

Integrated ADSL

PhUSE

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ADSL - Not Without Challenges

- Where to Begin
- Source Data
- One ADSL or Two
- Number of Records per Subject
- Update or Create New Variables
- Treatment and Recalculated Variables
- Period

Which End Is Up?

- **Start at the beginning**
 - Gather what was done
 - Determine if ADaM recreation is desired on a study level
 - Good luck integrating everything 😊
- **Start at the end**
 - Determine ISS/ISE analysis needs
 - Make sure study level ADaM are properly populated

What is the Basis?

- **Source Data**
 - Study SDTM
 - Integrated SDTM
 - Study ADaM

Study Level SDTM

- **Values needed for integration may not be available**
 - Events that cross studies are not combined
 - VISIT/TPT/TESTCD values are inconsistent
 - Traceability can be difficult – especially when looking across studies

Integrated SDTM

- Requires an extra level of dataset creation
- Requires harmonization of SDTM variables
 - VISIT/VISITNUM
 - TPT/TPTNUM
 - TEST/TESTCD
- Allows for putting data from multiple studies into one data section
 - Demographics not collected in roll-over studies
 - AE end dates captured in subsequent studies
- Will directly support integrated ADaM

Study Level ADaM

- Requires 100% preplanning
- Requires creation of variables that may not be relevant on a study level
- Allows for derived values to be used in ADSL calculations
 - Did subject take a prohibited medication (captured in study ADCM)

How Many ADSL?

- **Multiple**
 - ISS
 - Typically includes all studies with subgroups focused on Disposition, Exposure and AE groupings
 - ISE
 - Typically a focused set of studies with many more variables and subgroups
- **Single**
 - ISS/ISE
 - Are the same rules used for both?
 - Safety vs. ITT
 - Dosing date vs. randomization date

How Many Records Per Subject?

- **One Record Per Subject**
 - Redefine TRTSDT/TRTEDT if a subject is in more than one study
 - Much traceability gets lost in the transition
- **One Record Per Subject Per Studyid**
 - Leave study values as-is
 - TRTSDT/TRTEDT not useful for slotting
 - Subject basically treated as multiple unless summary programs “do the dancing” (not one proc-away!!)
- **One Record Per Subject Per “Experience”**
 - Double-blind -> open label
 - Placebo washout -> double-blind
 - Titration -> steady state

Decision Based On?

- **Analysis needs**

- Will the same subject's data be summarized across studies?
- How do I decide which AGE value to summarize?
- Will cross-study data be harmonized on an SDTM level?

ADSL Variable Values

- Traceability considerations
- Change in place vs. creating new variables

Update or Create?

- **Update Existing Variables**
 - Original value and source gets lost
 - AGE recalculated based on a different anchor date
- **Create New Variables**
 - Original values maintained
 - New variables do not exist in the current standard
 - Programs have to be modified for new variables

Update or Create - AGE

- Study 1 – based on randomization date
- Study 2 – based on enrollment date
- Study 3 – based on first dose date
- **ISS requires AGE based on first dose date**
 - Create “AGENEW” with consistent formula?
 - Create AGE with consistent formula?
 - Save original AGE as “AGEOLD” for traceability?

Treatment Variables

- **ISS – Low vs. High vs. Placebo**
- **Study 1- High vs. Placebo**
 - Built with the end in mind: TRT01PN = 1 vs. 3
 - Breaks functionality of having TRTxxPN define column order
 - Study level: TRT01PN = 1 vs. 2
 - Requires recoding on an integrated level
- **Study 2 – High vs. Low vs. Placebo**
 - TRT01PN = 1 vs. 2 vs. 3

Treatment Variables (cont.)

- Study 1: 30 mg vs. 60 mg :TRT01PN = 1 vs. 2
- Study 2: 20 mg Fed vs. 20 mg Fasted :TRT01PN = 1 vs. 2
- Study 3: 20 mg :TRT01PN = 1
- How does this get harmonized on an integrated level?
 - Create new treatment grouping variables?
 - Recreate TRTxxP based on integrated analysis needs?
- How do you handle subjects who get treated with multiple drugs if they are in the denominator for more than one column?

Grouping Variables

- median value requires recalculation
- Active vs. placebo can have different meaning on an ISS level vs. study level
- Dose groupings differ for integration

Recalculated Variables (example 1)

- Study 1 – baseline is the average of Screening and Day 1 values
- Study 2 – baseline is nominal Day 1 value
- ISS – needs harmonized definition – last non-missing value prior to dosing

Recalculated Variables (example 2)

- Study 1 – randomized trial - average daily dose based on titration period and then steady state dosing
- Study 2 – open label study - average daily dose based on dosing log
- ISS – requires recalculation looking across both studies

What Is Considered a Period?

- **Are two studies considered two periods?**
- **If study ADaM are used are integrated are ADSL treatment period variables needed at all?**
 - May not be needed for TRTP/TRTA assignment since those are calculated on a study level
 - Having all data on one record allows reviewers to calculate their own values without going back to the individual studies

Summary

- Decide where to start
- Gather all source data
- Structure (number of ADSL/obs)
- Update/Create New Variables
- Recalculate Necessary Variables
- Traceability and Period

Questions?

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