CDISC Italian User Network 2020

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CDISC SEND

Data Standardization and Exploration

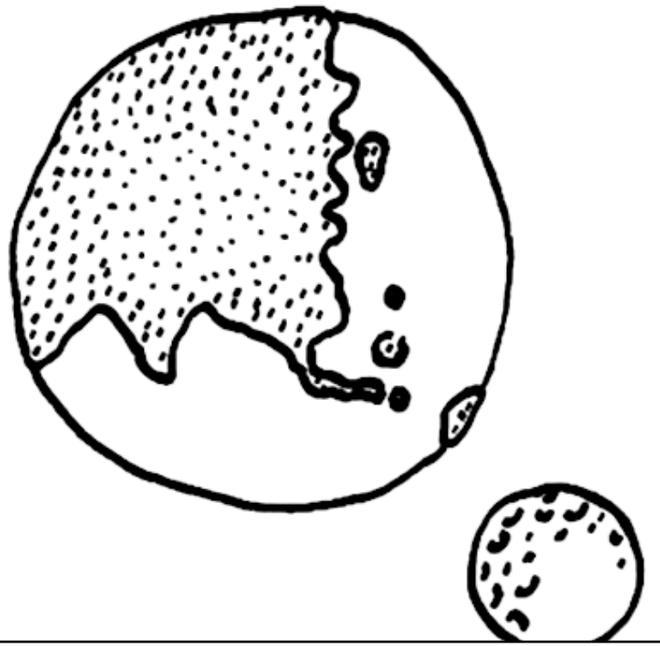
Agenda

CDISC Standards and FDA Submission Requirements

SEND v3.0 and SEND v3.1 Overview

SEND Data Standardization Process

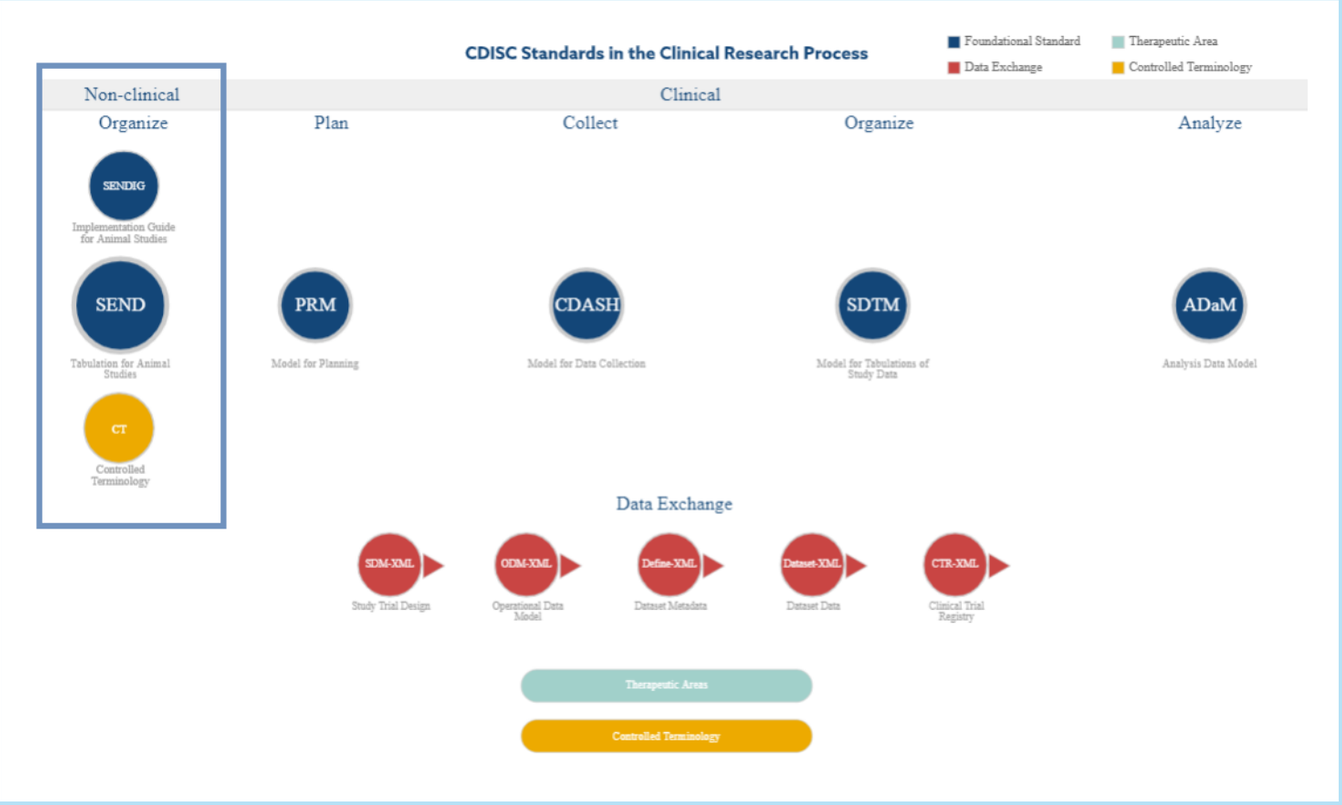
Standardised Data kick-start for Data Exploration



CDISC Standards

Standard for the Exchange of Nonclinical Data

- CDISC stands for Clinical Data Interchange Standard Consortium
  - supported by pharmaceutical companies, biotech companies, CROs / service providers, and technology providers
- CDISC has established WW industry standards to support
  - electronic acquisition
  - exchange
  - submission and archival
  - of clinical (SDTM / ADAM) and pre-clinical (SEND) trials data and metadata for medical and biopharmaceutical product development
- CDISC SEND is an implementation of the CDISC Standard Data Tabulation Model (SDTM) for non-clinical toxicology and safety pharmacology studies and is intended to:
  - provide an accurate standardized electronic representation of information included in study report



What is SEND?

Standard for Exchange of Nonclinical Data (SEND)

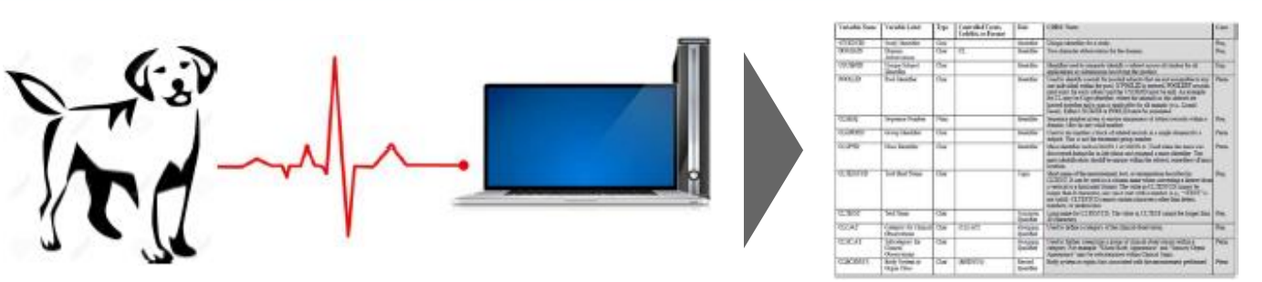
SEND Includes

- Study Design
- Individual animal details
- Dosing Informations
- Collected and derived individual results and observations

SEND Does Not Include

- Audit trails
- Analyses
  - No descriptive statistics
  - No incidence counts
  - No group comparative statistics
- Interpretations and conclusions

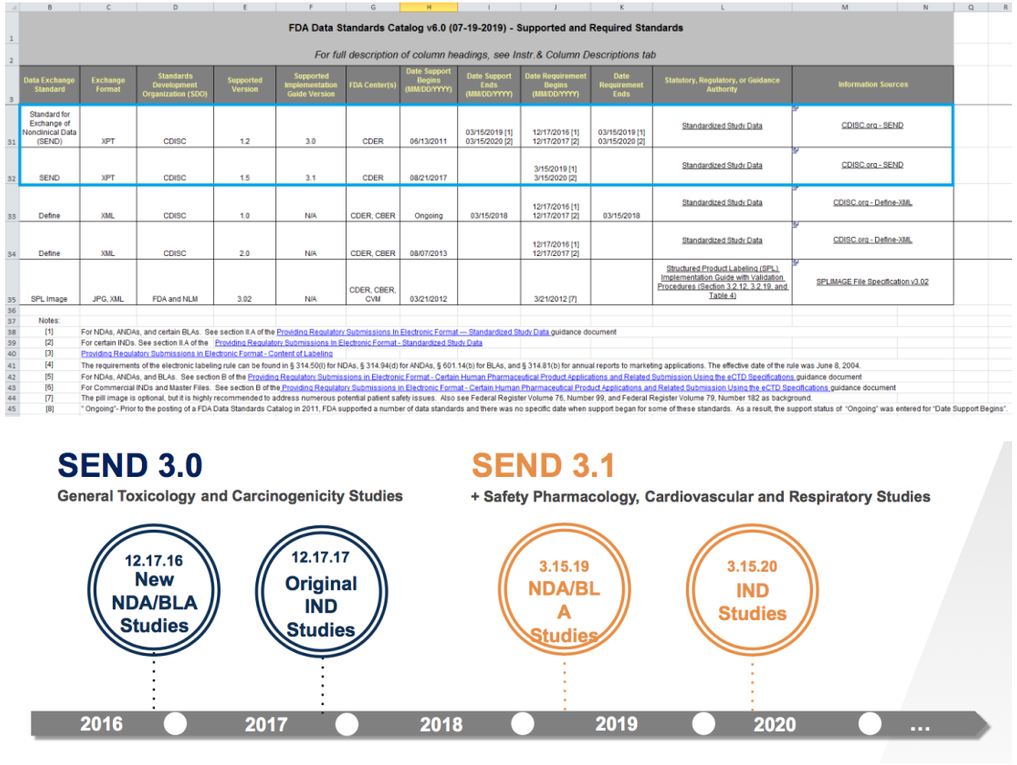
- SEND is built around the concept of observations collected about subjects included in a nonclinical study
- Test results, examinations, and observations are represented in a series of SEND domains through a list of variables



FDA Submission Requirements

Study Data for Submission to CDER and CBER

- FDA will no longer accept non-standardized and non-electronic submissions for studies started (Protocol Signature) after:
  - December 17 2016 for NDA's and BLA's
  - December 17 2017 for IND's.
- Data standards enable FDA to
  - Modernize and streamline the review process,
  - Enable more consistent use of analysis tools to better view drug data and highlight areas of concern.
- FDA accepts electronic submissions that provide study data using the standards, formats, and terminologies described in the FDA Data



FDA Data Standards Catalog v6.0 (07-19-2019) - Supported and Required Standards

For full description of column headings, see Instr.& Column Descriptions tab

Data Exchange Standard	Exchange Format	Standards Development Organization (SDO)	Supported Version	Supported Implementation Guide Version	FDA Center(s)	Date Support Begins (MM/DD/YYYY)	Date Support Ends (MM/DD/YYYY)	Date Requirement Begins (MM/DD/YYYY)	Date Requirement Ends	Statutory, Regulatory, or Guidance Authority	Information Sources
Standard for Exchange of Nonclinical Data (SEND)	XPT	CDISC	1.2	3.0	CDER	06/13/2011	03/15/2019 [1] 03/15/2020 [2]	12/17/2016 [1] 12/17/2017 [2]	03/15/2019 [1] 03/15/2020 [2]	Standardized Study Data	CDISC.org - SEND
SEND	XPT	CDISC	1.5	3.1	CDER	08/21/2017		3/15/2019 [1] 3/15/2020 [2]		Standardized Study Data	CDISC.org - SEND
Define	XML	CDISC	1.0	N/A	CDER, CBER	Ongoing	03/15/2018	12/17/2016 [1] 12/17/2017 [2]	03/15/2018	Standardized Study Data	CDISC.org - Define-XML
Define	XML	CDISC	2.0	N/A	CDER, CBER	08/07/2013		12/17/2016 [1] 12/17/2017 [2]		Standardized Study Data	CDISC.org - Define-XML
SPL Image	JPG, XML	FDA and NLM	3.02	N/A	CDER, CBER, CVM	03/21/2012		3/21/2012 [7]		Structured Product Labeling (SPL) Implementation Guide with Validation Procedures (Section 3.2.12, 3.2.19, and Table 4)	SPLIMAGE File Specification v3.02

Notes:

[1] For NDAs, ANDAs, and certain BLAs. See section II.A of the Providing Regulatory Submissions In Electronic Format — Standardized Study Data guidance document

[2] For certain INDs. See section II.A of the Providing Regulatory Submissions In Electronic Format - Standardized Study Data

[3] Providing Regulatory Submissions in Electronic Format - Content of Labeling

[4] The requirements of the electronic labeling rule can be found in § 314.50(l) for NDAs, § 314.94(d) for ANDAs, § 601.14(b) for BLAs, and § 314.81(b) for annual reports to marketing applications. The effective date of the rule was June 8, 2004.

[5] For NDAs, ANDAs, and BLAs. See section B of the Providing Regulatory Submissions in Electronic Format - Certain Human Pharmaceutical Product Applications and Related Submission Using the eCTD Specifications guidance document

[6] For Commercial INDs and Master Files. See section B of the Providing Regulatory Submissions in Electronic Format - Certain Human Pharmaceutical Product Applications and Related Submission Using the eCTD Specifications guidance document

[7] The pill image is optional, but it is highly recommended to address numerous potential patient safety issues. Also see Federal Register Volume 76, Number 99, and Federal Register Volume 79, Number 182 as background.

[8] "Ongoing"- Prior to the posting of a FDA Data Standards Catalog in 2011, FDA supported a number of data standards and there was no specific date when support began for some of these standards. As a result, the support status of "Ongoing" was entered for "Date Support Begins".

FDA Submission Requirements

Study Data for Submission to CDER and CBER

- Additional regulatory considerations:
  - The SEND version required for your submission is determined by the **study start date** (protocol signature date)
  - if you are including non-GLP studies in a regulatory submission, a **SEND package** is also required
  - If you have legacy studies in your submission, **an abbreviated TS file** (Trial Summary file) is required for each one
- What about PMDA and EMA?

EMA does not have formal plans to adopt CDISC standardized format

PMDA (Pharmaceuticals and Medical Devices Agency) will require drug makers to submit electronic data in CDISC standard format beginning 01 October 2016, with a 3.5 year transitional period

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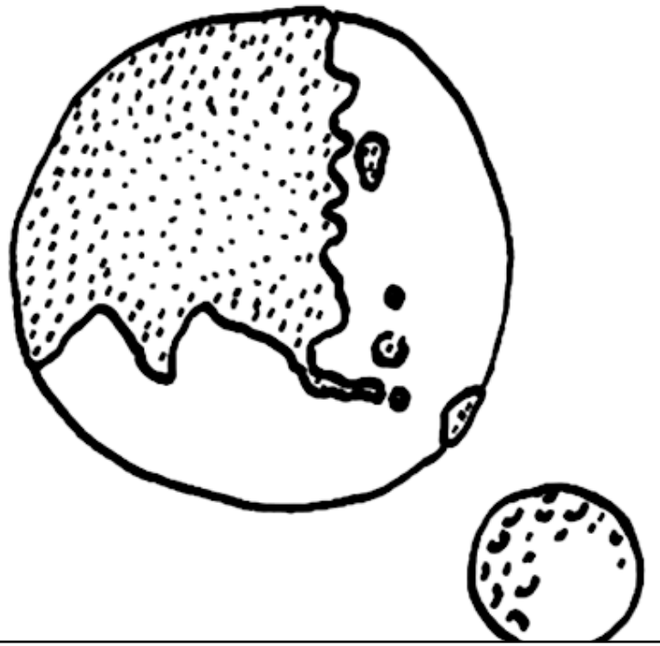


SEND 3.0 vs SEND 3.1

SEND Model Comparison

- SEND 3.0 was the first version accepted by FDA for nonclinical submissions and was designed to support:
  - General Toxicology
    - GLP / Non-GLP
    - Single-Dose / Repeat-Dose
  - Carcinogenicity studies
- SEND 3.1 (released by CDISC on June 27, 2016) expands on the previous version & supports the following study types:
  - General Toxicology
    - GLP / Non-GLP
    - Single-Dose / Repeat-Dose
  - Carcinogenicity studies
  - Safety Pharmacology
    - Cardiovascular studies
    - Respiratory studies

SEND 3.1

What is changing

- SEND 3.1 improve the standard model for the collection of Cardiovascular and Respiratory endpoints
  - Test results previously collected in Vital Signs are now placed in Safety Pharmacology domains
- New variables were added to relevant domains to improve completeness on specific topics (e.g. unscheduled test results and nominal timepoint)

	SEND 3.0			SEND 3.1		
Domain	**EG**	**VS**	**CV**	**EG**	**RE**	**VS**
Test / data type						
ECG Mean Heart Rate	X			X		
PR Interval	X			X		
QRS Duration	X			X		
QT Interval	X			X		
QTc Interval	X			X		
RR Interval	X			X		
Body Temperature		X				X
Diastolic Blood Pressure		X	X			
Heart Rate		X	X			
Mean Arterial Pressure		X	X			
Minute Volume		X			X	
Oxygen Saturation		X				X
Pulse Pressure		X	X			
Respiratory Rate		X			X	
Systolic Blood Pressure		X	X			
Tidal Volume		X			X	

SEND Data Model

Where is your data?

Study Design

- Trial Elements
- Trial Sets
- Trial Arms
- Trial Summary

Animal Details

- Demographics
- Subject Characteristics

Animal Disposition

- Disposition

In-Life observations

- Body Weight
- Body Weight Gain
- Clinical Observations
- Food and Water Consumption
- Laboratory Test Results
- Palpable Masses
- ECG Test Results
- Tumour Findings
- Exposure
- Vital Signs
- Cardiovascular Test Results
- Respiratory Test Results
- Pharmacokinetics Concentrations
- Pharmacokinetics Parameters

- Pool Definition
- Supplemental Qualifiers
- Comments
- Related Records
- Subject Elements

Post mortem observations

- Macroscopic Findings
- Microscopic Findings
- Organ Measurements

Unscheduled deaths Status and Causes

- Death Diagnosis

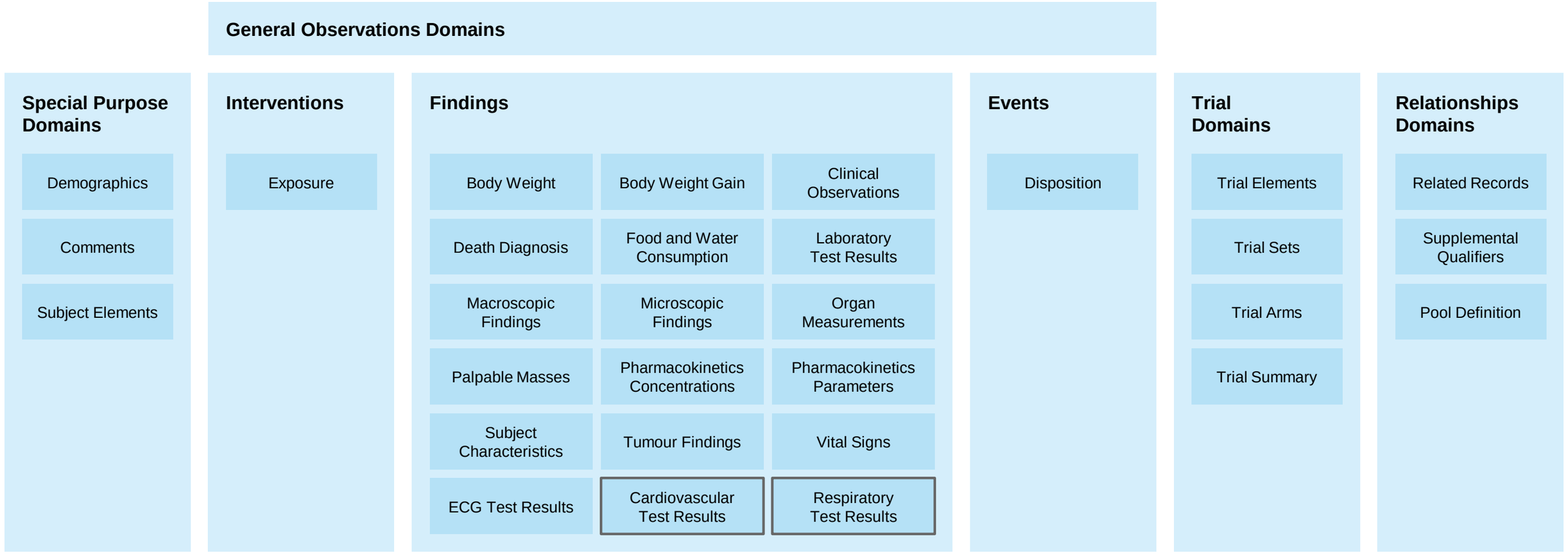
SEND Roadmap

Future Implementations

- DART (Developmental and Reproductive Toxicology)
  - extends the SEND standard into Reproductive Toxicology by supporting study data typically found in embryo-fetal development (EFD) toxicity studies (DART IG 1.1)
  - Fertility, Postnatal Development – Multi-generational will be covered in future releases
- Genetox
  - *In vivo* micronucleus
  - Comet test (*in vivo*) Single Cell Gel Electophoresis assay
  - *In vitro* micronucleus
  - Ames tests (*in vitro*) Mutagenic bacterial test named for Bruce Ames
- Dermal / Ocular – add domains
  - Local irritation assessments (IA)
  - Allocation to Treatment (AT)
- Safety Pharmacology
  - Addition of CNS domain
- The timing of Standard FDA adoption is a process separate from standards development

SDTM Standard Model and SEND IG

SDTM 1.5 → SEND IG 3.1



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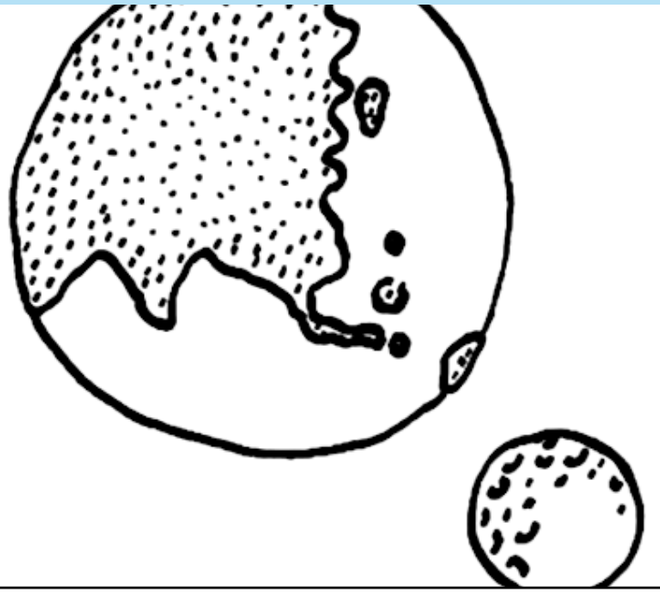


Evotec: SEND-ready Organisation

Data Standardisation Service for Nonclinical Studies and more

- SEND Data Standardisation Service Deliverables (SEND Package) for **studies internally** and **externally** executed:
  - SEND Standardised datasets in XPT format
  - Define.XML files compliant with CDISC specifications
  - Study Data Reviewer's Guide (nSDRG)
  - SEND dataset and define.xml validation reports generated by Pinnacle21 validator
- 3rd Party SEND Verification Service Deliverables:
  - Discrepancies between SEND datasets and Study Report
  - Discrepancies between SEND datasets and FDA standards requirements
  - SEND dataset and define.xml validation reports generated by Pinnacle21 validator
  - Suggestion how to solve SEND conformance issues identified by Verification Service
- ~80 SEND Packages standardised: 100% Successful Submission

Evotec: SEND-ready Organisation

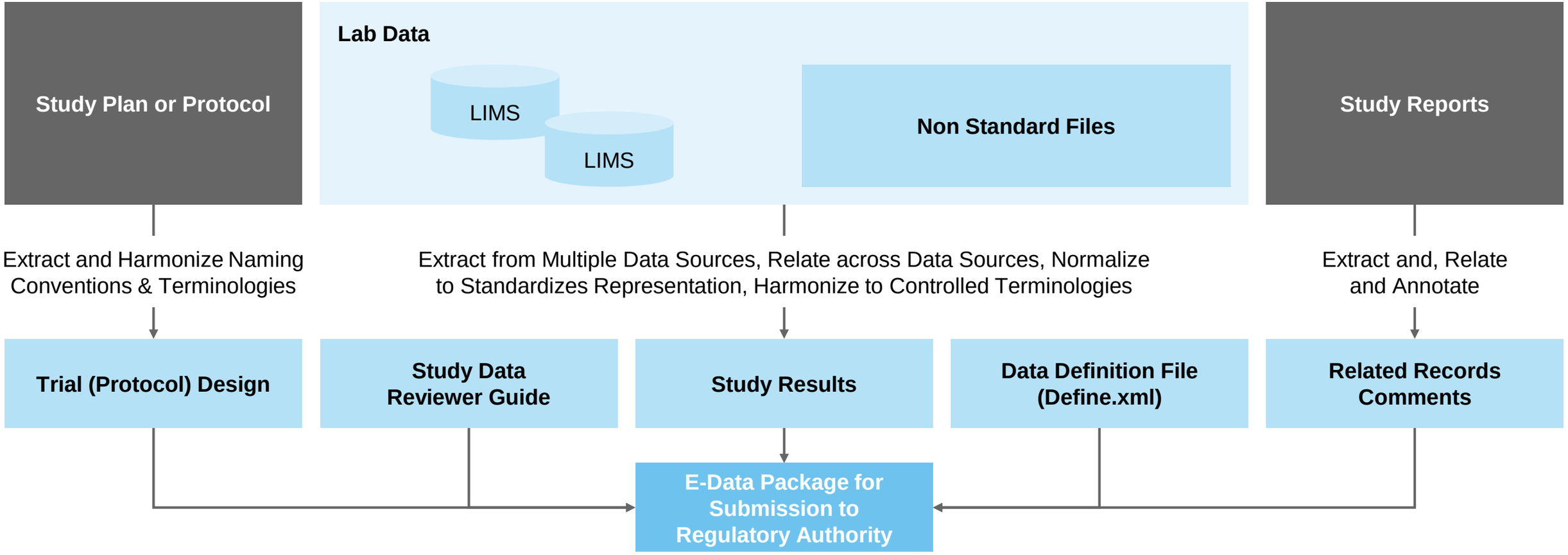
Evotec Standardisation Framework

Why an internal solution?

- Keep SEND domain & related compliance requirements full knowledge
- Keep complete control of the standardisation process (no black box perception)
- Take advantage of a Flexible Solution to:
  - Promptly and independently adopt any new controlled terminology version
  - Promptly and independently adopt any new SEND standard version released
  - Capability to develop adapter (data-model focused) to:
    - integrate with any additional external legacy system
    - read raw data externally generated (format independent)
  - Capability to manage and adapt framework configuration in case of complex Study Design (time effective solution w/o 3rd Party dependency)

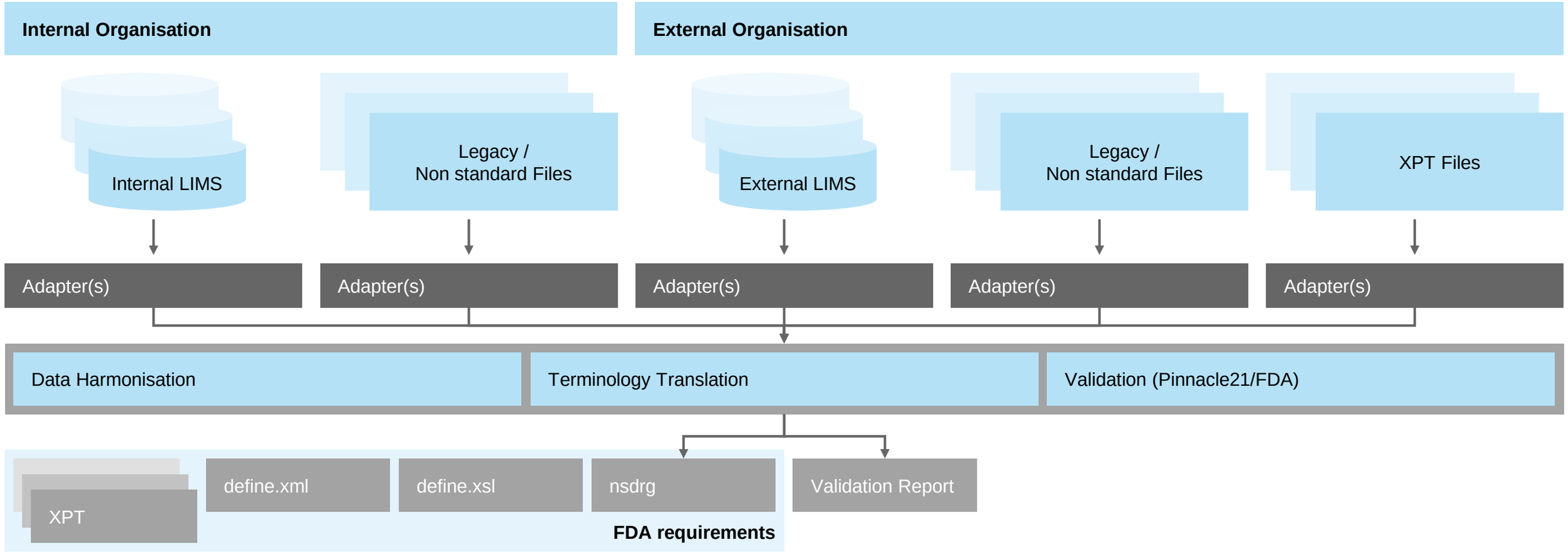
Evotec SEND Framework

Components of an e-Data Submission Package



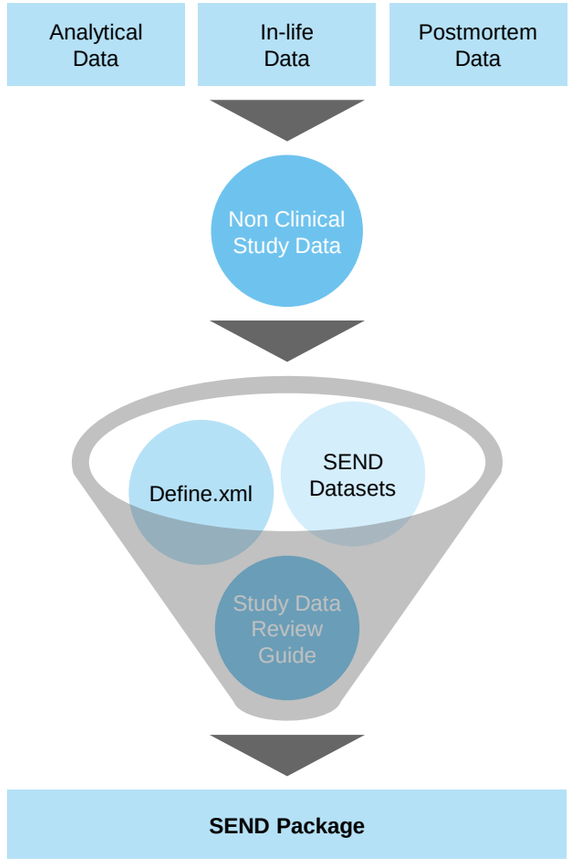
Evotec SEND Framework

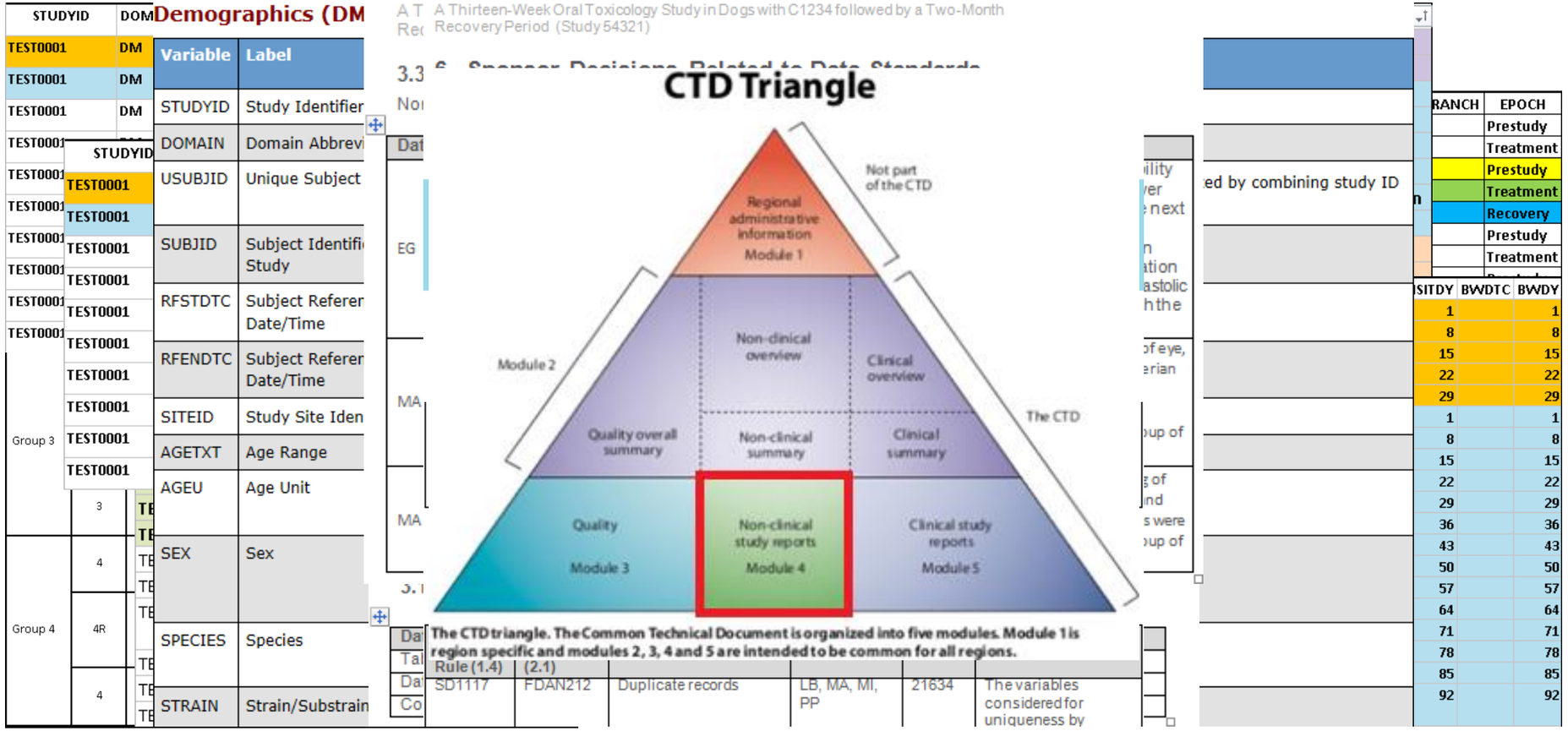
Architecture for Harmonisation and Aggregation of Data



SEND Package

Overview





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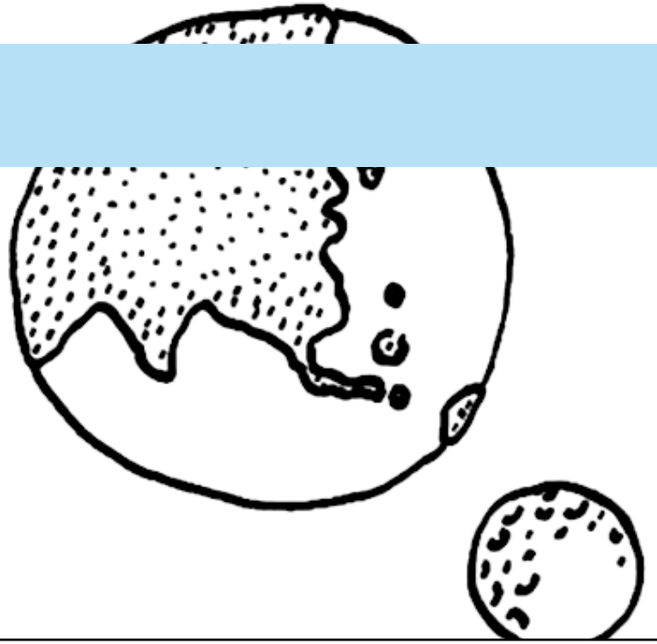

SEND Enlightening for Data Exploration

Enabling Better Decision Making

Standardised Data improve Data Exploration

- Single-Study-oriented: allow to generate individual or group summarisation with scientifically relevant visualisation to identify trends and patterns within a study
  - What were the most prevalent histopathology findings observed in the study?
  - Is there a changing trend between treatment and recovery period?
- Multi-Study-oriented: cross-study visualisations and comparison for analysis purposes
  - If there were observed trends in what other studies has this finding been observed?

SEND Enlightening for Data Exploration

Severity Heatmap by Tissue and by Findings

What were the most prevalent histopathology findings observed in the study?

SEND Enlightening for Data Exploration

Multi Endpoint Line Graph

Which is the time course pattern of following multiple endpoints: Body Weight, Food Consumption and Activated Partial Thromboplastin Time?

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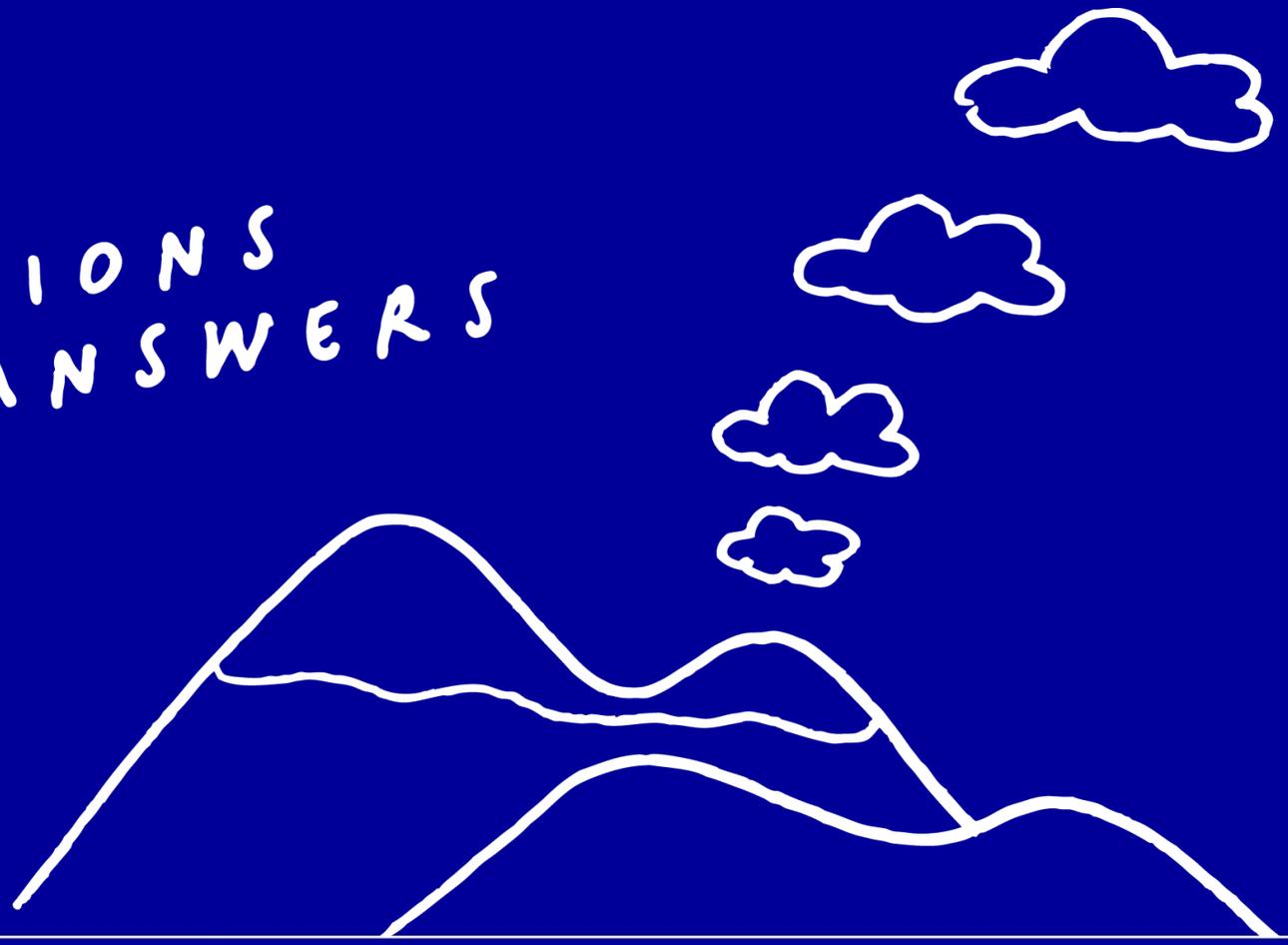
QUESTIONS AND ANSWERS



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Your contact:

Marco Pergher
Senior Manager, Biometry

+39.045.8218396
marco.pergher@aptuit.com