development.

### REFERENCES

Gregory Steffens, Principal Research Scientist, Eli Lilly & Co., Ian Fleming, Senior Statistical Programmer Analyst, Genentech." The Second CDISC Pilot Project: A Metastandard for Integrating Databases". SAS Global Forum, March, 2009; PharmaSUG, May, 2009. <http://support.sas.com/resources/papers/proceedings09/171-2009.pdf>

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