An approach of data conversion to CDISC SDTM/ADaM for a Regulatory Submission to the FDA (U.S. Food and Drug Administration)

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OBJECTIVE & REQUIREMENTS

Objective : Submission to the FDA (oncology division / CDER) :

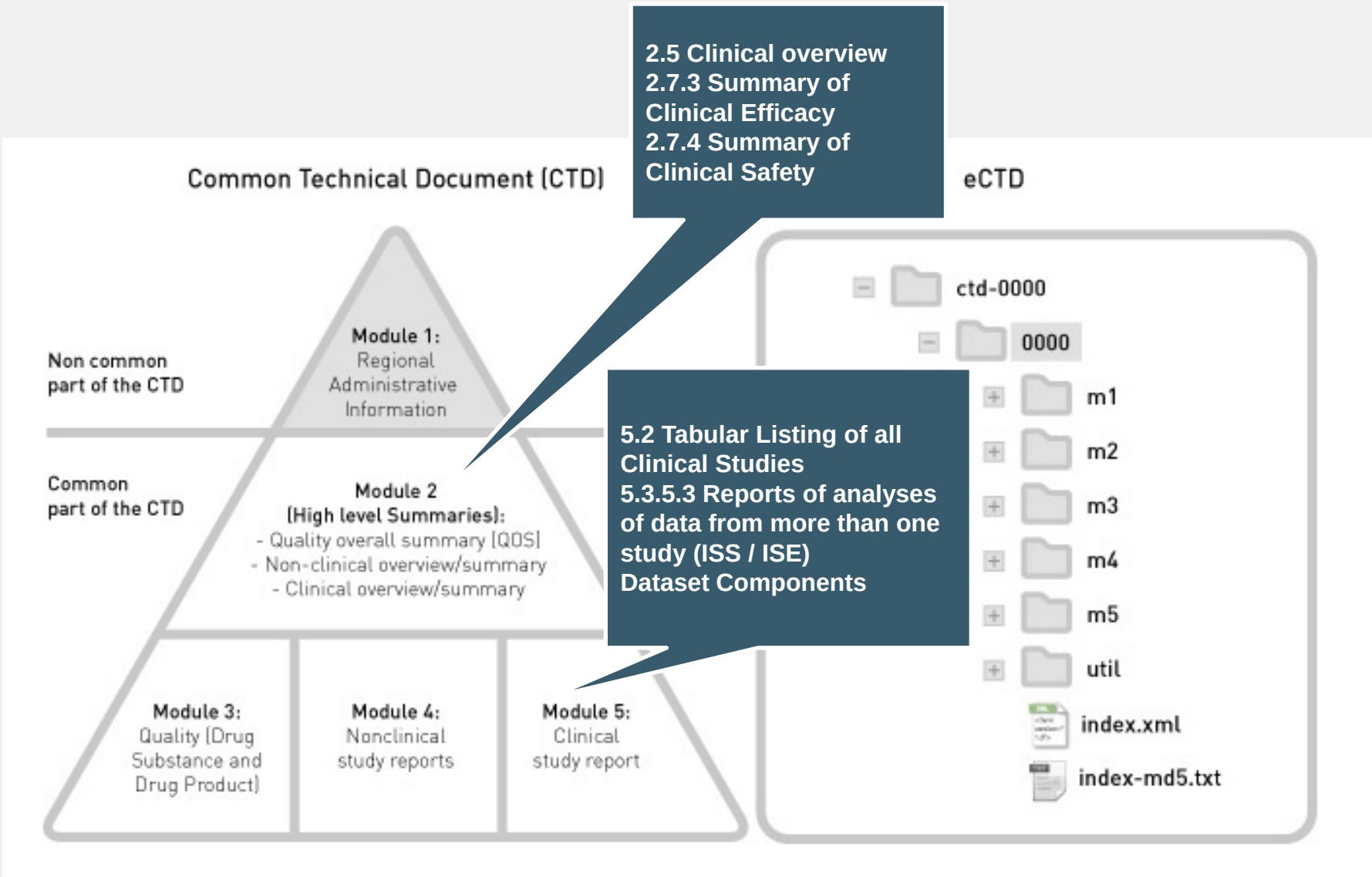
- of an eCTD (electronic Common Technical Dossier)
- for a sNDA (supplemental New Drug Application)

In order to comply with the **FDA recommendations** in term of **standardized study data**, the submission required:

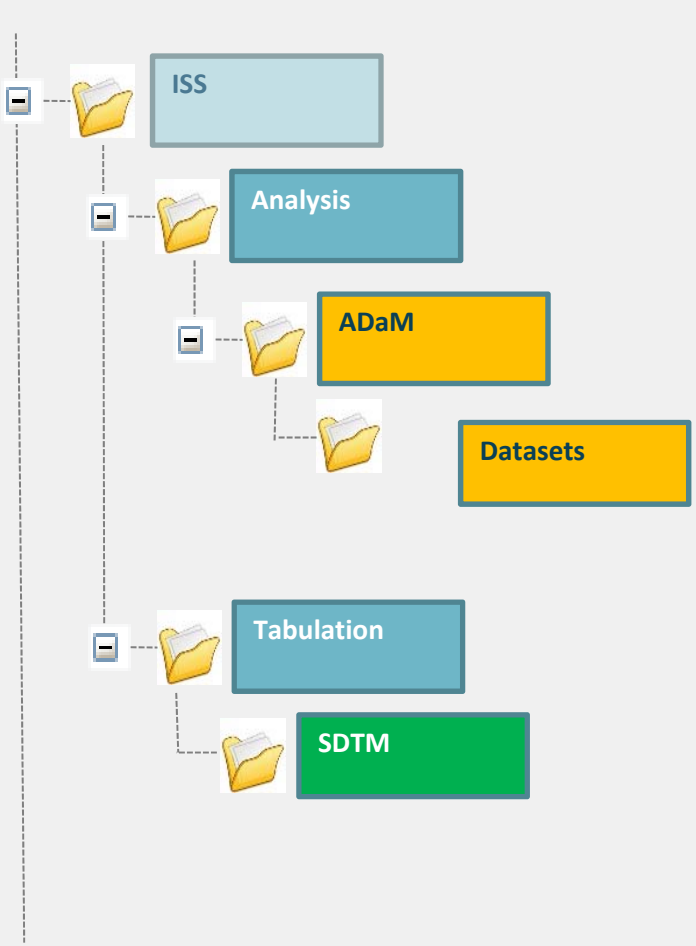
- The conversion of several non **CDISC databases into SDTM and ADaMs**

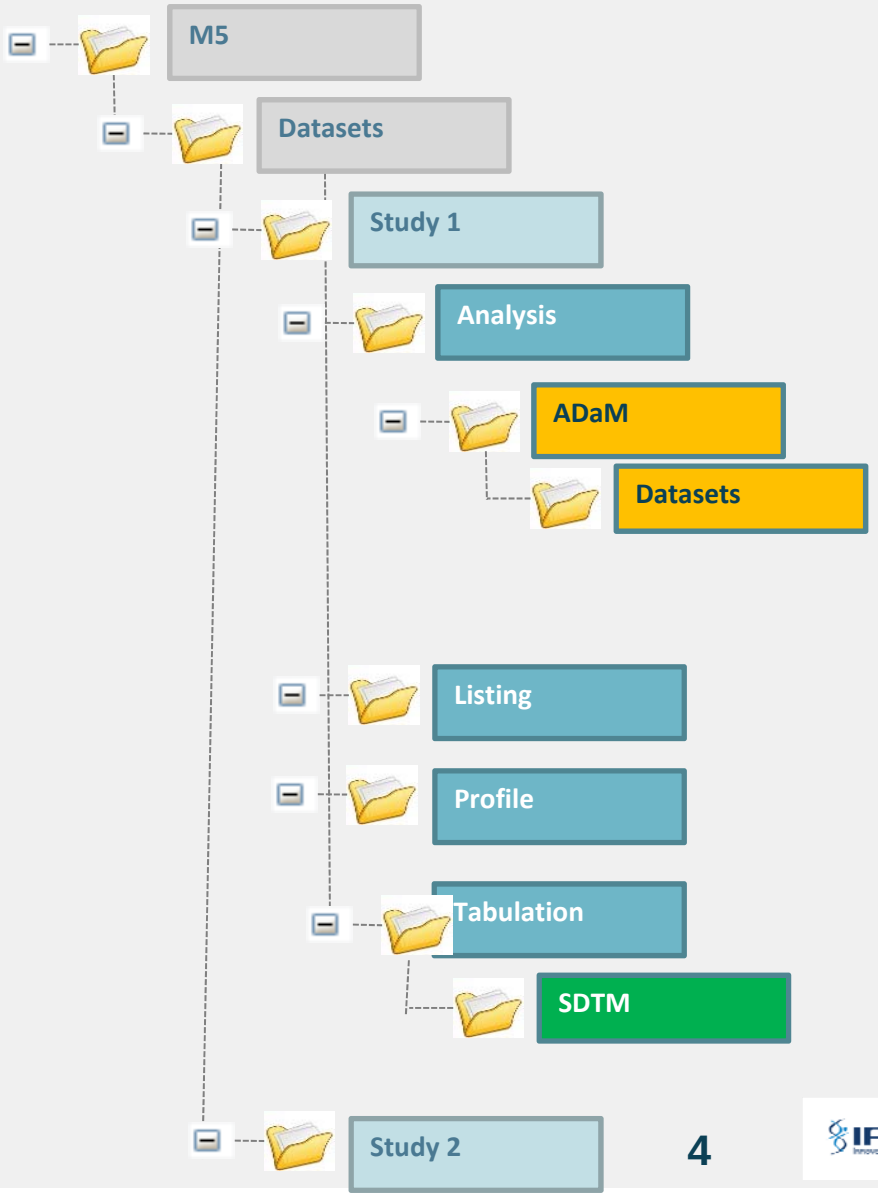
- The creation of **Safety pooled SDTM and ADaM database**, to be used to run an integrated safety summary (ISS).

eCTD – Module 2 & 5 – Clinical Components



eCTD – Module 5 – Structure





SUMMARY

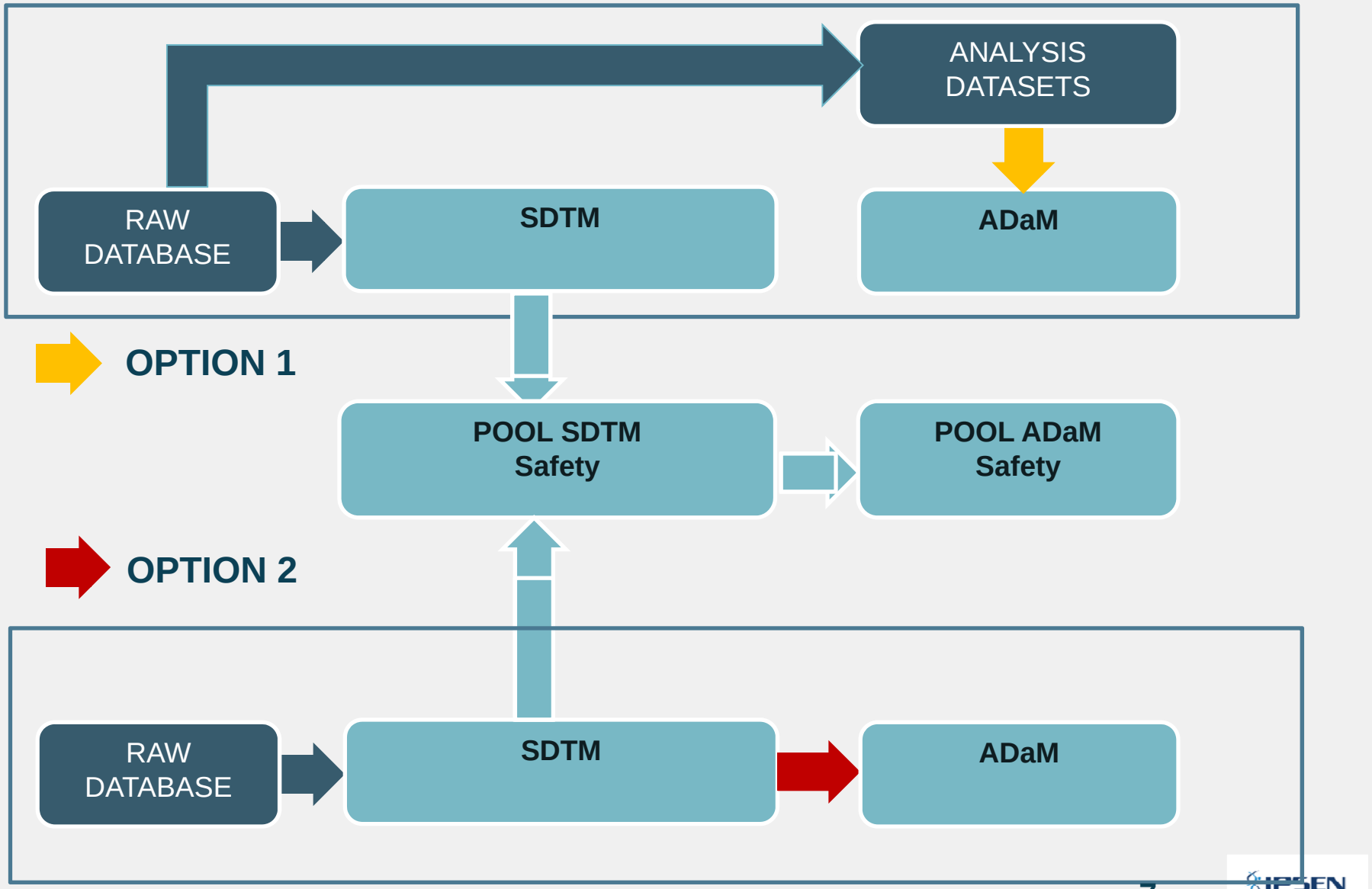
Introduction : What we have ? What we miss ?

What we have : Protocol - Annotated CRF – Final Interpretable Clinical Database - Statistical Analysis Plan – Analysis Datasets - Tables and listings - Clinical Study report

What we miss : derivation rules not always properly documented

Study	Year of completion N (active trt)	Design	Database Format	Raw Datasets	Analysis Datasets
PIVOTAL	2012 N=101	DB vs Placebo	Global IPSEN Data diction.	☺	☺
Supportive 1 (Pivot extension)	Ongoing N=47	Open Label	Global IPSEN Data diction.	☺	☺
Supportive 2	Ongoing N=103	DB vs Placebo + OL	Global IPSEN Data diction.	☺	☺
Supportive 3	2002 N=71	Open Label	Legacy	☺	☹
Supportive 4	2009 N=30	Open Label	Legacy	☺	☹
Supportive 5	2010 N=26	Open Label	Legacy	☺	☹

1. Overall conversion process : possible options

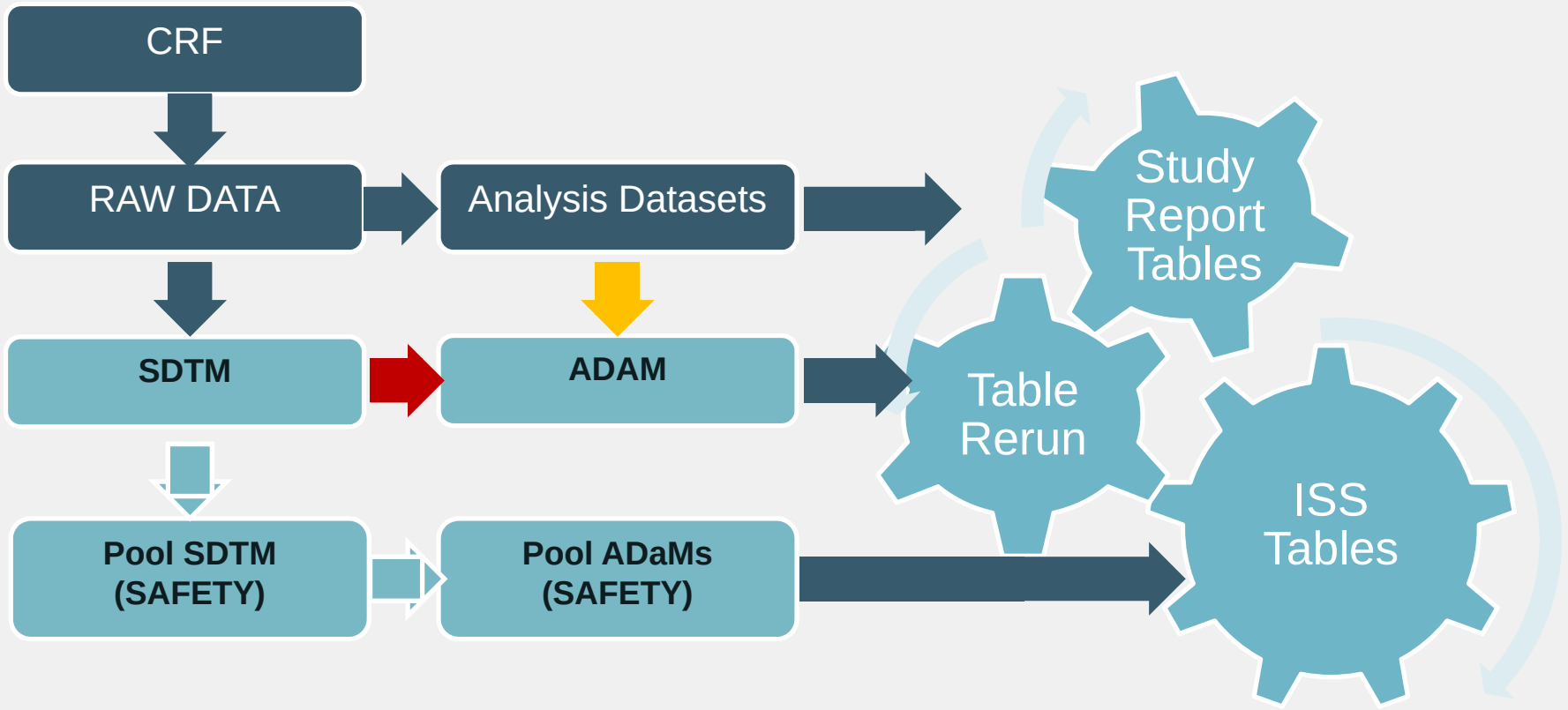


1. Overall conversion process : Traceability (1/2)

"If the reviewer is unable to trace study data from the data collection of individual subjects participating in a study to the analysis of the overall study data, this may compromise the regulatory review of a submission."

Study Data Technical Conformance Guide (FDA, Feb 2014 (Draft))

1. Overall conversion process : Traceability (2/2)



2. SDTM Conversion : Deliverables

1. SDTM domains

Modelled according to :
- **Study Data Tabulation Model** (SDTM) **V1.3**
- **SDTM Implementation guide** (SDTMIG) **V3.1.3**
- **Controlled Terminology** Version **21-Dec-2012**

2. SDTM Annotated CRF

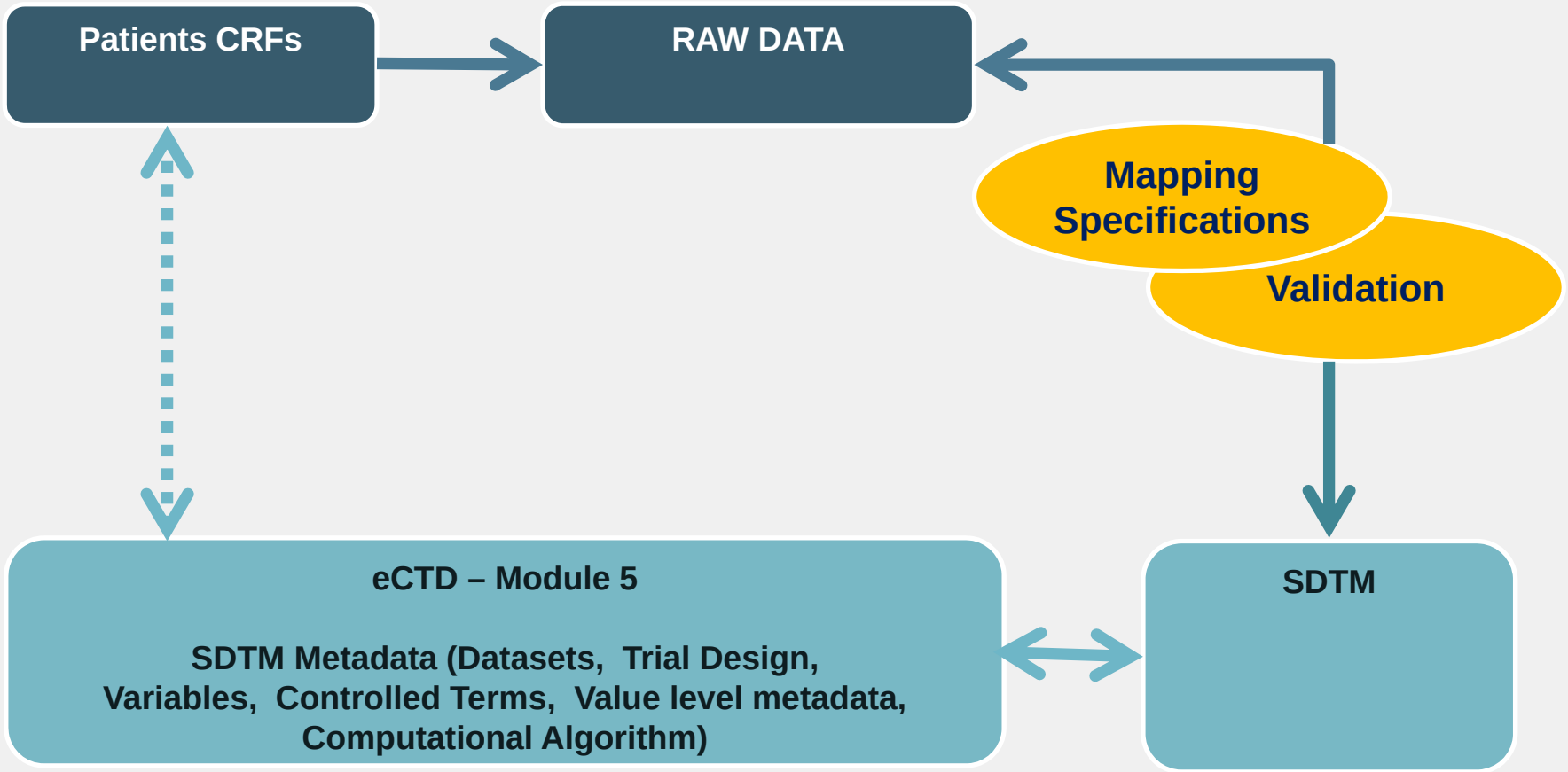
3. Overview of Inclusion/Exclusion Criteria (PDF)

4. Metadata : **Define.xml** (Define.pdf)

Created according to :
- Case Report Data Tabulation Data definition specification **V1.0**

5. FDA Reviewer's guide (inspired from Phuse template)

2. SDTM Conversion : Traceability



2. SDTM Conversion : Challenges (1/3)

- **Legacy databases**

Different ways to collect data for legacy studies
→ SDTM data conformance issues

Examples:

- The Treatment Administration form does not collect the date of administration, nor the actual administered dose
- The Concomitant medications were collected at each visit , not in an appendix form
- Informed Consent date not collected in the CRF
- Open CDISC errors

What we did:

✓ Specific rule in SDTM mapping specifications
✓ Documentation in Reviewer's Guide

2. SDTM Conversion : Challenges (2/3)

- **Source data issues**

Final source study databases contained source data issues
→ Systematic source data issues could be generically corrected
→ Single source data issue could only be accepted and documented

What we did:
✓ Specific rule in SDTM mapping specifications
✓ Documentation in Reviewer's Guide

- **Ongoing Studies**

Mapping and programming starting on a non-stable database can lead to :
→ re-work when database if final (new controlled-terms)

What we recommend:
✓ Work on a stable database is a preferred option (when possible)

2. SDTM Conversion : Challenges (3/3)

- **Trial Design – Trial Summary (TS) Domain**

Reporting in TS domain not always obvious, few rules in SDTMIG

Information comes from:

→ Protocol: Planned # of subjects, Trial Objectives, Trial Design …
→ Data: Actual # of subjects, Data cut-off date, Start/End Study date …
→ Other: Coding information (SNOMED) , DUNS code…

What we recommend:
✓ Definition of rules used for TS upfront

3. Pooling SDTM : Deliverables

1. SDTM domains

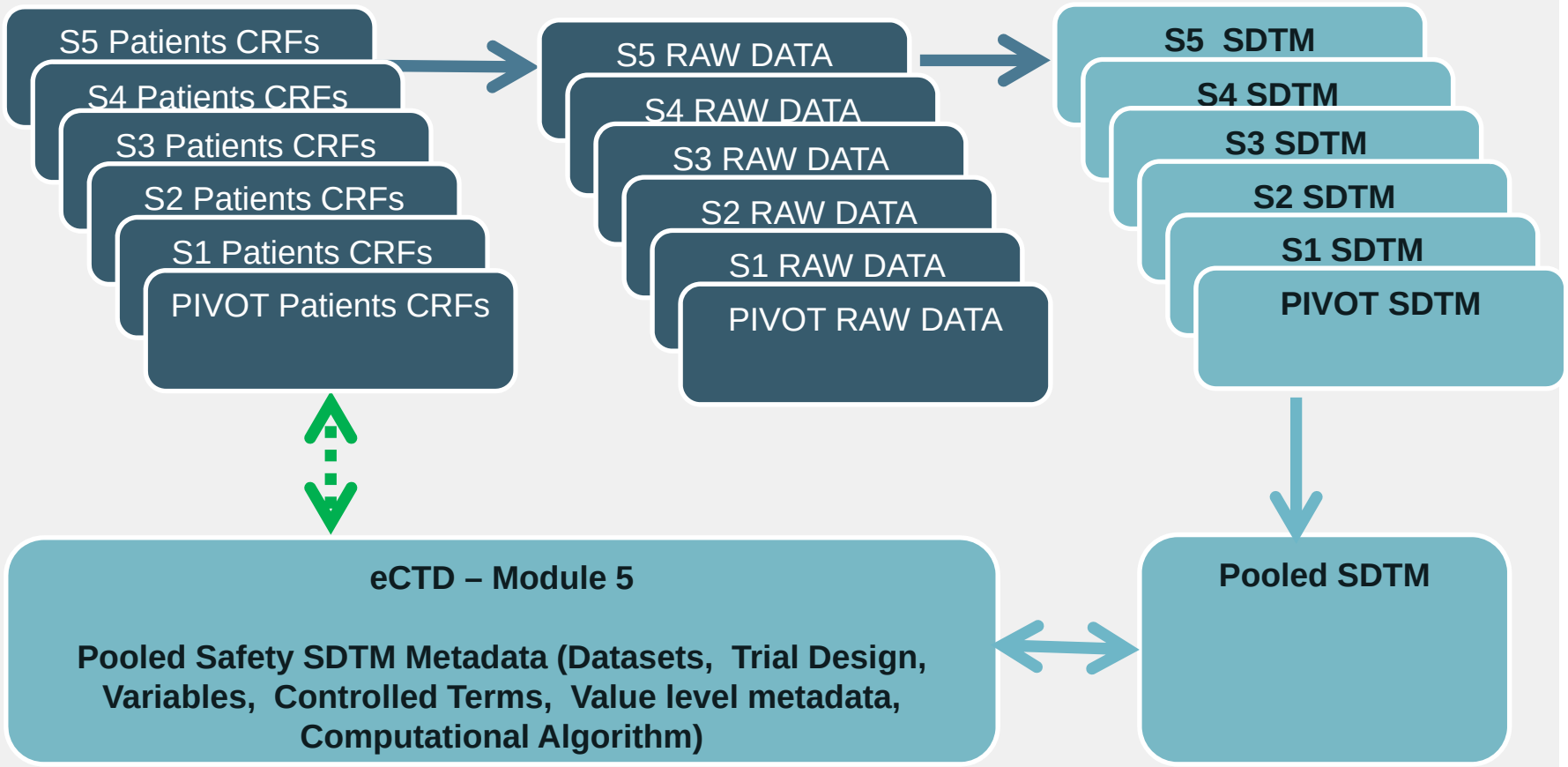
Modelled according to :
- **Study Data Tabulation Model** (SDTM) **V1.3**
- **SDTM Implementation guide** (SDTMIG) **V3.1.3**
- **Controlled Terminology** Version **21-Dec-2012**

2. Metadata : Define.xml (Define.pdf)

Created according to :
- Case Report Data Tabulation Data definition specification **V1.0**

3. A specific FDA Reviewer's guide for pool SDTM (lighter than for individual SDTM)

3. Pooling SDTM : Traceability



3. Pooling SDTM: Challenges (1/3)

- **Standard Data Hamonization between studies**

Different ways to collect data across studies / to map into SDTM
→ Pooled database not easily interpretable for some parameters

Examples:

- **Collection of clinical events in FACE different between two studies :** Severity is a CAT (MILD, MODERATE…) but a TEST ('Severity/Intensity') with ORRES as MILD, MODERATE…
- **AE Duration (AEDUR) only collected in one of the studies:** Keep in pool database ? Or derivation in ADaM is enough ?
- **Disposition DS Domain:** DSDECOD Harmonization required for same reason , e.g. 'Withdrawal of consent' = "Consent withdrawn' = 'Subject withdrawal of consent'

What we did/recommend:
✓Harmonization in SDTM mapping specifications upfront across studies (i.e. oversee all studies all together first)
✓Definition Standard Migration Rules and apply as much as possible

3. Pooling SDTM: Challenges (2/3)

- **Harmonization in TA domain**

Different ARM codes between studies whereas same study treatment
→ Ensure a single ARM Code (ARMCD) is used for the same study treatment, same formulation, same dose (independently from Study design)

Example:

ARMCD	ARM
A	Placebo
B	Study Treatment 10MG
C	Study Treatment 10MG
D	Placebo/Study Treatment 10MG
…	…

What we did:
✓Harmonization in SDTM mapping specifications upfront across studies (i.e. oversee all studies all together first)

3. Pooling SDTM: Challenges (3/3)

- **Coding Requirements and Harmonization**

FDA accepts to receive database coded with MedDRA and Who-DD
Use of the latest version of the dictionary versions is recommended
Legacy studies need to be re-coded
Unique dictionary versions should be used in the pooled database

What we did:
✓Use the dictionary versions applied to the pivotal study for recoding
✓Impact analysis of re-coding and/or Discrepancies vs. Tables and Listing from CSRs documented in Reviewer's Guide

4. ADaM Conversion : Deliverables

1. **ADaM domains**

Modelled according to :
- **Analysis Data Model** (ADaM) **V2.1**
- **Analysis Data Model Implementation guide** (ADaMIG) **V1.0**

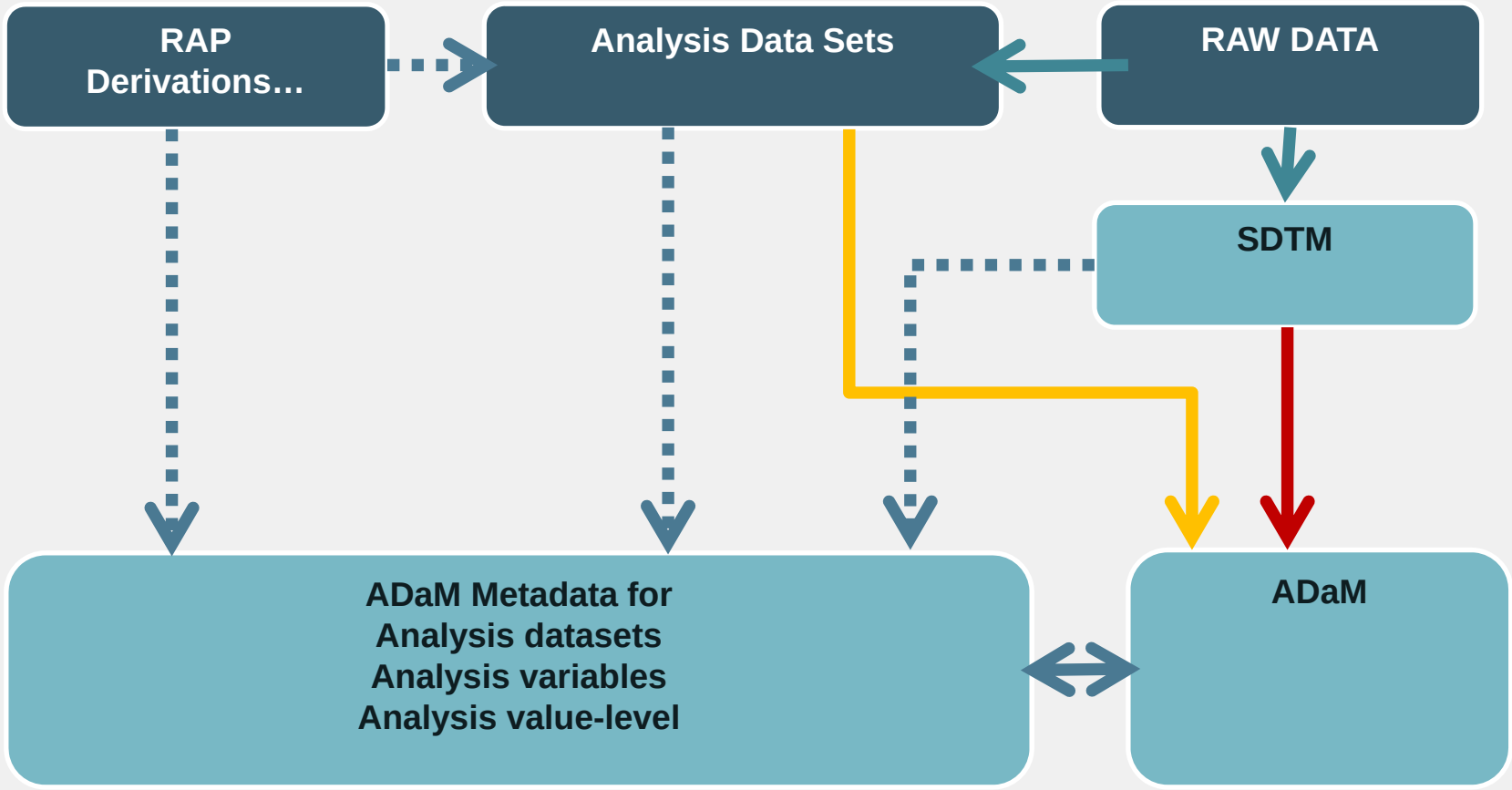
ADaM Datasets :
- ADSL
- ADAE, ADEX, ADMH, ADCM, ADLB, ADSV,…

2. Metadata : **Define.xml**

Created according to :
- Case Report Data Tabulation Data definition specification **V1.0**

3. Reviewer’s guide

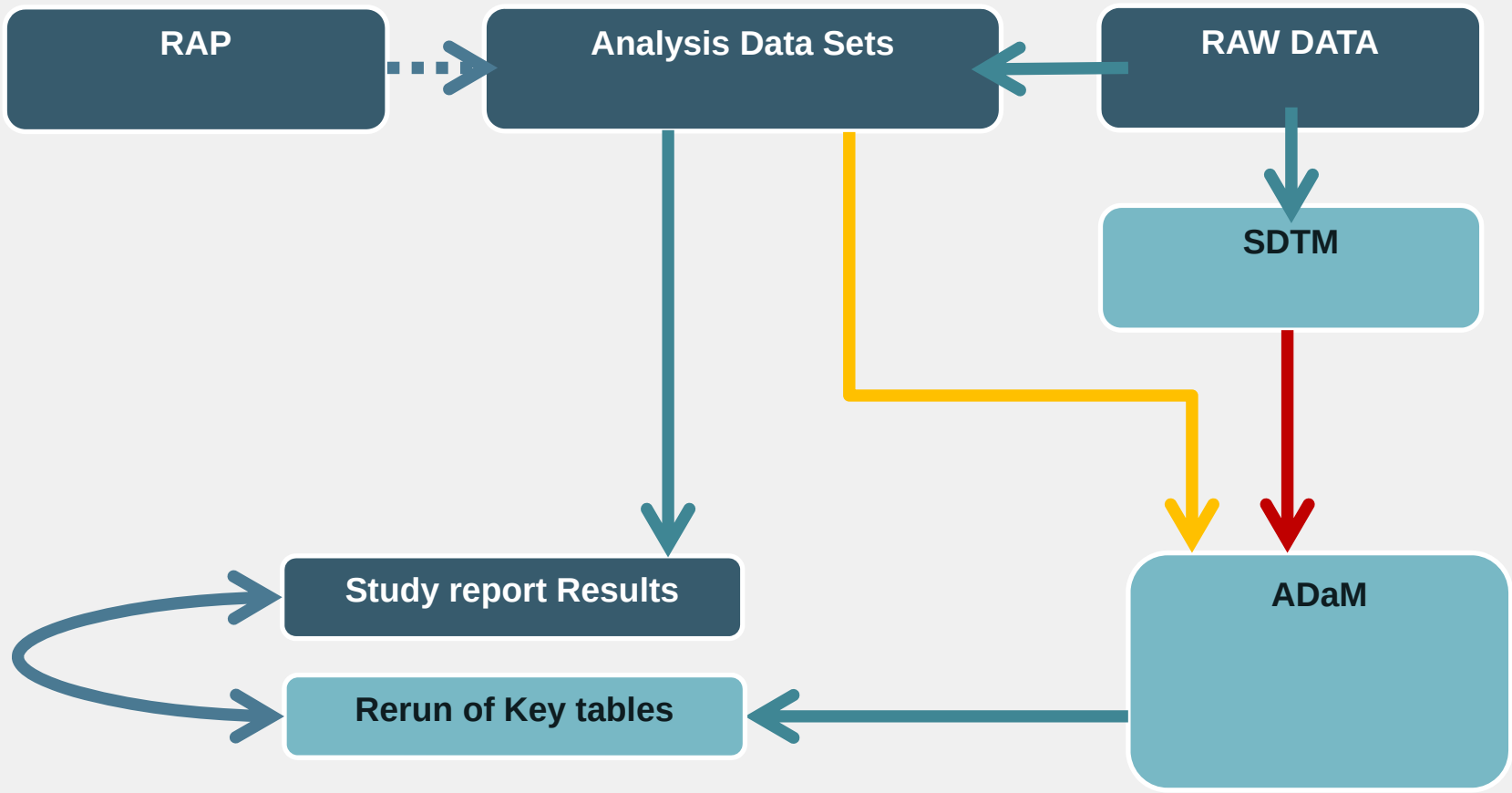
4. ADaM Conversion : Traceability (1/4)



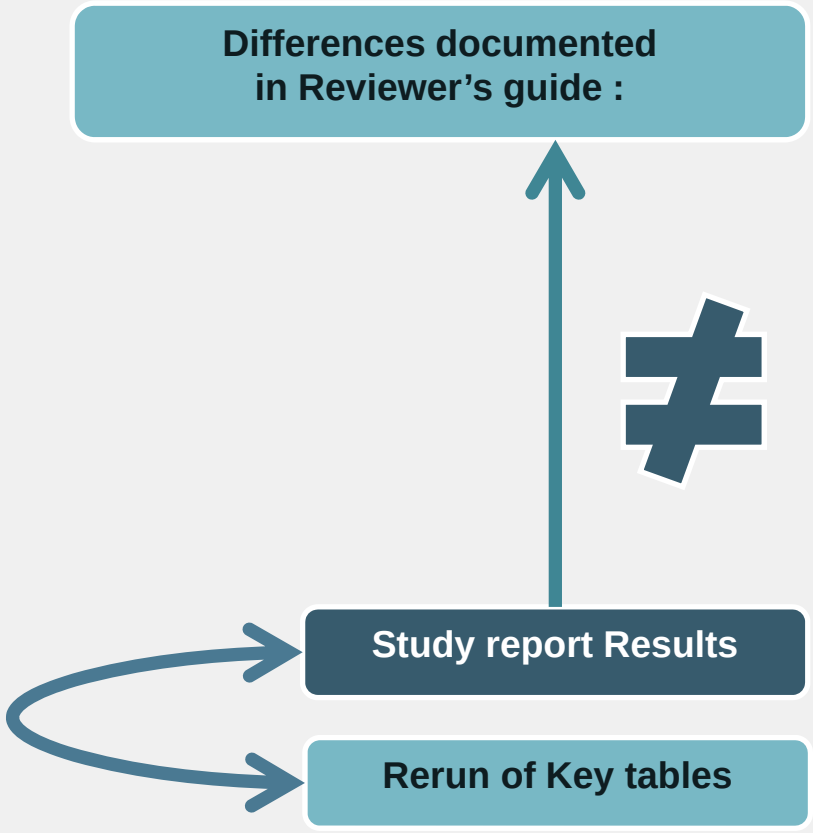
4. ADAM Conversion: Traceability (2/4)

ADaM Conversion	
OPTION 1 **From Analysis datasets**	**OPTION 2** **From SDTM**
• Analysis datasets close to ADaM format	• Considered as the normal path
• Minimize work when derived variable calculations are complex	• Analysis datasets not available
• Preferred when derivation rules not properly documented	
• Decrease the risk of not being able to reproduce tables of the study report.	
• Reviewer's guide document the process followed	
• Algorithms in define reference SDTM datasets and variables	
• Traceability checked along the process	

4. ADaM Conversion : Traceability (3/4)



4. ADaM Conversion : Traceability (4/4)



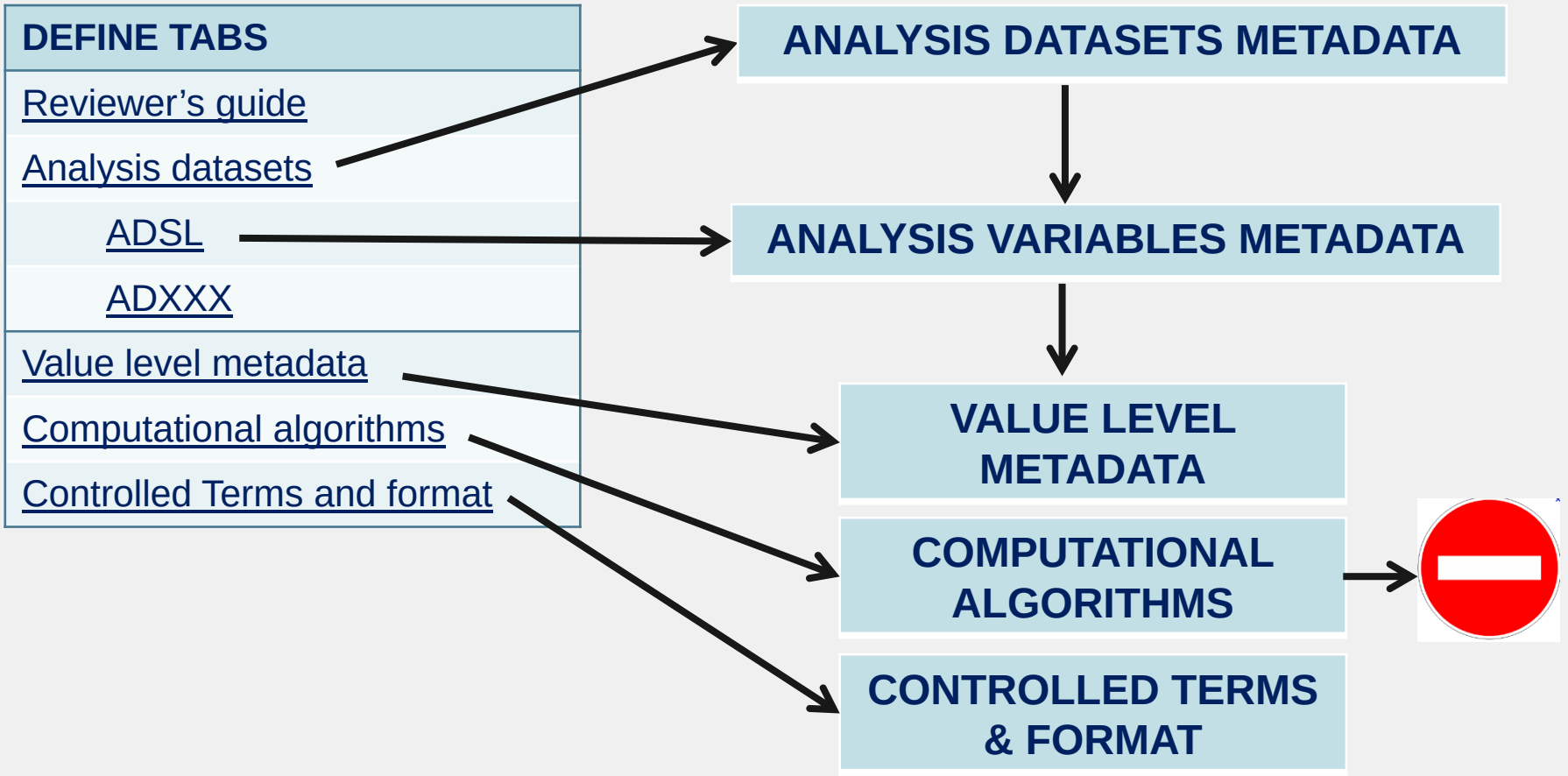
- Differences mainly observed in "old" studies
- Differences can be on:
  - Codes (due to recoding)
  - Rounding issues
  - Etc…
- BUT All differences did not have an impact on efficacy/safety conclusions

4. ADaM Conversion : Reviewer's guide elements

Details on :

- Data used for ADaM datasets
- How the traceability is ensured
- Principle of analysis value level metadata
- Analysis population flags
- Treatment variables
- Coding
- How the Define.xml is built
- Lengthy/complex computational algorithms
- List of ADaM datasets with their key variables
- Issues from compliance checker
- Issues with DOP2 (division of oncology) (discussed later in the presentation)
- Assessment of traceability and steps followed

4. ADaM Conversion : Define.xml hyperlinks



No Further links in algorithms despite expressed request from the FDA.

5. Pool ADaM Conversion : Deliverables

1. ADaM domains

Modelled according to :
- **Analysis Data Model** (ADaM) **V2.1**
- **Analysis Data Model Implementation guide** (ADaMIG) **V1.0**

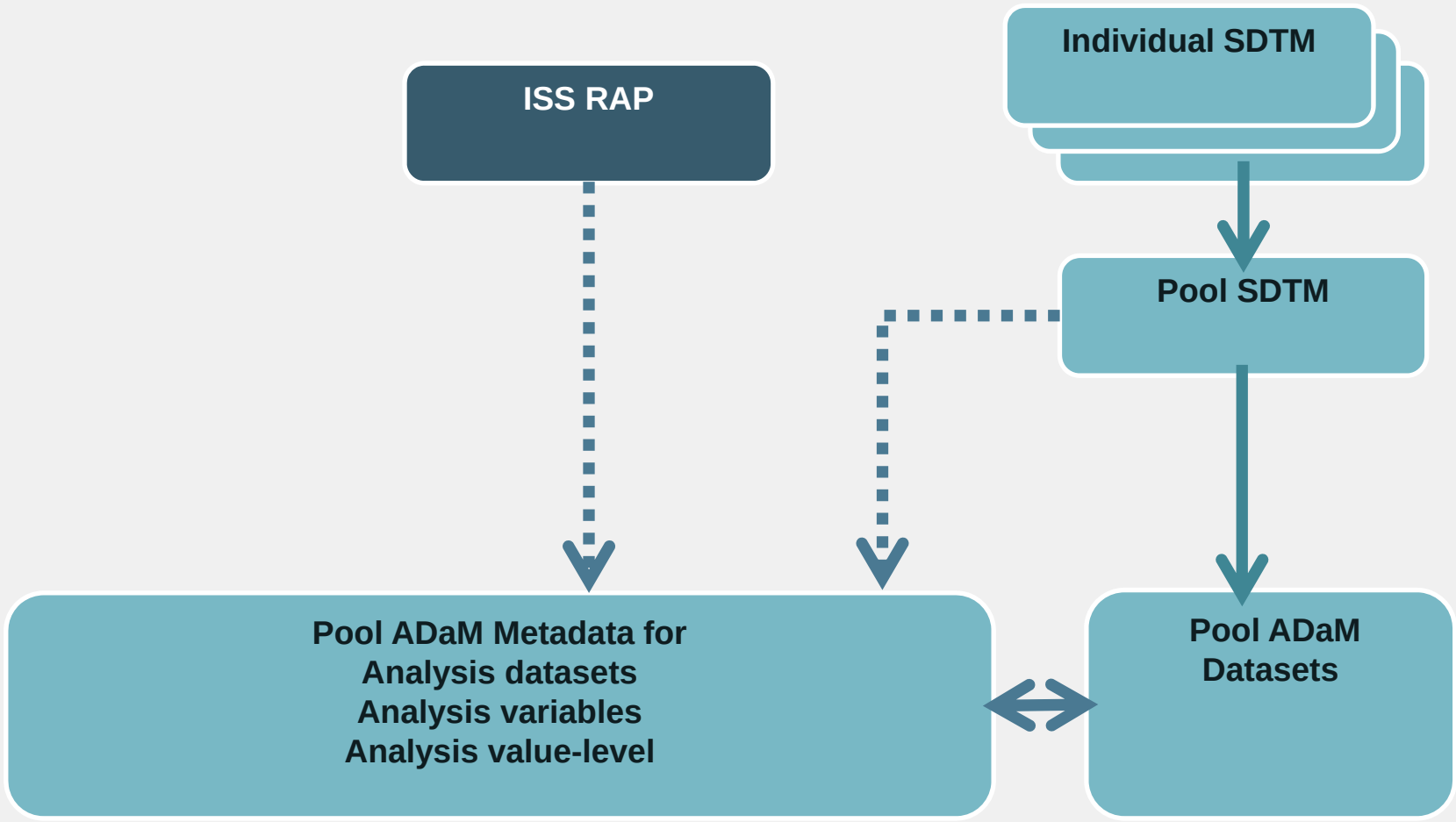
ADaM Datasets:
- ADSL
- ADSC, ADMH, ADEX, ADCM
- ADAE, ADLB,ADVS

2. Metadata : **Define.xml**

Created according to :
- Case Report Data Tabulation Data definition specification **V1.0**

3. Reviewer’s guide

5. Pool ADaM Conversion : Traceability



5. Pool ADaM Conversion : Standardization challenges

Issue	Situation	Remediation	Documentation
Reclassification of reason for withdrawal	**Categories used for reason for withdrawals different between studies**	**Alignment on categories used in pivotal studies**	**ISS RAP**
Labs	**Lab collected locally in one study**	**Rules for Adjustment of Normal Ranges adjusted on Normal ranges of the pivotal study**	**ISS RAP (*)**
TEAE Definition	**Definition varied according to AE collection method**	**Use of the worst case definition for the ISS**	**ISS RAP**

(*) “The statistical basis of laboratory data normalization.”
Juha Karvanen, Dsc (Tech), Signal Processing Laboratory, Helsinki, University of Technology, Helsinki, Finland
Documented in ISS RAP

5. Pool ADaM Conversion : Flags

- **FDA Comment from Pre-sNDA Meeting**: (…) In the pooled datasets, flags for different doses, durations of treatment and other identifying characteristics distinguishing the pooled populations would be expected.

Flags :

- **Mostly added in ADaM (few in SDTM)**
- **Documented in RAP**
- **Related to :**
  - Origin of data (study) (also in SDTM)
  - Baseline characteristics
  - Study Treatment duration
  - Study treatment dose

6. Further considerations: 120 days safety update

- Following feedback received from previous submissions (specifically from the CBER division)

- Flags to identify (on ongoing studies since the original submission):
- New data
- Modified data.

- Added in SDTM and reported in ADaM
- Documented in RAP
- Objective :
  - Analysis and reporting of new data
  - Especially important if additional cumulative study treatment exposure is more than 20%

- Challenges to flag new/modified data in SDTM :
  - Only possible in Supp Domain
  - Review and selection of “un-modified” keys by domains
    (if enterable fields are used as keys -> manual QC should be applied)

6. Further considerations: DOP2 (1/2)

- FDA recommendations received in response to the Pre-sNDA Briefing document sent by Ipsen before Pre-sNDA Meeting

- DOP2 = Division of Oncology Product 2

- Mainly guidance for Tumour Identification, results and responses domains (RS TR TS TU) and variables

- Required for the analysis of
  - Overall survival
  - Progression Free survival
  - Response Rate
  - Disposition
  - Adverse reactions

- FDA requests implementation in SDTM according to the draft CDISC :

"Oncology disease-specific Therapeutic area **supplement**
to the SDTM implementation guide"

- Other domain impacted : ADSL AE CM DM DS EX LB MH SV TA TS

6. Further considerations: DOP2 (2/2)

Deviations from DOP2 requirements
→ Documented in Reviewer's guide (SDTM & ADaMs) with justification

Examples:

Domain	DOP2 Deviations (examples)
CM	DOP2 suggests to use specific CMCAT (Category for medication) but the ones used in the study were different
LB	Required values by DOP2 for LBRIND are :“HIGH” or ” LOW”). This was in contradiction with controlled term used for this submission, i.e. “NORMAL” and “ABNORMAL” were used and this was compliant with SDTMIG V3.1.3.
RS	Best Response (RSTESTCD=BESTREP) assessment was expected but RECIST V1.0 was used in the study and consequently BestRep was not collected.
…	…

6. Further considerations: FDA OSI Requirements

- FDA Office of Scientific investigations (OSI) request, received during the two-months structure and format review period after initial submission

- FDA Objective: development of clinical investigator and sponsor/CRO/monitor inspections

To be provided :

1. General study related information and clinical investigator information
2. Subject level data listings by site
3. Submission of site level dataset is voluntary (Pilot phase)

What we did:
For the pivotal study, one PDF bookmarked file according to site # and category of data tables/listings

More information here:
Providing Submissions in Electronic Format — Summary Level Clinical Site Data for CDER's Inspection Planning (Draft Guidance, December 2012)

6. Further considerations: Additional Define.xml required

For one other submission ongoing at IPSEN, FDA (CBER division) requested the following :

For ADaM on pivotal studies :

- Define.xml of Raw data
- Define.xml of analysis datasets
- Analysis datasets creation programs
- Programs used to generate tables and listings from analysis datasets

in addition to the SDTM/ADAM deliverables

6. Conclusion

Some recommendations :

- Define upfront standard mapping rules at SDTM level
- Address any questions regarding standardization plan to the FDA prior to submission (e.g. during the pre-NDA meeting)
- Be prepared to receive additional requests from the FDA, which might not be included in the submission guidelines

Thank You……Q&A