Standardizing Data Cuts

Mercidita T. Navarro

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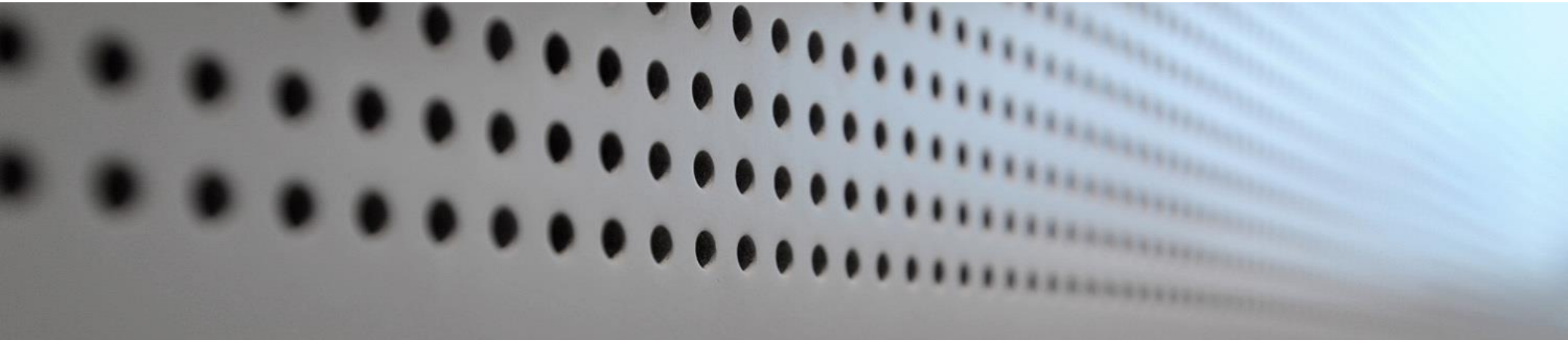
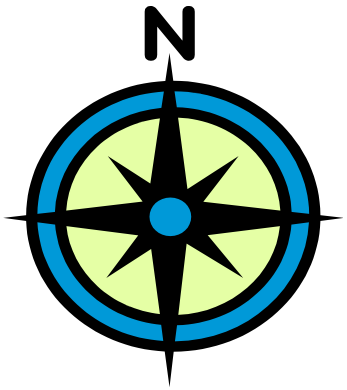


Outline

- Background
- Data Cut Standards
- Technical Implementation
- Summary



Background

Motivation

What is a Data Cut?

- A data cut is a predefined subset of the clinical study database
- Typically, all available data at a pre-specified point in time, or a subset of data collected up to that point in time

Why Use a Data Cut?

- Interim analyses are prepared to support the objectives of a study and enable decisions for a project
- A data cut provides a static set of data on which to perform an interim analysis
  - allows for traceability and reproducibility of results while the study is ongoing and data continue to be collected
- With a predefined data cutoff, relevant data can be “cleaned”

Why Standardize?

- Consistency leads to efficiency in resources
- Opportunity for workflow automation

Types of Data Cut

1. **Snapshot** – All data **available** on the date of the snapshot
   Example: Snapshot taken after enrolling 25% of target
2. **Fixed-cutoff data cut** – All data **collected** on or before a study milestone
   Examples:
   - Date of Week 12 visit of the last patient enrolled
   - Date of 100th event (e.g., death or disease progression)
3. **Variable-cutoff data cut** – All data **collected** as of a **subject-specific** milestone
   Examples: All data collected
   - On or before the Week 12 visit
   - On or before completion of 12 weeks of dosing
   - Before crossing over to the next treatment in a crossover-design study

DSMB = Data & Safety Monitoring Board

Choosing the Type of Data Cut

- The type of data cut to use will depend on the purpose of the interim analysis
- Possible scenarios:

Purpose	Example	Applicable Data Cut
Safety monitoring report	DSMB	Snapshot
Annual safety update	DSUR/PBRER	Fixed-cutoff = DLP
Efficacy: Time-to-event	Overall survival endpoint	Fixed-cutoff = date when required no. events have occurred
Efficacy/safety over a pre-specified exposure interval	Efficacy after 12 weeks of treatment	Variable-cutoff = date of milestone visit

- Determination of clinical cutoff date is study-specific

DSUR=Development Safety Update Report; PBRER=Periodic Benefit-Risk Evaluation Report; DLP=Data Lock Point

Data Cut Standards

Rules for Fixed- and Variable-Cutoff Data Cuts

- **Which subjects to include?**
  - All subjects enrolled on or before the clinical cutoff date
- **Which records to include?**
  - Records with assessment/milestone/start date on or before the clinical cutoff date
- **Which data elements to truncate?**
  - **Dosing** data and **time in study** will be truncated at the clinical cutoff date as part of the analysis
  - Allows for accurate documentation of
    a) duration of exposure to study drug
    b) time in study
    as of the clinical cutoff date

Addressing Potential Discrepancies

- Missing/Partial Dates: Include records in the data cut unless it is clear that the relevant date is after the clinical cutoff date, for example:

Assessment/Start Date	Clinical Cutoff Date	Include?
CM start date = 2014	30 NOV 2013	No
Lab test date = JAN 2015	01 DEC 2014	No
AE start date = missing	15 JUN 2014	Yes

- For AE and CM records: All data elements will be kept as tabulated from raw data in the snapshot, i.e., **no "rollback"** (e.g., AE end date, outcome, most extreme intensity)
  - Provides as much information as possible for data interpretation at the subject level
- Any inconsistencies in the following key data displays will be explained:
  - Summary/listing of AEs leading to study drug discontinuation/death
  - Time-to-event analyses

Adverse Event and Outcome

- Potential inconsistencies between summary tables/listings

	Topic	Source	Included in the Data Cut
1	Subjects with **AE** resulting in **death**	AE domain	All outcomes for AEs with start date on or before clinical cutoff
2	Subjects who **discontinued** from the study due to **death**	DS domain	All DS records with study discontinuation date on or before clinical cutoff

- The number of subjects may differ between (1) and (2) after applying the data cut rules
- Clearly indicate in a table/listing footnote what are included in the analysis
- Note discrepancies when interpreting results
- Similarly, review results for inconsistencies associated with AE outcome = study drug discontinuation

Adverse Event and Outcome – Example

- Clinical cutoff date = March 31, 2009
- Snapshot date = April 28, 2009
- As of the snapshot date, 4 patients experienced serious adverse events

Patient	AE	Onset Date	End Date	Reason Classified as Serious
10003	Diarrhea	**Sept. 14, 2008**	Sept. 28, 2008	Hospitalization
11105	Thrombocytopenia	**Dec. 15, 2008**	Dec. 29, 2008	Life threatening
10001	Pneumonia	**Jan. 1, 2009**	Feb. 28, 2009	Resulted in death
12345	Coronary artery disease	**March 1, 2009**	April 15, 2009	Resulted in death

- All **4 SAEs** will be included in the data cut
- All outcomes including **2 deaths** will be reflected in the data cut
- Two (2) deaths due to AE are included in the snapshot

Patient	Date of Death	Reason
10001	Feb. 28, 2009	Pneumonia
~~12345~~	~~**April 15, 2009**~~	Coronary artery disease

- Only **1 death record** (Patient 10001) will be included in the data cut

Discrepancy between the SAE listing and death listing must be noted in the report

Additional Considerations

- No records with assessment/milestone/start date after the clinical cutoff date will be included in any analysis
- For time-to-event analyses, death status and date last known to be alive will be updated in the VAD to be consistent with the clinical cutoff date, for example:

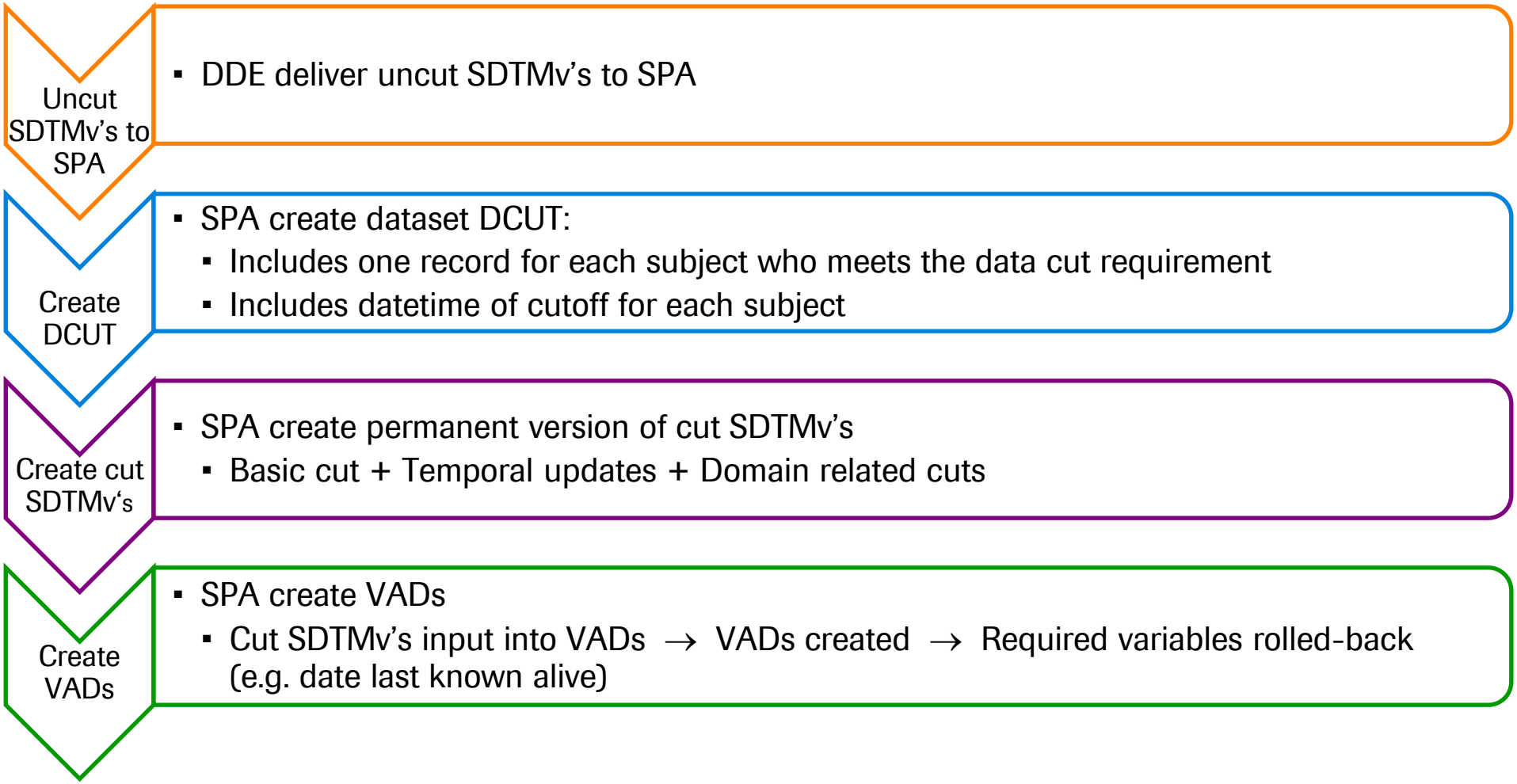
Analysis Variable	Derived Value	Source	Clinical Cutoff	Analysis Value
Patient died? (date)	"Y" (13 JUN 2014)	Fatal AE end date	30 MAY 2014	null[a]
Date last known alive	30 JUN 2014	CM end date	30 MAY 2014	30 MAY 2014[b]

[a]Delete record from Death VAD
[b]Create an analysis flag to indicate that value is truncated at the clinical cutoff date

- Additional steps may be required when analyzing other variables derived from end dates (e.g., duration of AE)
  - Note that data elements will be kept in the data cut as tabulated from raw data (i.e., no "rollback")

Technical Implementation

Process Flow



DDE=Database Development & Extraction; SPA=Statistical Programming & Analysis; VAD=Value-Added Dataset (analysis file)

Key Steps

- DCUT dataset is used to create cut SDTMv's which are the basis of VADs
- SDTMv's with no date component will be used as transferred from DDE (e.g., TS and other non-patient level data)
- Several levels of cutting data:
  1. **Basic cut** – Delete records with assessment/start date after the clinical cutoff date
  2. **Temporal update** – Update temporal derivations in DM and other affected domains (e.g., DM.ACTARM based on cut EX records)
  3. **Relational update** – Ensure that child-domain records link to a parent-domain record (e.g., RELREC, FA)
     - Some RELREC records may become meaningless after the basic cut—decision to delete these records is study-specific
  4. **VAD-specific update** – Roll back key derived variables (e.g., date last known alive)
- Important to validate all data cut steps at "high-risk" level

Summary

Main Takeaways

- A data cut is a predefined subset of the clinical study database that is used for an interim analysis
- Standard definitions and rules for creating a data cut allow for a consistent process flow
- Discrepancies will arise as a consequence of the data cutting steps
  - Need to carefully address inconsistencies with high impact
- Technical implementation is multi-faceted
  -- it will take several steps to achieve a robust data cut

Acknowledgments

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Doing now what patients need next

Backup

From Concept to Reality

3–4 mos.

Data Cut Working Group

- Cross-functional team with experience in various therapeutic areas proposed standard definitions and rules for data cuts
- Membership from Biostatistics, Statistical Programming, Clinical Science, Safety Science, Standards Group

2–3 mos.

Data Standards Governance Committee – Definitions

- Data Analysis Definitions Core Team reviewed proposal from Data Cut Working Group
- Key stakeholders consulted as needed
- Rules and definitions approved and added to Global Data Standards Repository

4–6 mos.

Data Standards Governance Committee – Technical Specifications

- Technical details published following focused discussion within the Technical Specifications Core Team

~12 mos.

Technical Implementation/Systems Development

- Pending development of standard data cut macros, teams were advised to apply the data cut standards following workflow recommended by Governance Committee
- Early adopters shared their experience including those from recent filings
- Dedicated SPA team developed a comprehensive, technical implementation guidance