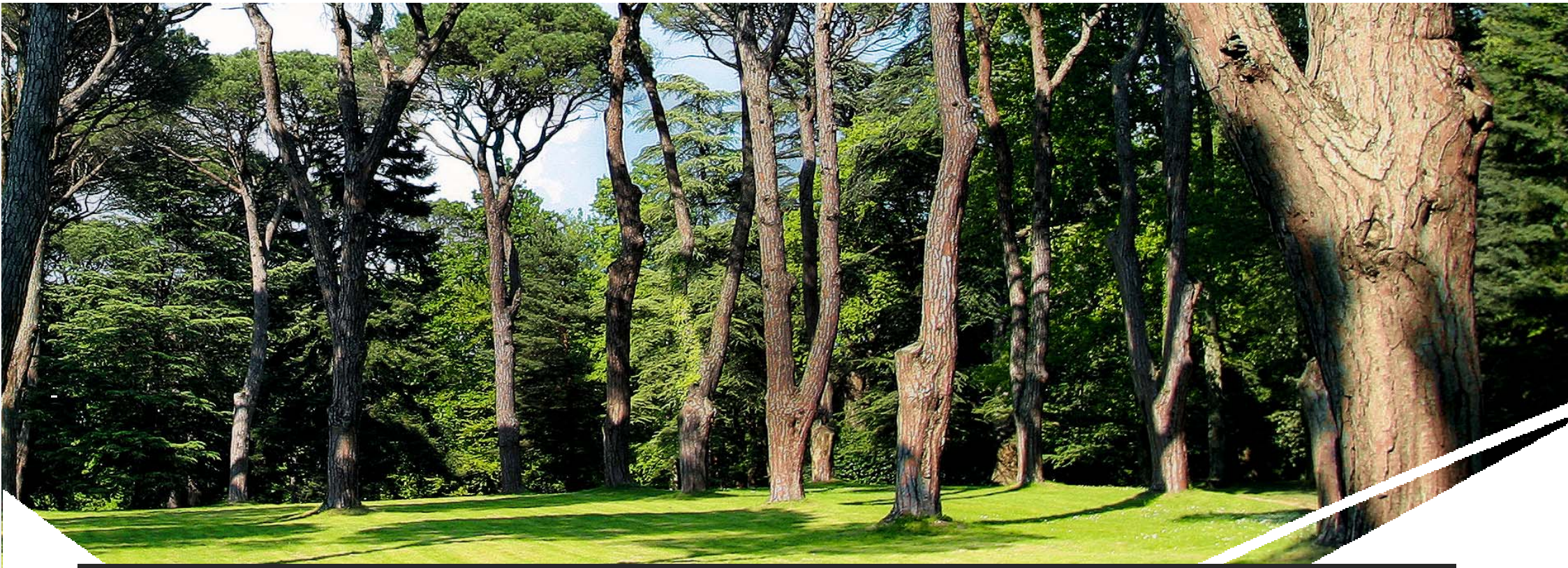
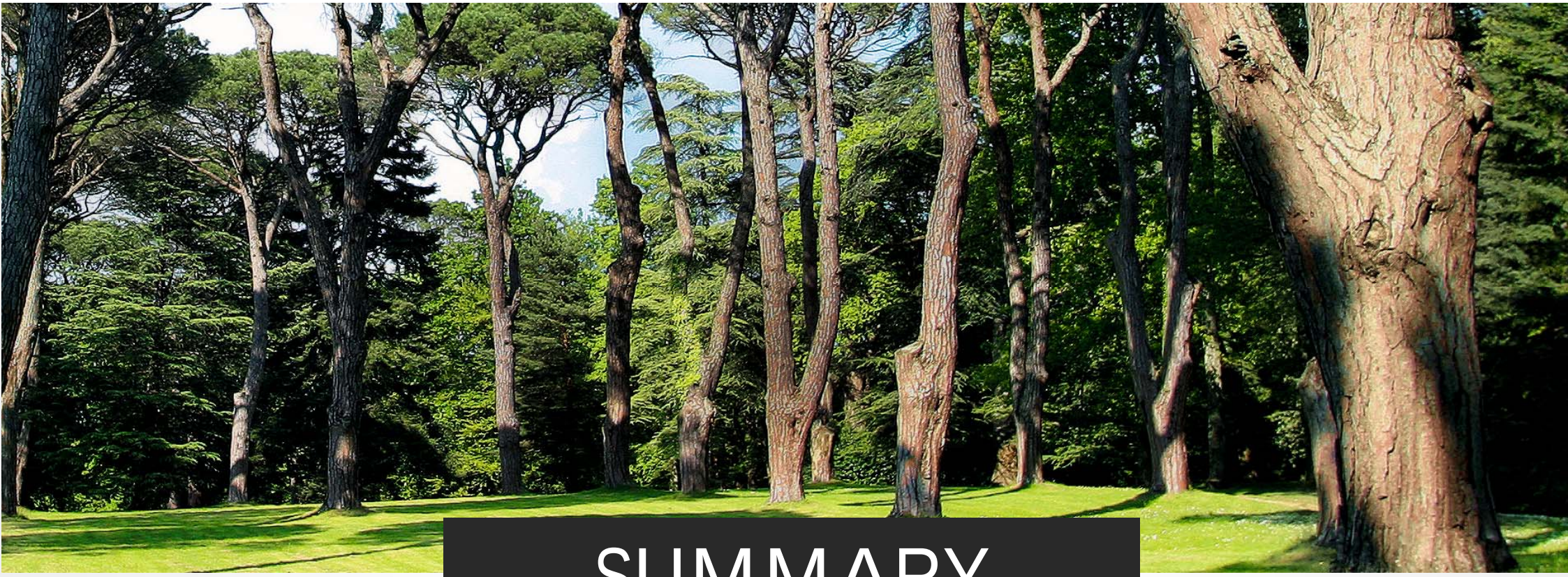


PF Process from clinical data Collection to SDTM

29 May 2018

PIERRE FABRE LABORATORIES

Pierre Fabre



SUMMARY

Context

Context (1)

- Over the last 2 years, PF model for managing studies has changed to full outsourcing, leading to impacts on:
  - Corporate restructuration
  - Change Management
  - CRO : Preferred partnership in construction
  - Procedures

In-House	Outsourced
DM and statistical inputs into protocol and drug development plans	**Database set-up, data cleaning and DM activities**
Maintenance of standards: -Data Acquisition -Data Integration -Data Quality	**Study specific statistical reporting and generation of analysis data**
Ensure availability of integrated clinical data for pooled analyses	

- Future planning of activity : 5-15 clinical studies per year (Excluding dermo-cosmetics)
- No real standard governance organization defined yet : We are working on it

Context (2)

Assumptions at the beginning	Today Situation
No preferred EDC systems : Use best ratio price/quality per CRO for the project	We prefer to use our EDC, our URL
There will be 3 preferred partners max	Landscape of CROs changed
CRO in charge of subcontracting external data production : Genomics, PK…	We subcontract this part because we have our preferred partners in these fields

→ We need to adapt ourselves and be flexible to work with a lot of partners

- Need to move from a fully internal process to an external process for data collection and standardization :
  - Legacy structure/collection standard : Standardization outsourced with light SDTM specs
  - In 2016, vision included investment in Metadata Repository, Data repository and use of XML/ODM to exchange data/metadata
    - → Still under discussion, but current situation does not allow us such investments
- Full outsourcing model, Sponsor responsibilities:
  - **Specify** – Define expectations for the datasets creation (e.g. special requirements)
  - **Receive** – Physically receive data from the CRO or provider and incorporate into its systems
  - **Review** – Review the data to satisfaction
  - **Submit** – Submit the data, as part of a larger package (e.g. eCTD)
  - **Archive** – Archive past data according to relevant archival policies and procedures

Actual Process

Actual process for eCRF build and Operational Database

Specify

Clinical Team

Standard Library

PF CRF/Data Guidelines (PF conventions and expectations)

PF Terminology

Protocol (CDISC Terminology included)

eCRF specifications (Adapted for study)

Review

Metadata Quality checks (QC Compare + Checklist)

Data Quality Checks

Archive

Windows Server

In-House

Receive

Tranfer agreements

SAFE ZONE EXCHANGE

If QC not OK

CRF Build & Operational Database creation

Scenario 1 : Sponsor EDC URL

Scenario 2 : CRO EDC URL (Any EDC)

RAW

Operational Database

SAS datasets

CRO

IRPF CRF/Data Guidelines

➢ Sponsor implementation guide :

- Additional document provided to our partners describing our standards interpretation
- Provides IRPF best practices for eCRF creation
- Provides rules/policies for cases not covered by CDISC Guidelines, some examples are:

  - o Handling of re-screened subjects in eCRF and databases (Operational & SDTM)
  - o General rules such as how to create values for unique subject identifier, study identifier etc.
  - o Handling of Unscheduled visits in eCRF and databases (Operational & SDTM)
  - o Description of custom domains created by Pierre Fabre to collect and store data not planned in the standard guidelines
  - o Rules to create new terms in SDTM/PF Terminology
  - o …

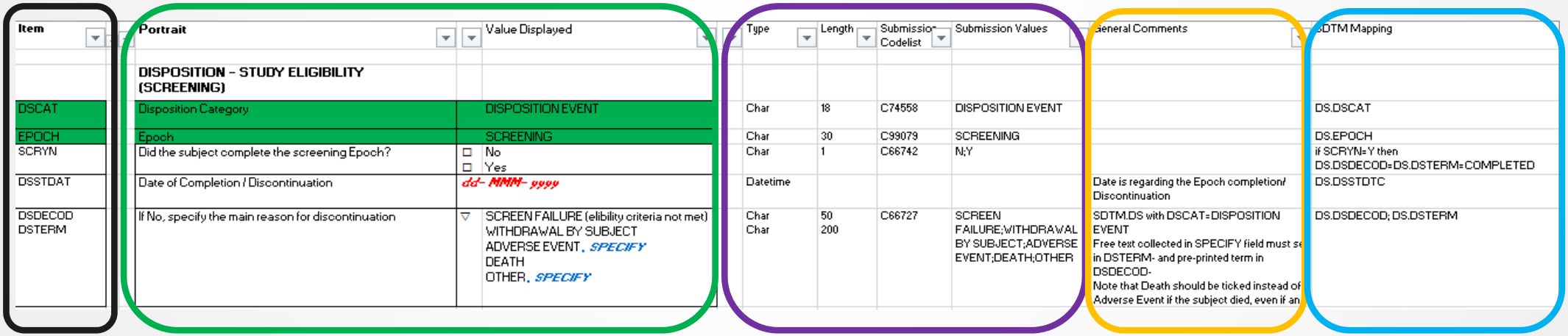
→ Ensure consistency between studies on rules that cannot be described by Metadata only

→ Provides standard text to populate submission documentation such as eCRF completion guidelines, Study Data Reviewer's Guide…

eCRF Specifications

➢ Created by sponsor to :

- Provide eCRF Mock-up for a study using standard information
- Describe basic information on the EDC forms such as pages and fields properties for CRO implementation
- Describe the structure of the Operational Database CDASH
- Pre-define mapping to SDTM



Item	Portrait		Value Displayed	Type	Length	Submission Codelist	Submission Values	General Comments	SDTM Mapping
	DISPOSITION – STUDY ELIGIBILITY (SCREENING)								
DSCAT	Disposition Category		DISPOSITION EVENT	Char	18	C74558	DISPOSITION EVENT		DS.DSCAT
EPOCH	Epoch		SCREENING	Char	30	C99079	SCREENING		DS.EPOCH
SCRYN	Did the subject complete the screening Epoch?	☐ ☐	No Yes	Char	1	C66742	N;Y		if SCRYN=Y then DS.DSDECOD=DS.DSTERM=COMPLETED
DSSTDAT	Date of Completion / Discontinuation		*dd- MMM- yyyy*	Datetime				Date is regarding the Epoch completion/ Discontinuation	DS.DSSTDTC
DSDECOD DSTERM	If No, specify the main reason for discontinuation	▽	SCREEN FAILURE (elibility criteria not met) WITHDRAWAL BY SUBJECT ADVERSE EVENT, *SPECIFY* DEATH OTHER, *SPECIFY*	Char Char	50 200	C66727	SCREEN FAILURE;WITHDRAWAL BY SUBJECT;ADVERSE EVENT;DEATH;OTHER	SDTM.DS with DSCAT=DISPOSITION EVENT Free text collected in SPECIFY field must se in DSTERM- and pre-printed term in DSDECOD- Note that Death should be ticked instead of Adverse Event if the subject died, even if an	DS.DSDECOD; DS.DSTERM

Operational Data Item name (CDASH)

CRF Item text + Layout +eDC build recommandations

Data Type/Length & Controlled Terminology

Comments for Collection & Operational database creation

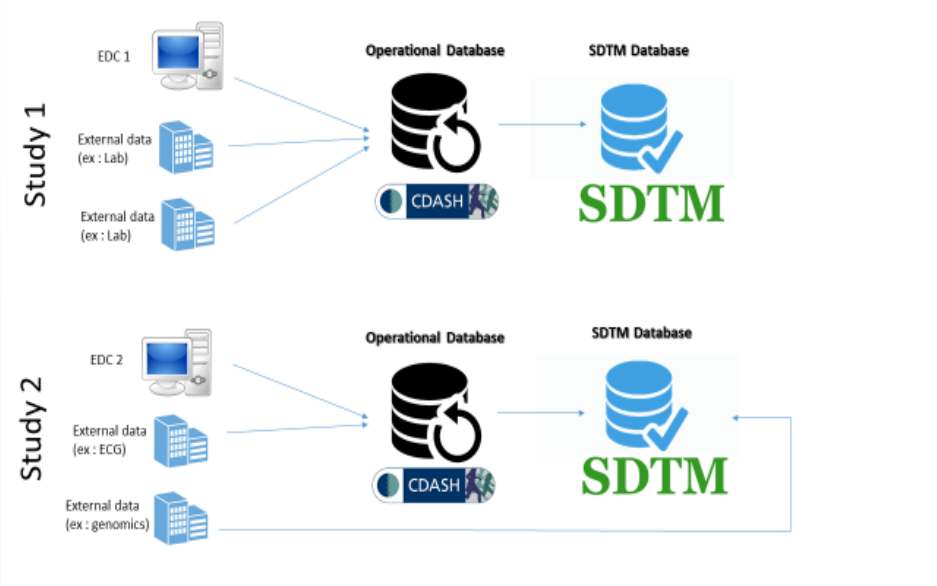
SDTM Mapping

Operational Database

➢ Bridge between collected clinical data and submission database (SDTM):

- Allows integration of non-EDC data before SDTM creation
- Retains operational EDC variables to facilitate data cleaning and review
- Preserves formats for ease of programming
- Maintains dates and times in programmable and analyzable formats
- Transposes horizontal EDC structure to vertical structure (as per SDTM) for Findings
- Retains data organization of the CRF (order, page) to facilitate data review
- Future SDTM SUPP-- variables are kept in the main domain

→ Live data for ongoing Data review & CRO oversight (Data quality & Metrics)



Actual process for SDTM Database

Specify

Standard Library

SDTM Standard specifications
(PF Structure for file)
Trial Design specs completed

Review

WORK IN PROGRESS

Metadata Checks + PF Rules Checks
QC Compare + P21 Report for SDTM datasets

Archive

Windows Server

Submit

eCTD

In-House

Receive

Tranfer agreements

SAS EXCHANGE

If QC not OK

SDTM Specifications

SDTM Study specifications
(PF Structure for file)
100% Completed

aCRF SDTM

SDTM Database creation

Operational Database

Scenario 1:
Operational
data as source

Scenario 2:
Raw data
(EDC extracts)
as source

Source → Target

SDTM Database

SDTM

SAS datasets (XPT)

Define.XML

aCRF SDTM

SDRG

CRO

Actual process : Pros and Cons (first impressions)

- Lot of control on files structure exchanged with partners : QC can be automated
- eCRF specifications are well understood & we believe that it can lead the following benefits :
  - Reduces questions regarding SDTM mapping
  - Reduces rounds of review during EDC development
- Operational database is more flexible than SDTM (ex: Adding EDC variables) to query for data management reporting
- Process is vendor-neutral and works with any EDC

- Operational Database building can be challenging for CRO as this is kind of SDTM+/-. Can we do this internally?
- Can implies some re-work : CRO mostly have their own file structure of SDTM specifications and prefer to use it rather than ours. Do we really need to have them in our file stucture?
- Still a lot of manual steps/tools :
  - Automating is difficult by lack of interoperability in systems used
  - Standards governance & versioning management will not be efficient as we expect

→ Ensure consistency between studies and good quality deliverables but need to be more flexible for CRO and efficiency must be improved by adding more interoperability/automation between systems

Areas for Improvement

Areas for improvement

Specify

Clinical Team

PF CRF/Data Guidelines (PF conventions and expectations)

METADATA REPOSITORY

Protocol (CDISC Terminology included)

Standard Library

ODM/Define.XML

or

Metadata eCRF + SDTM

CRF Build & SDTM Database Creation

Sponsor EDC URL

RAW

Operational Database creation & Review

Operational Database

Metadata Quality checks (QC Compare + Governance KPI + P21 Reports)

Data Quality Checks

SDTM Database

SDTM

XPT

Receive & Archive & Submit

Data Repository

Define.XML

aCRF SDTM

SDRG

In-House

CRO

Conclusion

- Process depends on your internal resources skills and vision of the CRO Oversight if you're outsourcing activities
- Some CDISC standards benefits are the following :
  - Improve Data Exchange
  - Improve Data Quality
  - Reduce the regulatory questions and accelerate speed of approval
  - Improve study efficiency

→ Last point cannot be 100% achieved without tools & technology !

- Some thoughts to improve our process include :
  - Invest in a Metadata Repository for :
    - Better standard management and versioning : Achieve standard governance purposes
    - Better exchange of standard metadata
  - Keep our own EDC URL and give access to the CRO :
    - Connection to Metadata Repository and Standard library development for study re-use
    - Connection to Visualization tool for more efficient reporting
    - Build Operational database internally & easily + keep coding capabilities
    - Improve some other processes, ex: eSAE form with direct information sending to safety PV database
  - Invest in a storage system (Data repository) :
    - Better exchange of data with partners by giving direct access to the system for example
    - Connection to Visualization tool for more efficient reporting
    - Develop specific validation checks within it to avoid external development

Questions and Remarks

- We (The community in general : CRO, Sponsors, External providers, academic …) really need to start thinking by exchanging with « new » technology such as ODM or XML

→ Define.XML is not just a submission document, it is easily machine readable