Case Study of CDISC Submission at Novartis Oncology

PhUSE Boston – May 7, 2014

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Introduction

- The following presentation will focus on the process flow for the creation of FDA submission data in CDISC[1] format for a recent submission at Novartis Oncology
- Emphasizes on the Metadata driven systems and their effective use in CDISC compliant submissions
- Covers the data flow from source to SDTM[2] & ADaM[3]
- Explains about Metadata and it's use in the derivation of elements in the data
- Illustrates generic templates for the creation of SDTM+ data

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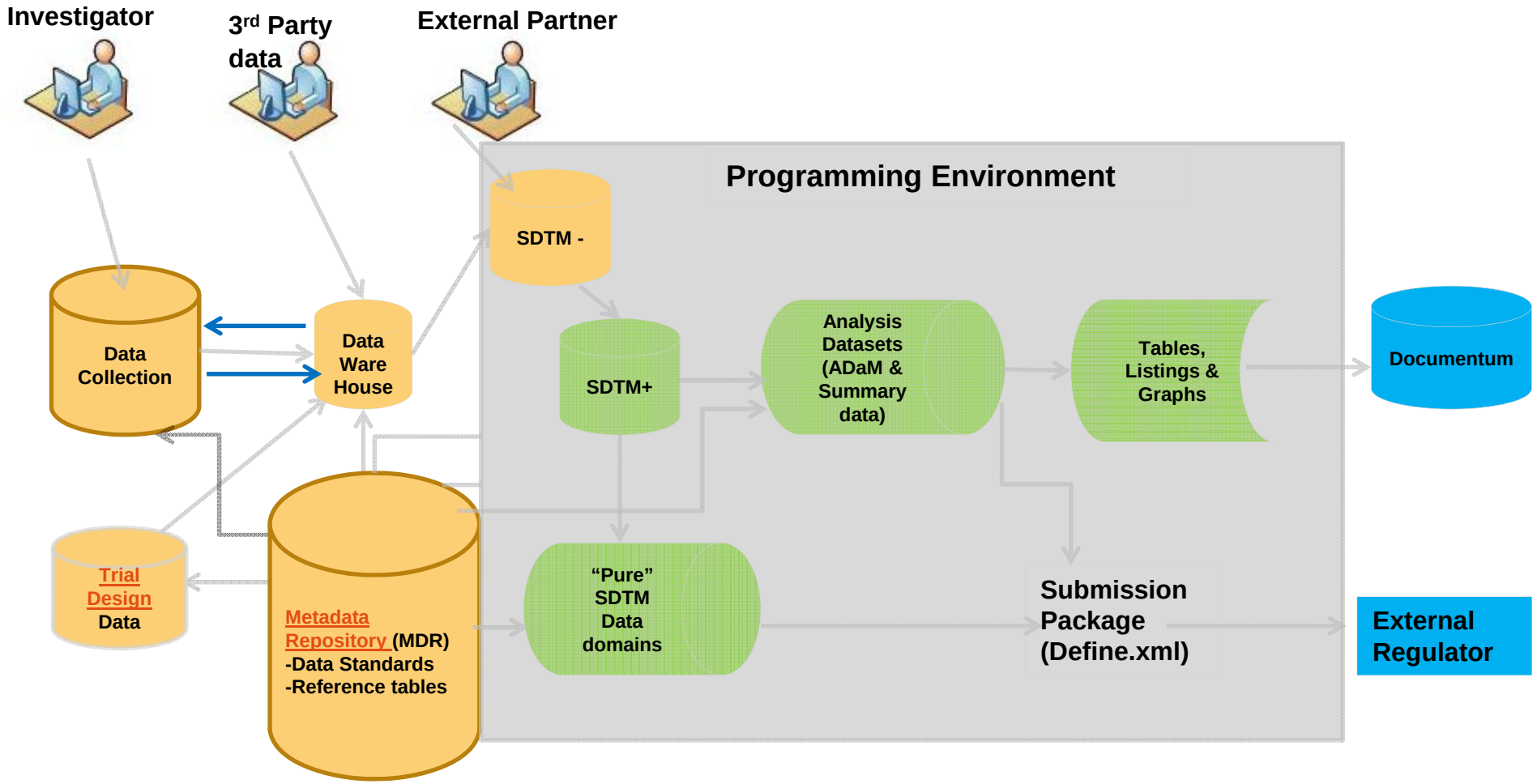
1 CDISC = Clinical Data Interchange Standards Consortium

Data Flow

Flow Chart – Global Picture

Data Std. Governance Boards / ADaM Governance Board / Oncology Std Outputs GB



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Data Flow – Cont'd

- As shown in the flow chart, collected data from Database including data from 3rd party transfer(s) (eg. Lab, Biomarker etc.) will be loaded into the Data Warehouse
- Data then goes through pre-defined derivations and transformations in the Warehouse and subsequently extracted into the programming environment (this data is referred as SDTM-)
- SDTM+ data that contains a given SDTM and its corresponding Supplemental Qualifier variables in one domain, will be derived from SDTM- data
- ADaM datasets and pure SDTM domains (along with Supplemental Qualifiers) will be created from SDTM+ domains

Global Metadata

Key points

- Consistency in the Submission data
- Compliance with CDISC standards
- Standard programming templates were created based on Metadata
- Global Metadata contains data structure details for staging area within GPS for every data domain:
  - Source (RP) – SDTM-
  - Derived (DR) – SDTM+
  - Pure SDTM and Supplemental Qualifier (SD)
  - ADAM (AD)

Key fields in Metadata

Key fields:

- DSTYPE: Dataset type related to staging area. (S = Source (RP), D = Derived (DR), B = Pure SDTM and Supplemental Qualifier (SD), A=ADAM (AD))
- DSNAME: Dataset name (Ex: AE)
- ETNAM: Element name. This is the name of the variable represented in the OC / LSH systems and is different to the SAS variable name (Ex: CPEVENT)
- NAME: SAS variable name as it appears in SDTM / SDTM+ / ADaM (Ex: VISIT)
- FETNAM: Also called FQE for Fully Qualified Element name; this is the unique identifier for an element, within a given domain for a giving staging area. FQE value are composed of Staging area, Data Domain name (dataset name) and Element name separated by “.” Sign (Ex: DR.AE.CPEVENT)
- CODELIST: Codelist associated to the element (Ex: NOYES for corresponding AEYN field)

Key fields in Metadata (cont'd)

- CT_TERM: Controlled Terminology Term (Ex: SDTM, ABBREVIATED etc.)
- CONET: Contributing element: List of FQE used for the derivation (Ex: RP.AE.CPEVENT)
- DRVNAM: Derivation name (Ex: COPY_ELEMENT, DECODE etc.). Detailed description of derivations available in SPS Share point.
- DRVSEQ: Derivation sequence number (setup for a given domain for a given staging area) (Ex: 1)
- DRVDOM: List of domain (logical name) involved in the related derivation (Ex: RP.AE)
- DRV_LOGIC: Derivation logic description (Ex: VISIT = AE.CPEVENT)
- DRV_PARAM: Derivation parameter: Addition information (parameters, list of additional FQE) (Ex: RANDOMIZATION)
- KEY: Key variable number, populated only for key fields and missing otherwise (Ex: 1)

Key fields in Metadata (cont'd)

- LABEL: SAS variable label (Ex: Visit Name)
- LENGTH: SAS variable length (Ex: 20)
- MAND: Mandatory status (Y/N)
- SORT: Sorting variable number. Similar to Key field, populated only for sort fields and missing otherwise (Ex: 1)
- TYPE: SAS variable Type like Character, Numeric etc. (Ex: C)
- SASFMT: SAS variable format (Ex: e8601dt.)

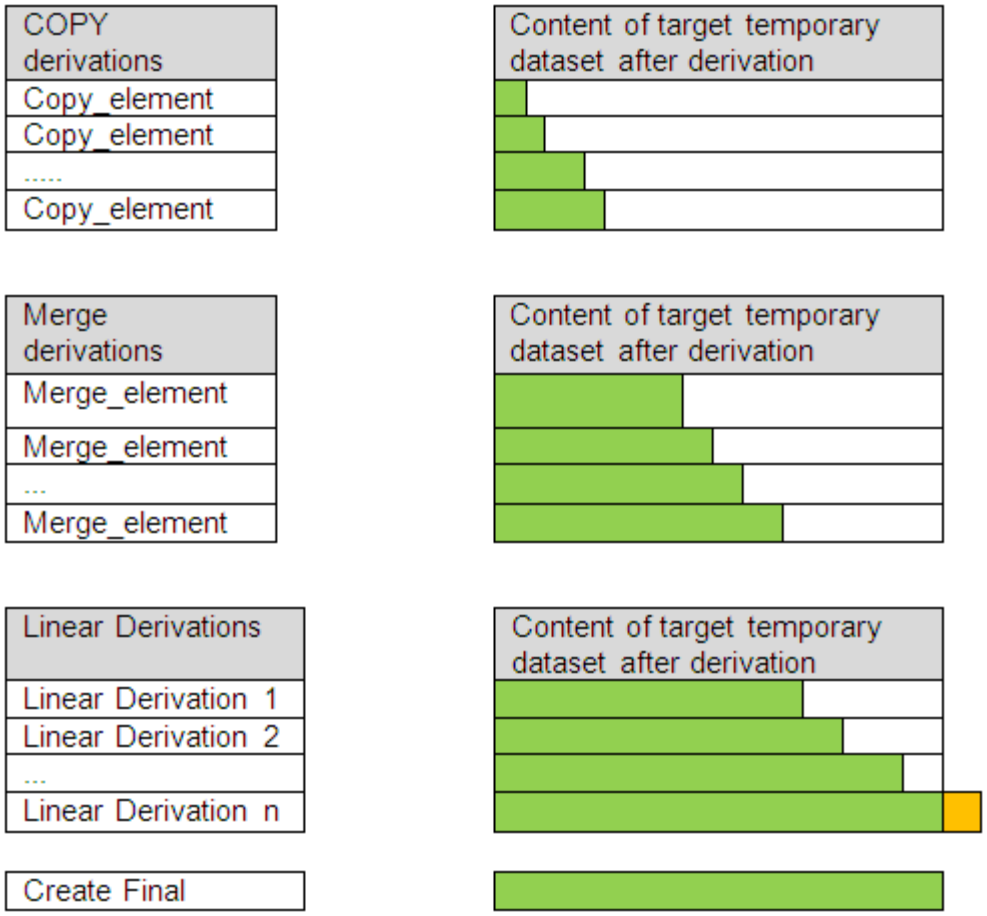
Creating SDTM+ / SDTM / ADaM datasets

- Following are three generic logical steps followed to create the datasets:
  - Get Main input data information (COPY_ELEMENT)
  - Merge information from secondary file(s) (MERGE_ELEMENT)
  - Apply existing derivation and/or add user code
- Standard template programs are created for applying it to a study. Some of the study specific domains like SE and EX have to be created by study teams (generic templates are available)
- For ADaM datasets, the variables SRCSEQ, SRCDOM, SRCVAR were included for the purpose of traceability between SDTM and ADaM
- Efficacy ADaM programs as chosen by Biostatistics were included along with the submission package

SDTM+ Templates

Template Structure

Derivation Part



General logic is to follow 3 main steps:

1 - Get Main input data information

2 – Merge information from secondary file(s)

3 – Apply existing derivation and/or add user code

Keeping in mind that for variable dependency data flow reason step 2 and 3 can be repeated e.g. 1-2-3-2-3-2-3

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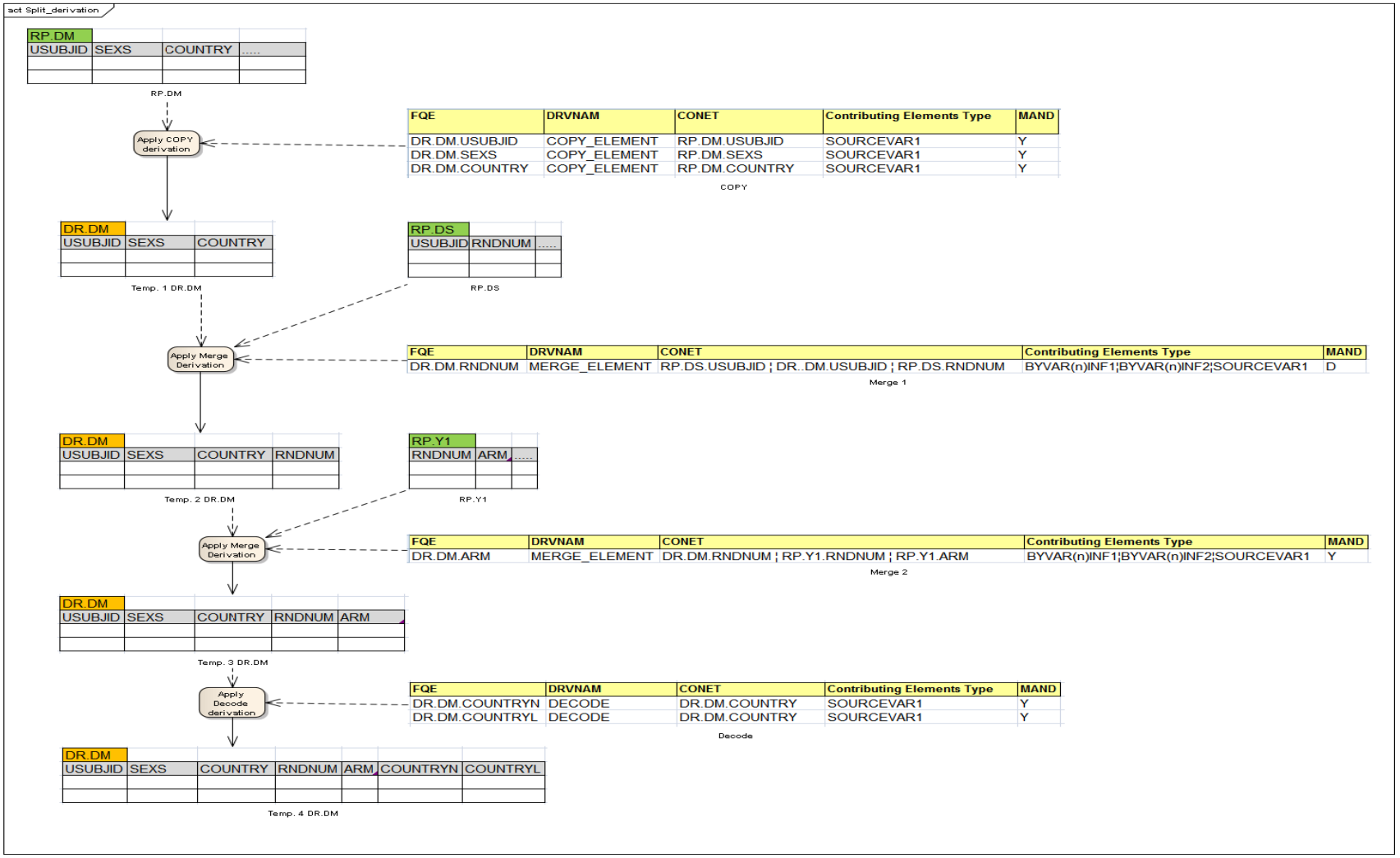
SDTM+ Templates

Derivation Process Overview



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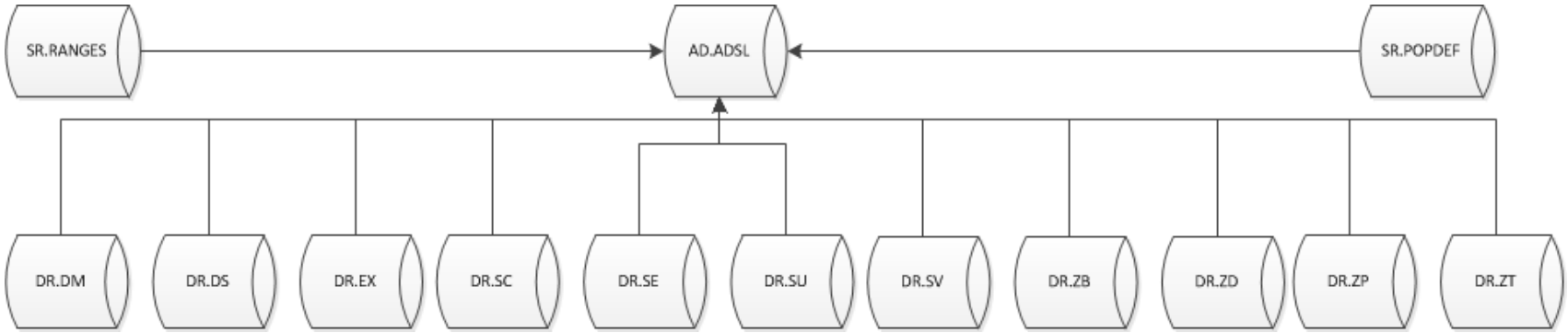
Which data files are needed for ADSL



- **Means, potentially 13 input data files are need to create ADSL**
- **RANGES and POPDEF are the reference files to define variable grouping and Analysis Set definition**

Controlled terminology re-mapping

- Open CDISC® validator was ran on SDTM+ data primarily to find the discrepancies in the Controlled terminology used (Novartis Controlled terminology).
- A re-mapping file was created and applied to the data for the code list items that could be mapped
- Traceability between SDTM and ADaM was maintained as the above SDTM+ data was the source for both of them
- Other Sponsor defined codelist items that couldn't be re-mapped were explained under Data Conformance Summary in the Study Data Reviewer's guide along with any other discrepancies in the data (reported by Open CDISC® validator)

Conclusion

- Creation of SDTM and ADaM using the standard templates and Metadata was effective since:
  - Time was spent only on the study specific custom derivations
  - For the future studies too, the data produced would be consistent between studies and compounds created in this standard approach
- There were lessons learned in terms of Metadata, Controlled terminology and Standard templates and were reported back to the respective functions
- Challenge would be to maintain Metadata, Controlled Terminology and other reference files with the latest CDISC standards

Questions?