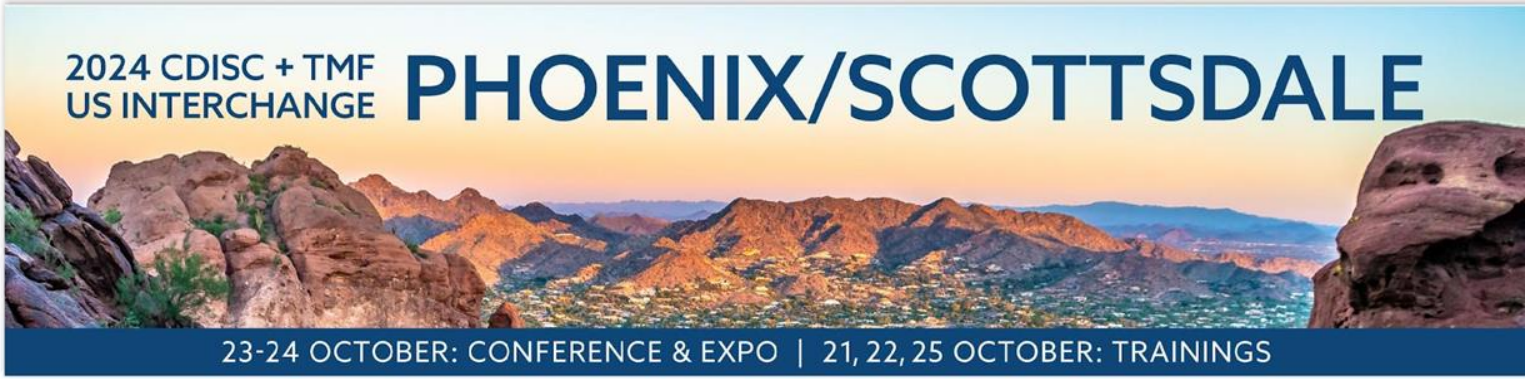


Harmony and Melody - The Role of Metadata Standards in Improving Machine Learning Efficiency

Meet the Speaker

Steve Ross

Title: Director, Statistics and Life Sciences Consultancy

Organization: Beaconcure

Steve has worked in clinical research for more than 25 years, in statistics and programming roles for Big Pharma, Small Pharma, CROs, Biotech, and Consultancy. In his current role at Beaconcure, Steve works with clients to reduce obstacles to TLF production, streamline statistics and programming processes, and reduce deliverable timelines.

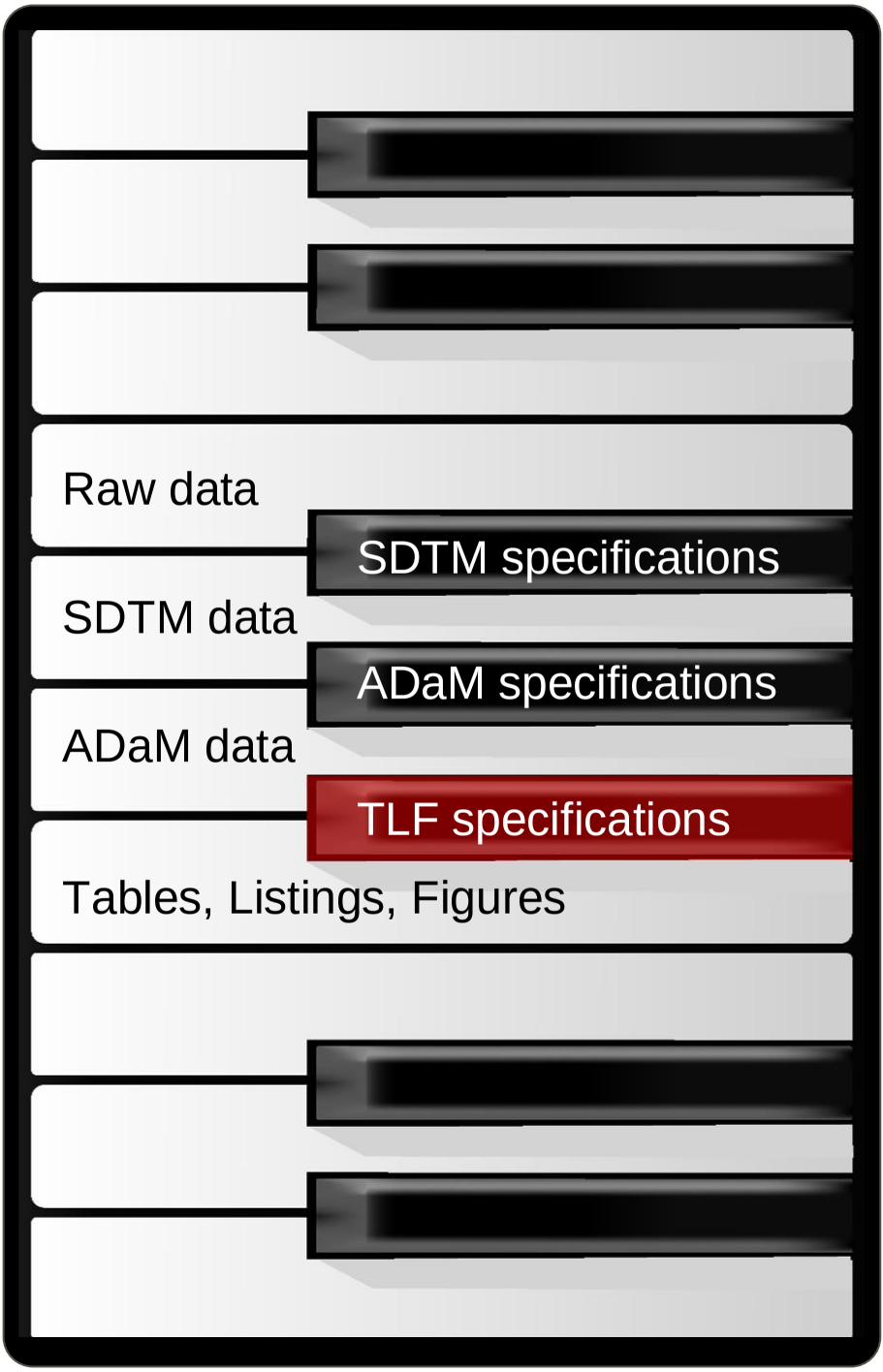
Disclaimer and Disclosures

- *The views and opinions expressed in this presentation are those of the author(s) and do not necessarily reflect the official policy or position of CDISC.*

Agenda

1. Current State of TLF Production and Validation
2. The Problem: What Lies Between ADaM and TLFs
3. Future State: CDISC to the Rescue!

Current State of TLF Production and Validation


Raw data
SDTM specifications
SDTM data
ADaM specifications
ADaM data
TLF specifications
Tables, Listings, Figures

Current State of TLF Production and Validation

- Tables, Listings, and Figures are designed and shells created.

Current State of TLF Production and Validation

- Tables, Listings, and Figures are designed and shells created.
- Raw data is transformed to SDTM structure using a robust CDISC SDTM methodology.

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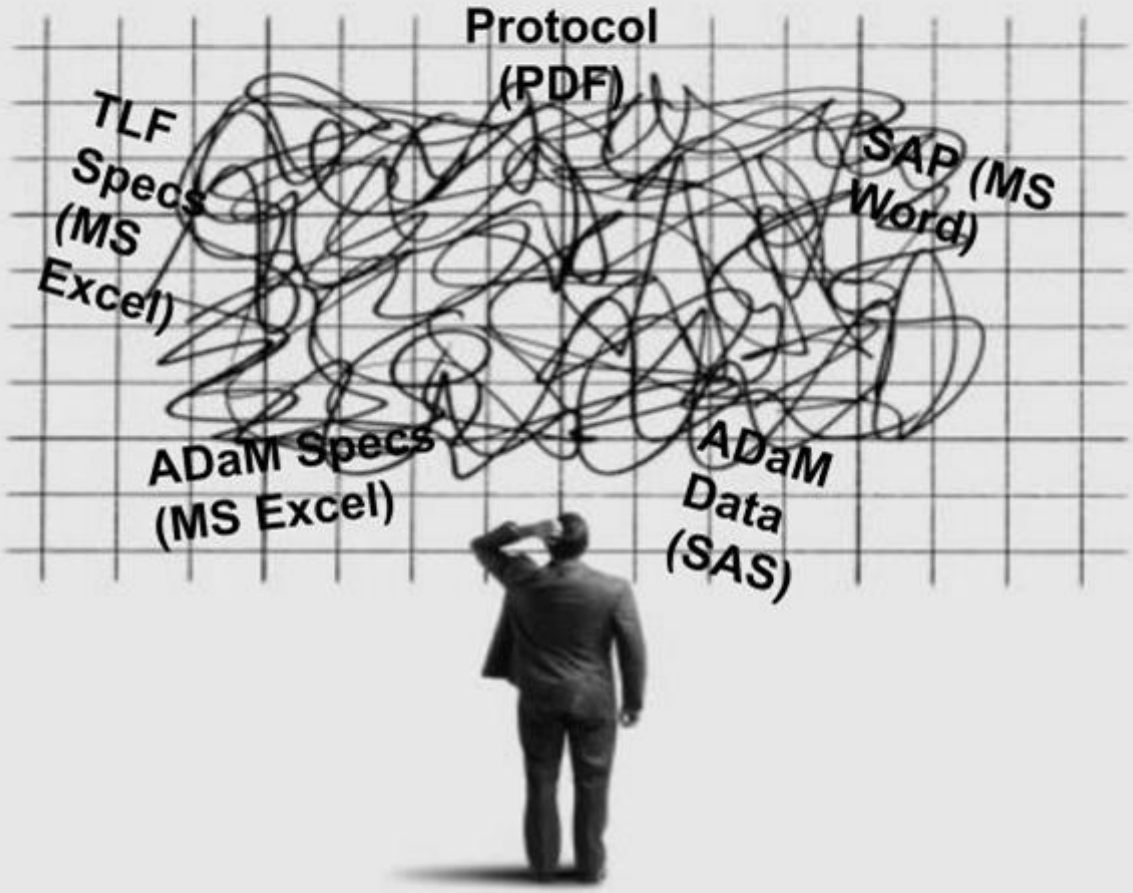
- Tables, Listings, and Figures are designed and shells created.
- Raw data is transformed to SDTM structure using a robust CDISC SDTM methodology.
- SDTM is then transformed to ADaM structure for analysis using a combination of CDISC ADaM structural framework and the statistical analysis plan.

Current State of TLF Production and Validation

- Tables, Listings, and Figures are designed and shells created.
- Raw data is transformed to SDTM structure using a robust CDISC SDTM methodology.
- SDTM is then transformed to ADaM structure for analysis using a combination of CDISC ADaM structural framework and the statistical analysis plan.
- Tables, Listings, and Figures are then generated using…


Protocol
(PDF)
TLF
Specs
(MS
Excel)
SAP (MS
Word)
ADaM Specs
(MS Excel)
ADaM
Data
(SAS)

The Problem:
What Lies Between ADaM and TLFs

- Obstacles to effective TLF development

General instructions in the protocol

9.1.2. Vital Signs

Vital signs assessments will include respiratory rate (breaths per minute), systolic and diastolic BP (mmHg), heart rate (HR) (beats per minute [bpm]) and body temperature, which will be measured after a participant has rested for at least 5 minutes in the supine or recumbent position, as age appropriate and feasible and will be collected as per Table 1, Table 3, Table 4, and Table 6.

Any clinically significant abnormal vital sign assessment requires at least one repeat measurement.

Vital signs abnormalities that are (1) considered clinically significant initially and on confirmation, (2) require a participant to be discontinued from the study, (3) require a participant to receive treatment, or (4) require a change or discontinuation from the study drug (if applicable) will be recorded as AEs.

Programming/Statistics Notes in SAP

Table of Contents

3.6 Study Specific Programming Instructions

3.6.1 Baseline

Variable	Baseline Visit
Laboratory tests	The baseline value is defined as the last non-missing measurement collected prior to the first administration of study drug at Day 1. For the lab values, if the calculated study day for the labelled baseline visit is not study Day 1 but falls within 28 days before the start of the study dosing, then that data should be used for the baseline instead of leaving baseline
Concomitant Medications	Baseline for systemic steroid, NSAIDs and opioids is defined as on stable dose at least 4 weeks prior to the first dose of study drug and analysis end time after date of first exposure. Baseline for anti-malarial is defined as treated on Day 1. Start time before the first dose of study drug and analysis end time after date of first exposure.

```
proc mixed data=ds ;
        class       id trt (ref="Control")  time (ref="2");
        model       cfb = base time trt  time*trt  time*base / ddfm=kr;
        repeated    time /subject= id type= un;
        lsmeans     visit*trt / pdiff at base= &basemean alpha=0.10 cl;
        ods output  diffs= dlancova  lsmeans= dlancova;
run;

data  dlancova;
  set dlancova;
  if( (trt="Active" & _trt="Control") & (time=_time));
run;
```

Programming Notes in Standard TLF Specs

General Notes:

1. A "Missing" row will be added if there are unreported results for any category.
2. For tables and listings where patients are stratified by MP500 dose, patients will also be stratified by treatment with corticosteroid premedication.
3. MP500 single agent dose escalation tables, listings, and figures shells are included. Upon initiation of the MP500 + Standard of Care (SOC) dose escalation, MP500 + SOC Dose Escalation treatment arms and Total columns will be added to the outputs. Duplicate table, listing, and figure shells will be added if needed as noted in the programming notes. Additionally, shells specific to SOC, crossover, or dose expansion have not been included at this time; they are available in the TOC.
4. Only cohorts that have subjects will be included in the TLFs. No dummy columns or rows will be presented for cohorts that do not yet have subjects or data.

Now We're getting somewhere…

	T_ANL_SUM_01					
	Title1	Miracle Pharmaceuticals			<DRY RUN/DRAFT/FINAL/CSR1/CSR2/DMC>	
	Title2	PROTOCOL: MP-XXX-XXXX (<Data Cutoff/Last Subject Out>: DDMMMYYYY)			Page x of y	ADSL.STUDYID
	Title3					
Table 15.1.2.x	Title4	Table 15.1.2.x				
	Title5	Analysis Sets				
	Title6	(Enrolled Analysis Set)				ADSL.ENRLFL='Y'
			Placebo (N=xx)	<Miracle Drug> (N=xx)	<Active Comparator> (N=xx)	Total (N=xx)	ADSL.TRT01P
		All Enrolled				xx (xx.x)	ADSL.ENRLFL = 'Y'
		Number of Screen Failures				xx (xx.x)	ADSL.SCRNFL= 'Y'
		Randomized Analysis Set	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	ADSL.RANDFL = 'Y'
		Safety Analysis Set	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	ADSL.SAFFL='Y'
		Full Analysis Set	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	ADSL.FASFL='Y'
		Per Protocol Analysis Set	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	ADSL.PPROTFL='Y'
		Completer Analysis Set	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	ADSL.COMPLFL = 'Y'
	Footnote1	<Add footnotes to define subject populations that appear in this table>					
	Lastfoot	/compound/study/..../tables/xxxxxxxxx				DDMMMYYYY xx:xx	
		Note: Include only analysis sets described in the SAP. Add/remove the analysis sets based on the Study Protocol.					
		Note: Treatment can be a column variable (as shown in the shell) or instead added as pageby variable.					

Current State Obstacles to Effective Programming

- **Each of these documents is bespoke**, tailored to the requirements of the protocol that governs the trial.

Current State: Obstacles to Effective Programming

- **Each of these documents is bespoke**, tailored to the requirements of the protocol that governs the trial.
- **Each of these documents takes multiple weeks to develop** and is continually updated (save for the protocol) and refined right up until database lock.

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- Each of these documents appears to have structure, but natural variability in study purposes results in **limited carryover from study to study** within a compound's development, and **even from table to table** within the same study.

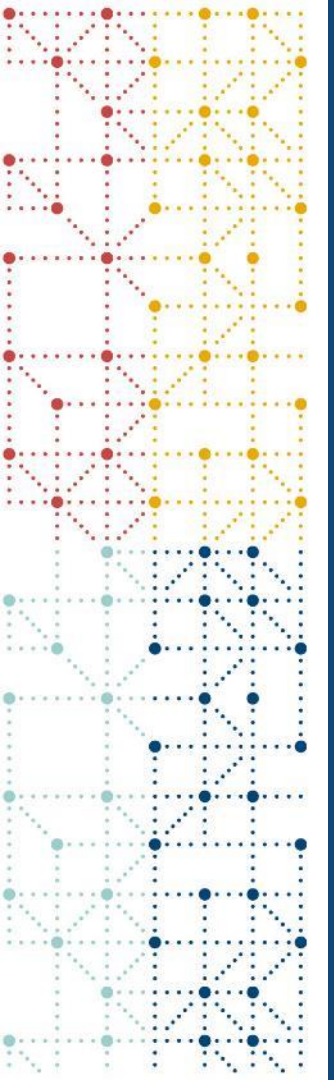
Current State: Obstacles to Effective Programming

- **Each of these documents is bespoke**, tailored to the requirements of the protocol that governs the trial.
- **Each of these documents takes multiple weeks to develop** and is continually updated (save for the protocol) and refined right up until database lock.
- Each of these documents appears to have structure, but natural variability in study purposes results in **limited carryover from study to study** within a compound's development, and **even from table to table** within the same study.
- **Study level metadata and results data are generated post-hoc** (in the define.xml); however, it does not facilitate automation, repeated use, and reflects the lack of standardization found in the source documents.

Common Theme

Even within these ‘standard documents’ the metadata and results data *are not standardized.*

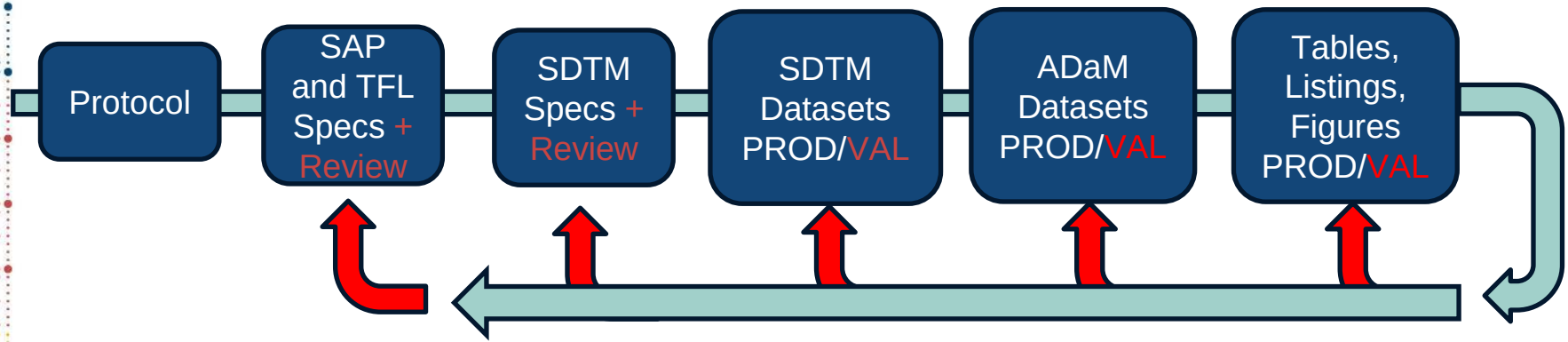
How do we know this?



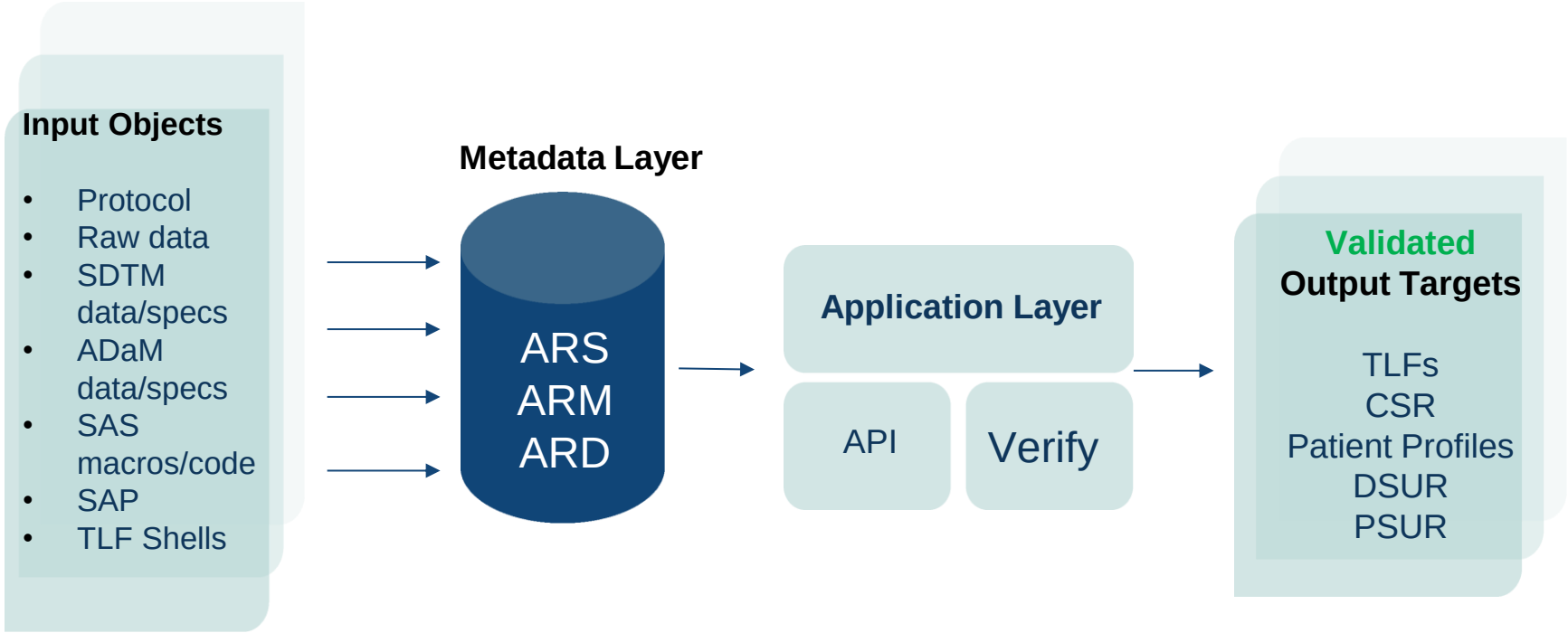
Future State: CDISC to the Rescue!

Refining the metadata layer between ADaM and TLFs with
Analysis Results Standards (ARS) and
Analysis Results (Meta)data (ARD)

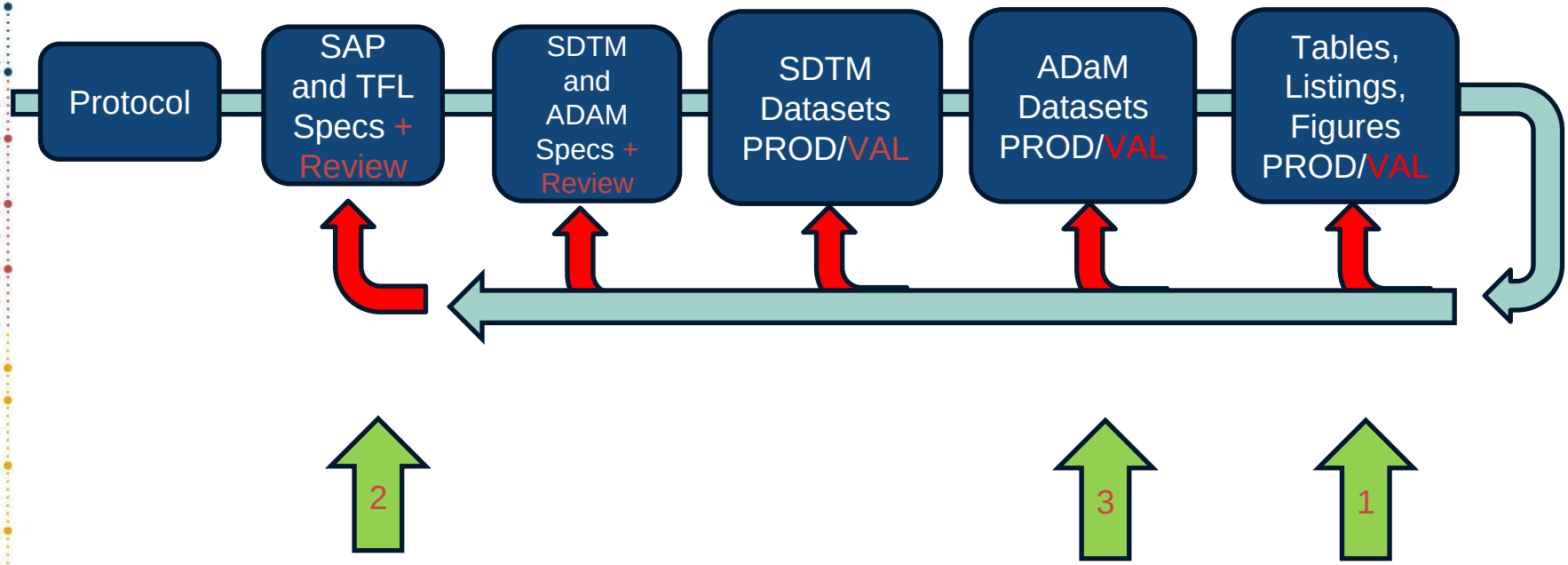
TLF (Meta)data Ecosystem: Current State



TLF (Meta)data Ecosystem: Future State

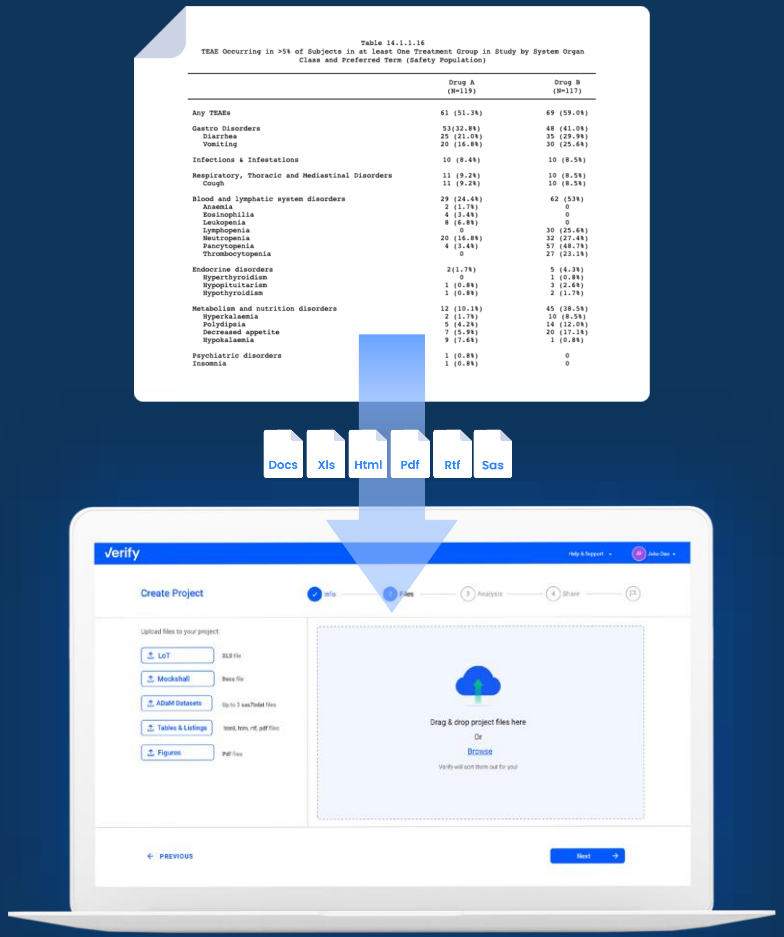


TLF (Meta)data Ecosystem: Current State



Model data ingestion

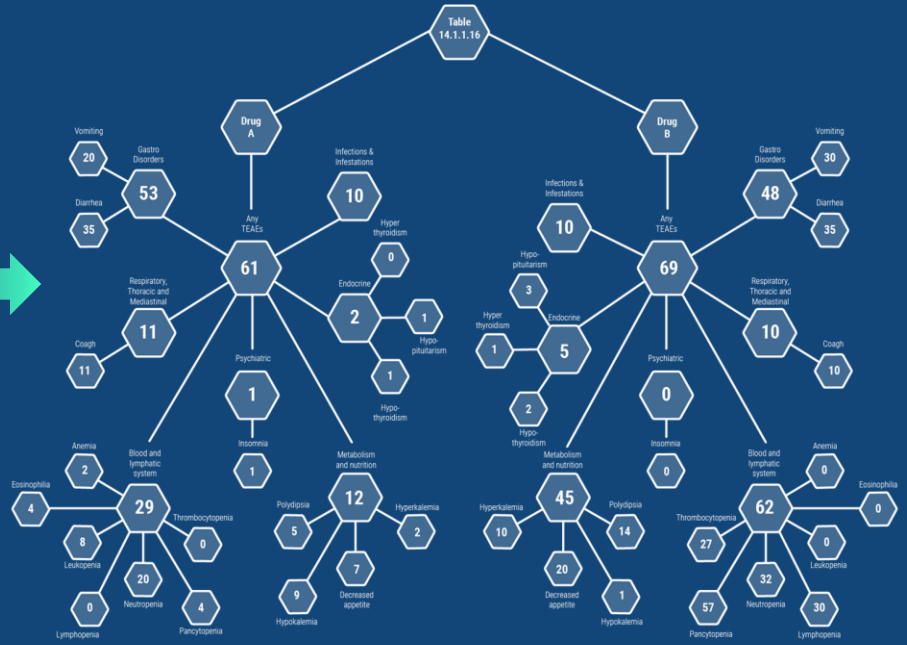
- Either upload all your delivery files(TLFs, Table of Contents, TLF shell documents) to Verify application, or link directly through an API
- Application parses your files, deconstructing down to the cell level, categorizing and linking objects



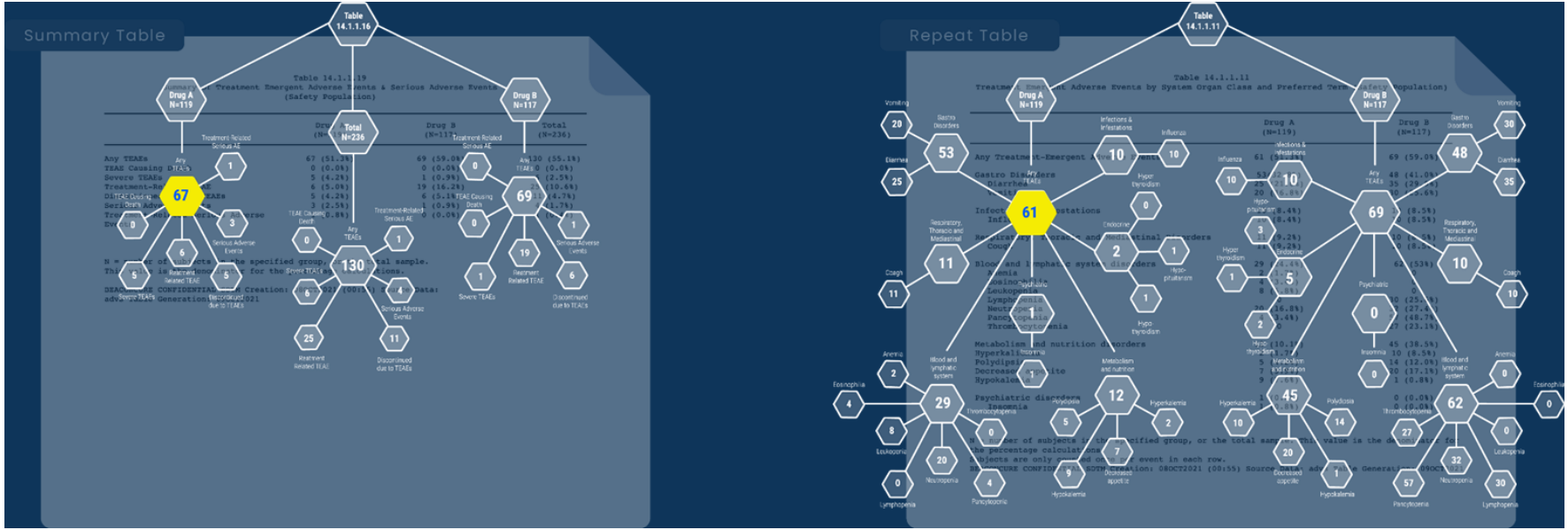
AI-Enabled Conversion of TLFs into a Robust Structured Database

Table 14.1.1.16
TEAE Occurring in >5% of Subjects in at least One Treatment Group in Study by System Organ Class and Preferred Term (Safety Population)

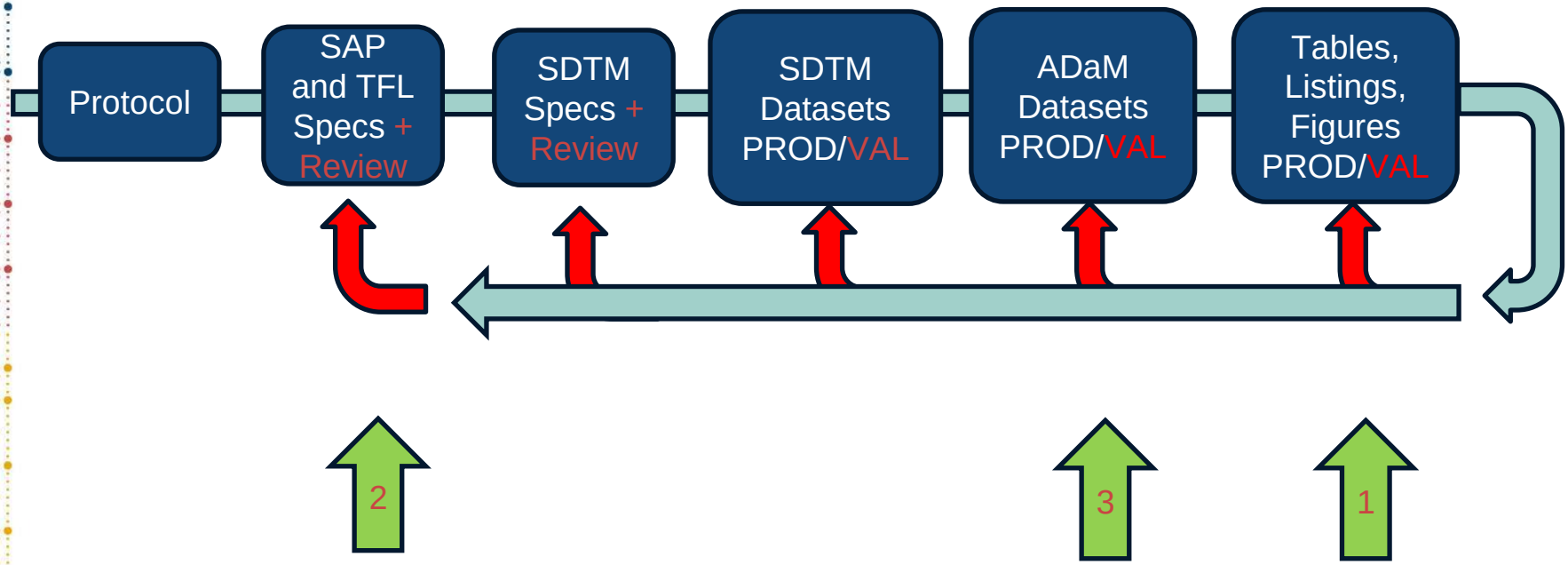
	Drug A (N=119)	Drug B (N=117)
Any TEAEs	61 (51.3%)	69 (59.0%)
Gastro Disorders	53(32.8%)	48 (41.0%)
Diarrhea	25 (21.0%)	35 (29.9%)
Vomiting	20 (16.8%)	30 (25.6%)
Infections & Infestations	10 (8.4%)	10 (8.5%)
Respiratory, Thoracic and Mediastinal Disorders	11 (9.2%)	10 (8.5%)
Cough	11 (9.2%)	10 (8.5%)
Blood and lymphatic system disorders	29 (24.4%)	62 (53%)
Anaemia	2 (1.7%)	0
Eosinophilia	4 (3.4%)	0
Leukopenia	8 (6.8%)	0
Lymphopenia	0	30 (25.6%)
Neutropenia	20 (16.8%)	32 (27.4%)
Pancytopenia	4 (3.4%)	57 (48.7%)
Thrombocytopenia	0	27 (23.1%)
Endocrine disorders	2(1.7%)	5 (4.3%)
Hyperthyroidism	0	1 (0.8%)
Hypopituitarism	1 (0.8%)	3 (2.6%)
Hypothyroidism	1 (0.8%)	2 (1.7%)
Metabolism and nutrition disorders	12 (10.1%)	45 (38.5%)
Hyperkalaemia	2 (1.7%)	10 (8.5%)
Polydipsia	5 (4.2%)	14 (12.0%)
Decreased appetite	7 (5.9%)	20 (17.1%)
Hypokalaemia	9 (7.6%)	1 (0.8%)
Psychiatric disorders	1 (0.8%)	0
Insomnia	1 (0.8%)	0



Fully parsed data facilitates semantic understanding of different tabular data.



TLF (Meta)data Ecosystem: Current State



Standard Demographics Table

Table 15.1.4.1
Demographics
Safety Analysis Set

Characteristic	MP500 Single Agent Dose Escalation			
	MP500 8 ug/kg (N=3)	MP500 16 ug/kg (N=5)	MP500 16 ug/kg + 1 DEX (N=3)	MP500 16 ug/kg + 2 DEX (N=3)
Age (years) [a]				
n	3	5	3	3
Mean (SD)	66.7 (6.11)	70.6 (5.81)	57.3 (11.68)	57.0 (8.89)
Median	68.0	68.0	55.0	54.0
Min, Max	60, 72	65, 80	47, 70	50, 67
Age categories [a] [n (%)]				
18 to 64	1 (33.3)	0	2 (66.7)	2 (66.7)
65 to 84	2 (66.7)	5 (100)	1 (33.3)	1 (33.3)
85 or above	0	0	0	0
Sex [n (%)]				
Male	3 (100)	5 (100)	2 (66.7)	2 (66.7)
Female	0	0	1 (33.3)	1 (33.3)
Missing	0	0	0	0
Ethnicity [n (%)]				
Hispanic or Latino	0	1 (20.0)	1 (33.3)	0
Not Hispanic or Latino	3 (100)	4 (80.0)	2 (66.7)	3 (100)
Not Reported	0	0	0	0

DEX = Dexamethasone
[a] Age is calculated as the integer part of (Date of informed consent - Date of birth) / 365.25.
[b] Body Mass Index is defined as weight(kg) / [height (m)]2.

Standard Demographics Table

Miracle Pharmaceuticals — Page 1 of 5

Protocol No.: MP500-1001--Data Cutoff Date:21Nov2021

Table 15.1.4.1
Demographics
Safety Analysis Set

Identifiers

Group Vars

Result Vars

Statistics

Characteristic	MP500 Single Agent Dose Escalation			
	MP500 8 ug/kg (N=3)	MP500 16 ug/kg (N=5)	MP500 16 ug/kg + 1 DEX (N=3)	MP500 16 ug/kg + 2 DEX (N=3)
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Median	68.0	68.0	55.0	54.0
Min, Max	60, 72	65, 80	47, 70	50, 67
Age categories [a] [n (%)]				
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65 to 84	2 (66.7)	5 (100)	1 (33.3)	1 (33.3)
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Male	3 (100)	5 (100)	2 (66.7)	2 (66.7)
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Ethnicity [n (%)]				
Hispanic or Latino	0	1 (20.0)	1 (33.3)	0
Not Hispanic or Latino	3 (100)	4 (80.0)	2 (66.7)	3 (100)
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DEX = Dexamethasone
[a] Age is calculated as the integer part of (Date of informed consent - Date of birth) / 365.25.
[b] Body Mass Index is defined as weight(kg) / [height (m)]2.

/bios/MP500/studies/1001/dryrun/tables/t15.1.4.1-demo — 04Dec2021 19:44

Standard Demographics Table Shell

	T_DEM_SUM_01					
Title1	Miracle Pharmaceuticals				<DRY RUN/DRAFT/FINAL/CSR1/CSR2/DMC>	
Title2	PROTOCOL: MP-XXX-XXXX (<Data Cutoff/Last Subject Out>: DDMMMYYYY)				Page x of y	ADSL.STUDYID
Title3						
Table 15.1.4.x Title4	Table 15.1.4.x					
Title5	Demographic Characteristics by Treatment Group					
Title6	(<Randomized Set/Safety Set/Analysis Set>)					<ADSL.RANDFL='Y'/SAFFL='Y'/*FL='Y'>
			MP500	<Active		ADSL.TRT01A
		Placebo	Drug xx mg>	Comparator xx mg>	Total	
	Characteristic	(N=xx)	(N=xx)	(N=xx)	(N=xx)	
	Age (years) [a]					ADSL.AGE
	n	xx	xx	xx	xx	
	Mean (<SD>)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	
	Median	xx.x	xx.x	xx.x	xx.x	
	Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	
	Age Categories (n[%])					non-missing unique values for ADSL.AGEGRy
	< XX	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	
	XX - XX	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	
	XX - XX	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	
	> XX	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	

Analysis Results (+) Metadata

Identifiers		Group Vars			Result Vars		Statistics		
Number	Title	Dataset	Variable	Value	Variable	Label	Value	Name	Label
15.1.4.1	Demographics Safety Analysis Set	ADSL	TRT01a	MP500 8 ug/kg (n=3)	AAGE	Age (years) [a]	3	Count	N
15.1.4.1	Demographics Safety Analysis Set	ADSL	TRT01a	MP500 8 ug/kg (n=3)	AAGE	Age (years) [a]	66.7 (6.11)	Mean (standard deviation)	Mean (SD)
15.1.4.1	Demographics Safety Analysis Set	ADSL	TRT01a	MP500 8 ug/kg (n=3)	AAGE	Age (years) [a]	68	Median	Median
15.1.4.1	Demographics Safety Analysis Set	ADSL	TRT01a	MP500 8 ug/kg (n=3)	AAGE	Age (years) [a]	60, 72	Minimum, Maximum	Min, Max

Future State of TLF Development

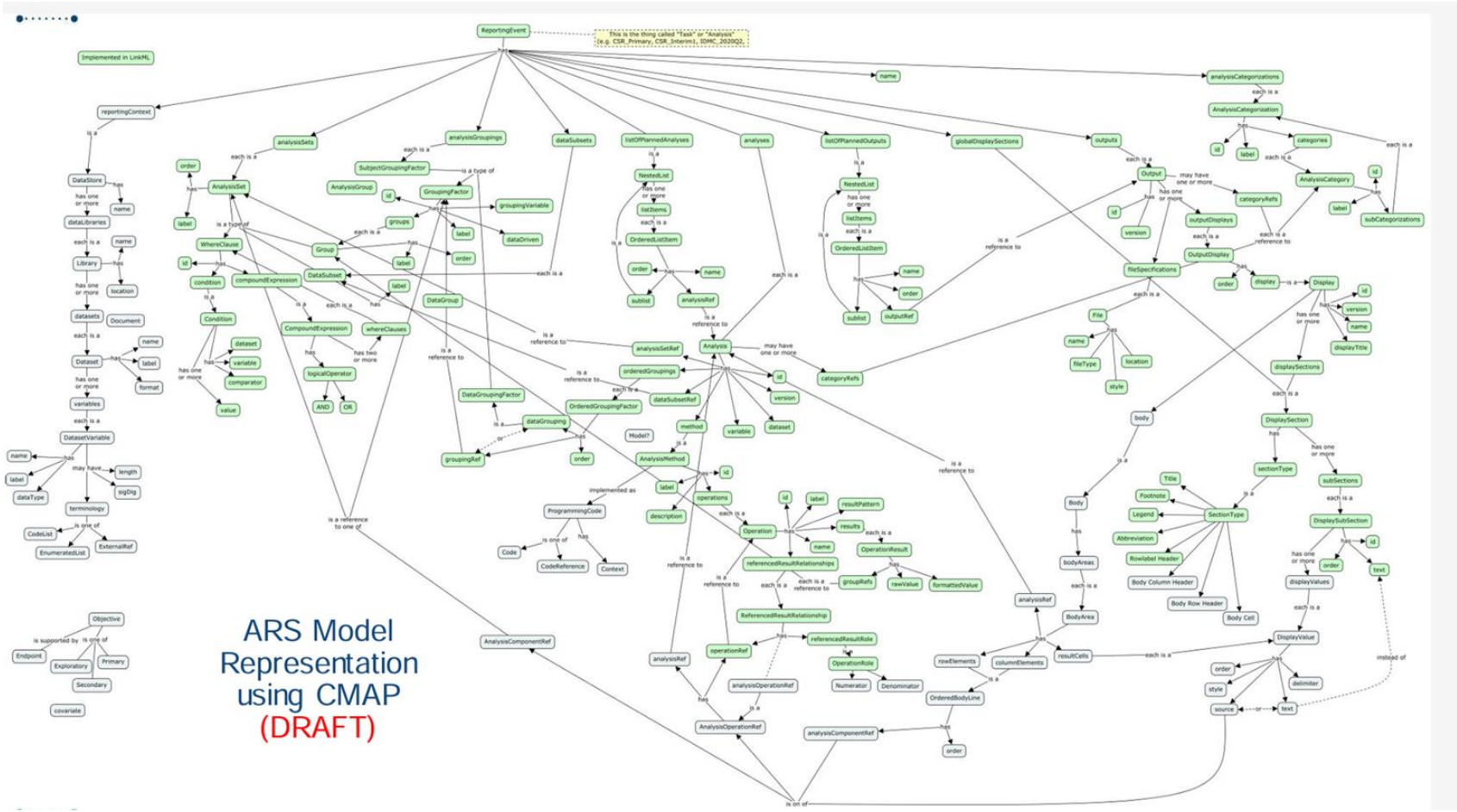
- ARS-standardized TLF metadata enables rapid TLF identification and selection from a growing database of displays of all shapes and sizes
- Where new displays are required, software will make suggestions based on input parameters.
- Where existing metadata are not sufficient for production or validation tasks, Humans-in-the-loop provide last-mile input once to complete
- As metadata store grows at an organization, the AI algorithms become more efficient and more accurate, making better suggestions and requiring less human-in-the-loop interventions

Summary

Analysis Results Standards (ARS) provide a framework to capture structural aspects of the displays, as well as the results data in the body of the TLFs.

This common structure of ARS data facilitates:

- Rapid development of TLFs during the statistical analysis design phase
- Consistency in TLF design across compounds/phase/TAs/organizations
- Linkages back to ADaM datasets, creating automated validation pathways, opportunities for data reuse


ReportingEvent
This is the thing called "Task" or "Analysis" (e.g. CSR_Primary, CSR_Interim1, IDMC_2020Q2,
Implemented in LinkML
reportingContext
DataStore
dataLibraries
Library
datasets
Dataset
variables
DatasetVariable
name
label
dataType
length
sigDig
terminology
CodeList
EnumeratedList
ExternalRef
format
location
Document
analysisSets
AnalysisSet
order
label
WhereClause
condition
compoundExpression
Condition
dataset
variable
comparator
value
Group
DataSubset
CompoundExpression
whereClauses
logicalOperator
AND
OR
analysisGroupings
AnalysisGroup
SubjectGroupingFactor
GroupingFactor
groupingVariable
groups
dataDriven
DataGroupingFactor
dataGrouping
groupingRef
dataSubsets
listOfPlannedAnalyses
NestedList
listItems
OrderedListItem
sublist
analysisRef
analyses
Analysis
analysisSetRef
orderedGroupings
OrderedGroupingFactor
dataSubsetRef
method
variable
dataset
AnalysisMethod
description
operations
Operation
resultPattern
results
OperationResult
groupRefs
rawValue
formattedValue
referencedResultRelationships
ReferencedResultRelationship
operationRef
referencedResultRole
OperationRole
Numerator
Denominator
analysisOperationRef
AnalysisOperationRef
analysisComponentRef
ProgrammingCode
Code
CodeReference
Context
listOfPlannedOutputs
outputRef
globalDisplaySections
outputs
Output
version
outputDisplays
OutputDisplay
fileSpecifications
File
fileType
style
categoryRefs
analysisCategorizations
AnalysisCategorization
categories
AnalysisCategory
subCategorizations
Display
displayTitle
displaySections
DisplaySection
sectionType
SectionType
Title
Footnote
Legend
Abbreviation
Rowlabel Header
Body Column Header
Body Row Header
Body Cell
subSections
DisplaySubSection
displayValues
DisplayValue
body
Body
bodyAreas
BodyArea
resultCells
rowElements
columnElements
OrderedBodyLine
delimiter
source
text
Objective
Endpoint
Exploratory
Primary
Secondary
covariate
is supported by
is one of
ARS Model Representation using CMAP (DRAFT)

References

Large-scale TFL Automation for regulated Pharmaceutical trials using CDISC Analysis Results Metadata (ARM); Malcolm

Pre-launching CDISC Analysis Results Standards PHUSE US Connect 2023; Busa, LeRoy

Thank You!