THEOREM CLINICAL RESEARCH SM

Integrated ADSL

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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

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
    - Generally more straight forward
    - Typically includes all studies with subgroups focused on Disposition, Exposure, Laboratory, 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
    - Lots of flag variables not populated for all non ISE datasets

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?
- **Do we care about the original study value?**

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

Other Considerations

- **Are two studies considered two periods?**
- **If study ADaM used are integrated 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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