

TT10 - PHUSE EU Connect 2023

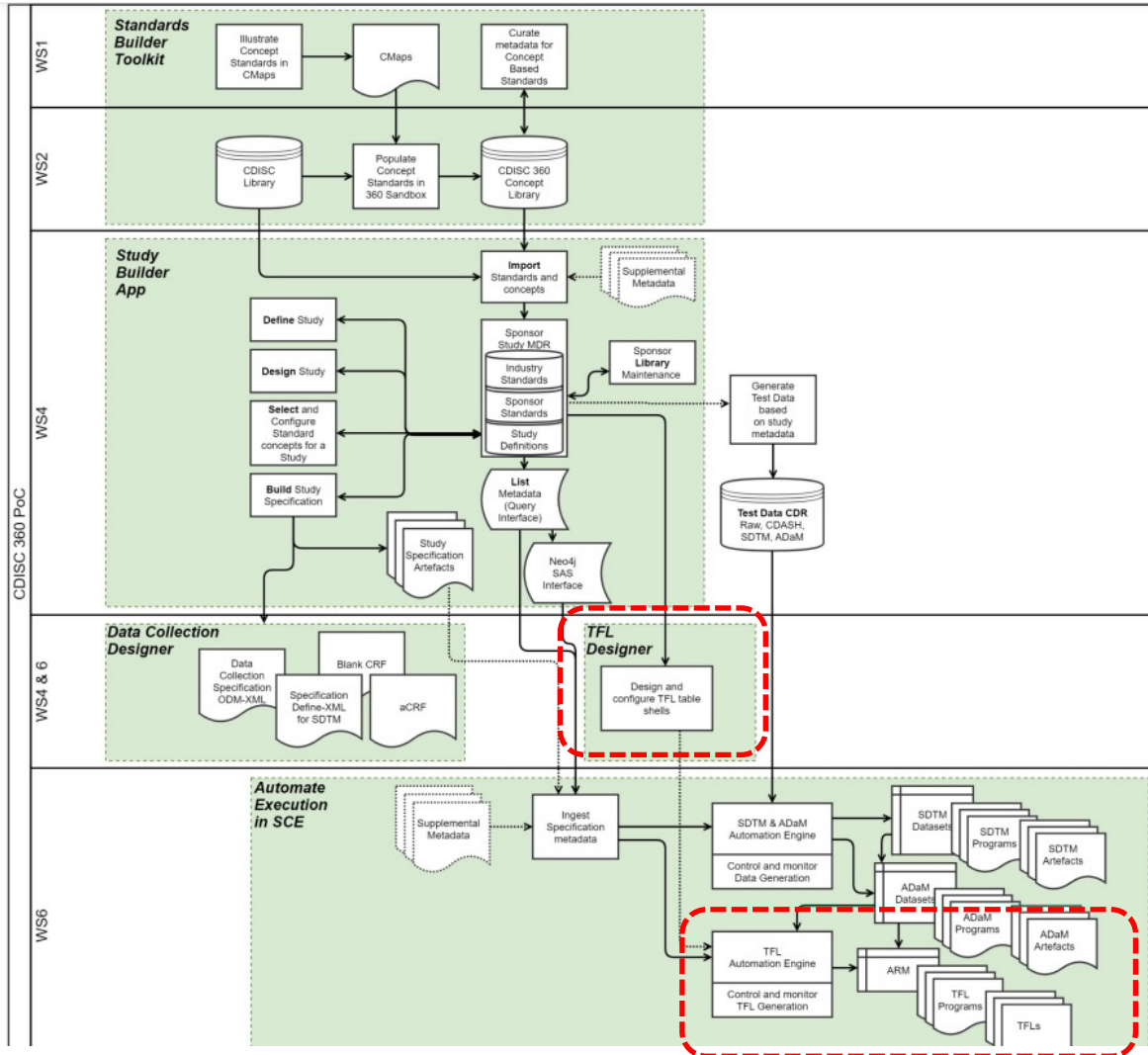
TFL Automation the CDISC 360 way!

**John McDade
Alison Macnab**



Contents

- CDISC 360
- Excel to Web-Application
- Process Flow
- Metadata Management
- TFL code and ADaMs
- Conclusion



“CDISC 360 aims to support standards-based, metadata-driven automation across the end-to-end clinical research data lifecycle.”

Analysis Results Metadata - ARM

Table 14-5.02

Display	Table 14-5.02 [page=3] Incidence of Treatment Emergent Serious Adverse Events by Treatment Group
Analysis Result	Incidence of Treatment Emergent Serious Adverse Events by Treatment Group
Analysis Parameter(s)	
Analysis Variable(s)	AEBODSYS (Body System or Organ Class) AEDECOD (Dictionary-Derived Term)
Analysis Reason	SPECIFIED IN SAP
Analysis Purpose	PRIMARY OUTCOME MEASURE
Data References (incl. Selection Criteria)	ADAE [TRTEMFL = "Y" and AESER = "Y"] ADSL [SAFFL = "Y"] Get denominators for percentages from ADSL and counts and numerators from ADAE. Join ADAE with ADSL based on the unique subject identifier (USUBJID) keeping only records in ADAE for the numerator.
Documentation	Unique count of subjects that experienced an Adverse Event by Preferred Term, System Organ Class, and Treatment Group and percentages based on the number of subjects in the safety population within each treatment group. The total number of times an event occurred was recorded by Preferred Term, System Organ Class, and Treatment Group. Fisher's exact test was used for treatment comparison of event rates. See page 5 (section 11.2) in the Statistical Analysis Plan. Statistical Analysis Plan [page=5]
Programming Statements	[SAS version 9.2] at14-5-02.sas

Analysis Results Metadata - ARM

Study - CDISC 360		Table 14.1.1.1 Demographic characteristics (Safety Population)	
<u>Result</u> ResultOID Description Reason Purpose Dataset WhereClause AnalysisVariable Documentation ProgrammingCode	Characteristics	METFORMIN (N=XX)	HUMAN INSULIN (N=XX)
	Age (years)		
	n	XX	XX
	Mean	XX.X	XX.X
	SD	XX.XX	XX.XX
	Min	XX	XX
	Q25	XX.X	XX.X
	Median	XX.X	XX.X
	Q75	XX.X	XX.X
	Max	XX	XX
	Age Group - n (%)		
	15 - <30 years	XX (XX.X)	XX (XX.X)
	30 - <45 years	XX (XX.X)	XX (XX.X)
	>=45 years	XX (XX.X)	XX (XX.X)
	Gender - n (%)		
	Male	XX (XX.X)	XX (XX.X)
	Female	XX (XX.X)	XX (XX.X)
Max = Maximum. Min = Minimum. N = Number of subjects in treatment group. n = Number of subjects included in analysis. SD = Standard deviation. Datasets used - adsl Executed by <Username> on DDMMYYYY:HH:MM			
		<u>Display</u> DisplayOID Name Title Document	

Analysis Results Metadata - ARM++

Output (Study, Analysis, Group, Filename/Type, Style)

Result
Version
DisplayPattern
Grouping
- AnalysisVar
- ByVar
CodeReference

Study - CDISC 360

Table 14.1.1.1
Demographic characteristics (Safety Population)

Characteristics	METFORMIN (N=XX)	HUMAN INSULIN (N=XX)
Age (years)		
n	XX	XX
Mean	XX.X	XX.X
SD	XX.XX	XX.XX
Min	XX	XX
Q25	XX.X	XX.X
Median	XX.X	XX.X
Q75	XX.X	XX.X
Max	XX	XX
Age Group - n (%)		
15 - <30 years	XX (XX.X)	XX (XX.X)
30 - <45 years	XX (XX.X)	XX (XX.X)
>=45 years	XX (XX.X)	XX (XX.X)
Gender - n (%)		
Male	XX (XX.X)	XX (XX.X)
Female	XX (XX.X)	XX (XX.X)

Max = Maximum. Min = Minimum. N = Number of subjects in treatment group. n = Number of subjects included in analysis. SD = Standard deviation.
Datasets used - adsl
Executed by <Username> on DDMMYYYY:HH:MM

Display

Parent
Version
Grouping:
- Dataset
- WhereClause
- AnalysisVar
- ByVar
Template
Title 1..N
RowLabelHeade
Header 1..N
Footer 1..N

ARM++ Metadata

Study - CDISC 360

Table 14.1.1.1
Demographic characteristics (Safety Population)

Characteristics	METFORMIN (N=XX)	HUMAN INSULIN (N=XX)
Age (years)		
n	XX	XX
Mean	XX.X	XX.X
SD	XX.XX	XX.XX
Min	XX	XX
Q25	XX.X	XX.X
Median	XX.X	XX.X
Q75	XX.X	XX.X
Max	XX	XX
Age Group - n (%)		
15 - <30 years	XX (XX.X)	XX (XX.X)
30 - <45 years	XX (XX.X)	XX (XX.X)
>=45 years	XX (XX.X)	XX (XX.X)
Gender - n (%)		
Male	XX (XX.X)	XX (XX.X)
Female	XX (XX.X)	XX (XX.X)

Max = Maximum. Min = Minimum. N = Number of subjects in treatment group. n = Number of subjects included in analysis. SD = Standard deviation.
Datasets used - adsl
Executed by <Username> on DDMMYYYY:HH:MM

Study	Analysis	Group	Order	DisplayID	DisplayVersion	Filename	Type	StyleID
CDISC	CDISC 360	Safety	1	T14111_SAF_DEMOG	1	tdemog_saf	rtf	table_rtf
CDISC	CDISC 360	Safety	2	T14131_SAF_AE2TIER	1	tae_soc_pt_saf	rtf	table_rtf
CDISC	CDISC 360	Efficacy	3	T1421_EFF	1	tmace_edpt_fas	rtf	table_rtf

Output Display Result WhereClause Style TFL Metadata Tables TFL Metadata ...

DisplayID	DisplayName	DisplayTitle	Title1	Title2	Title3
T14111_SAF_DEMOG	Table 14.1.1.1	Demographic characteristics (SAF)	Study - CDISC 360	Table 14.1.1.1	Demographic characteristics (Safety Population)

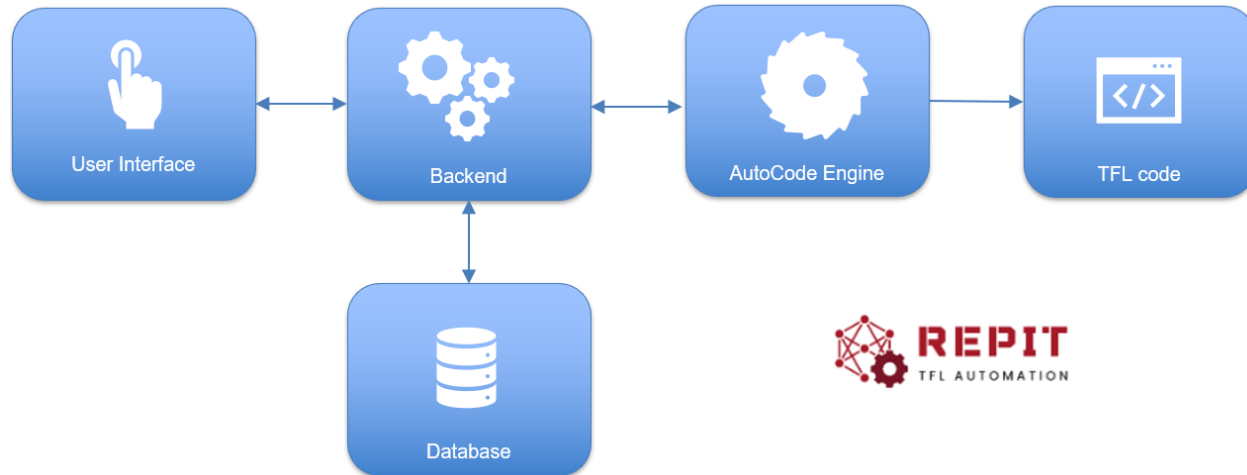
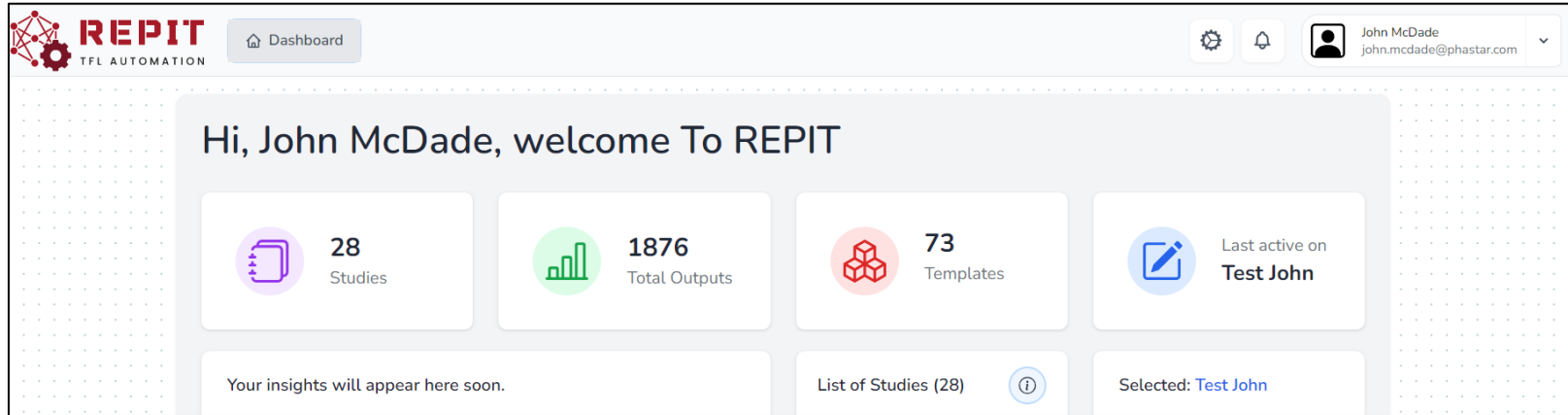
Output Display Result WhereClause Style TFL Metadata Tables TFL Metadata Variables ...

ResultDisplayOID	AnalysisResultOID	Version	ResultDescription	DisplayPattern
T14111_SAF_DEMOG	T14111_01_SAF_DEMOG	1	n	XXX
T14111_SAF_DEMOG	T14111_01_SAF_DEMOG	1	Mean	XX.X
T14111_SAF_DEMOG	T14111_01_SAF_DEMOG	1	SD	XX.XX
T14111_SAF_DEMOG	T14111_01_SAF_DEMOG	1	Min	XX
T14111_SAF_DEMOG	T14111_01_SAF_DEMOG	1	Q25	XX.X
T14111_SAF_DEMOG	T14111_01_SAF_DEMOG	1	Median	XX.X
T14111_SAF_DEMOG	T14111_01_SAF_DEMOG	1	Q75	XX.X

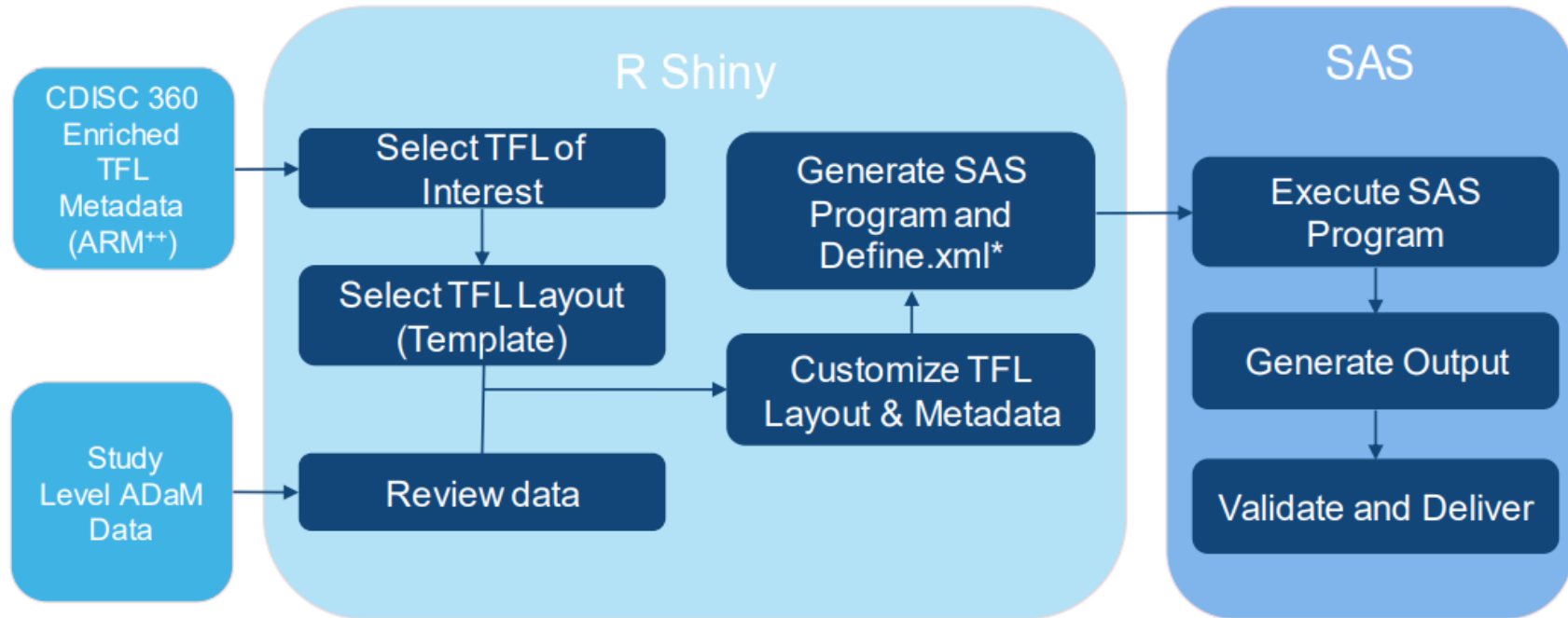
Output Display Result WhereClause Style TFL Metadata Tables TFL Metadata Variables ...

WhereClauseOID	Dataset	Variable	Comparator	Value
T14111_02_SAF_DEMOG_01	ADSL	AGEGR1	EQ	15 <= to <30 years
T14111_02_SAF_DEMOG_02	ADSL	AGEGR1	EQ	30 <= to <45 years
T14111_02_SAF_DEMOG_03	ADSL	AGEGR1	EQ	>=45 years
T14111_03_SAF_DEMOG_01	ADSL	SEX	EQ	M
T14111_03_SAF_DEMOG_02	ADSL	SEX	EQ	F

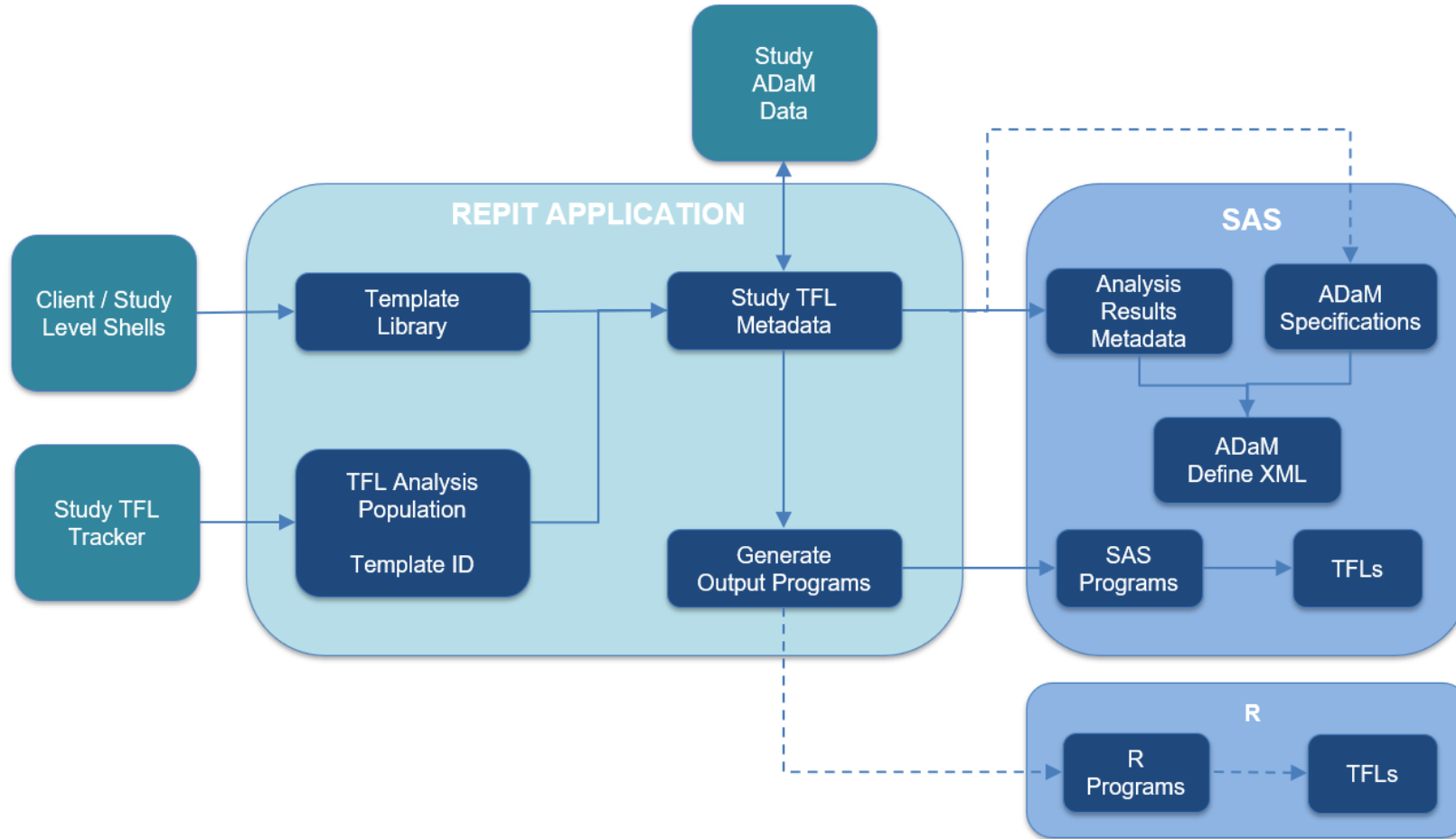
Web Application



CDISC 360 – TFL Automation Proof of Concept



REPIT TFL Automation Workflow



User Interface – Treatment Groups

Treatment Groups

Global Formats

List of tables

Group Label - FASFL

Population = FASFL

Order	Treatment Label	Where Clause		
1	Drug 1^n<<low dose>>	TRT01PN=1	✓	✗
2	Drug 2^n<<high dose>>	TRT01PN=2	✓	✗
3	Total	TRT01PN in (1 2)	✓	✗

Group Label - RANDFL

Population = RANDFL

Order	Treatment Label	Where Clause		
1	Drug 1^n<<low dose>>	TRT01PN=1	✓	✗
2	Drug 2^n<<high dose>>	TRT01PN=2	✓	✗
3	Total	TRT01PN in (1 2)	✓	✗

Group Label - SAFFL

Population = SAFFL

Order	Treatment Label	Where Clause		
1	Drug 1^n<<low dose>>	TRT01AN=1	✓	✗
2	Drug 2^n<<high dose>>	TRT01AN=2	✓	✗

Output Type	Output Number	Title	Population	REPIT Template Category	REPIT Unique Template ID
All Adverse Events					
Table	14.3.2.1.1	Overall summary of adverse events - subject count <<Period>> (Safety set)	SAFFL	EVENTSUM	PHAE01
Table	14.3.2.1.2	Overall summary of adverse events <<optional text>> - subject count ([[Safety set]])	SAFFL	EVENTSUM	PHAE01A
Table	14.3.2.1.3	Overall summary of adverse events <<optional text>> - event count ([[Safety set]])	SAFFL	EVENTSUM	PHAE01B
Table	14.3.2.2	Adverse events by system organ class and preferred term <<- Period>> (Safety set)	SAFFL	EVENTS2	PHAE02A
Table	14.3.2.3.1	Adverse events of special interest by system organ class and preferred term <<- Period>> (Safety set)	SAFFL	EVENTS2	PHAE02B
Table	14.3.2.4	Adverse events sorted by decreasing frequency on preferred term level <<- Period>> (Safety set)	SAFFL	EVENTS1	PHAE03
Table	14.3.2.5.1	Adverse events by maximum intensity on preferred term level <<- Period>> (Safety set)	SAFFL	EVENTS3	PHAE04

User Interface – Treatment Groups

Treatment Columns			
Treatment group for table			Treatment column header formatting
SAFFL			Column header text
Population Flag	Order	Treatment Label	
SAFFL	1	Drug 1^n<<low dose>>	
SAFFL	2	Drug 2^n<<high dose>>	
SAFFL	3	Total	

	Line	Text	
	1	[TREAT X]	
	2	N=xxx	
	3	n (%)	

	Drug 1 <<low dose>> N=8	Drug 2 <<high dose>> N=9	Total N=17
	n (%)	n (%)	n (%)
System organ class			
Preferred term			
(MedDRA version 25.0)			
Any Adverse Events	8 (100)	9 (100)	17 (100)
INFECTIONS AND INFESTATIONS	5 (62.5)	5 (55.6)	10 (58.8)
COVID-19	3 (37.5)	3 (33.3)	6 (35.3)
Fungal skin infection	1 (12.5)	0	1 (5.9)
Herpes virus infection	1 (12.5)	0	1 (5.9)
Herpes zoster	1 (12.5)	0	1 (5.9)
Latent tuberculosis	0	1 (11.1)	1 (5.9)

Output Formats

	Statistic	Drug 1 <<low dose>> N=8	Drug 2 <<high dose>> N=9
Age (years)	n	8	9
	Mean	68.9	67.9
	SD	7.57	5.51
	Min	52	62
	Median	71.5	66.0
	Max	77	75
Age group (years)			
>=12 - <18	n (%)	0	0
>=18 - < 65	n (%)	1 (12.5)	4 (44.4)
>= 65	n (%)	7 (87.5)	5 (55.6)
Missing	n (%)	0	0
Sex			
Male	n (%)	6 (75.0)	7 (77.8)
Female	n (%)	2 (25.0)	2 (22.2)
Total	n (%)	8 (100)	9 (100)
Missing	n (%)	0	0

1

2

3

Format: SUMSTAT_1A					Add new label
Order	Label	Source condition	Statistics	Actions	
1	n		N		
2	Mean		MEAN		
3	SD		STD		
4	Min		MIN		
5	Median		MEDIAN		
6	Max		MAX		

Format: AGECAT_1A					Add new label
Order	Label	Source condition	Statistics	Actions	
1	>=12 - <18	AGE>=12 AND AGE<18	NSubj COL%		
2	>=18 - < 65	AGE>=18 AND AGE<65	NSubj COL%		
3	>= 65	AGE>=65	NSubj COL%		
4	Missing	AGE=.	NSubj COL%		

Format: GENDER_1A					Add new label
Order	Label	Source condition	Statistics	Actions	
1	Male	SEX="M"	NSubj COL%		
2	Female	SEX="F"	NSubj COL%		
3	Total	SEX ne ""	NSubj COL%		
4	Missing	SEX=""	NSubj COL%		

Output Formats

Block Level	Block Order	Block Indent	Block title	Source Table	Source Column	Block Filter	Format	Decimal	Sort By		
1	1	0	Age (years)	ADSL	AGE		SUMSTAT_1A	0		✓	✗
2	0	0	Age group (years)							✓	✗
2	1	1	n (%)	ADSL	AGE		AGECAT_1A			✓	✗
3	0	0	Sex							✓	✗
3	1	1	n (%)	ADSL	SEX		GENDER_1A			✓	✗

	Statistic	Drug 1 <<low dose>> N=8	Drug 2 <<high dose>> N=9
Age (years)	n	8	9
	Mean	68.9	67.9
	SD	7.57	5.51
	Min	52	62
	Q1	67.0	63.0
	Median	71.5	66.0
	Q3	72.5	73.0
	Max	77	75

Format = SUMSTAT_1B					Add new label	
Order	Label	Source condition	Statistics		Actions	
1	n	✎	✎ N	▼	✓	✗
2	Mean	✎	✎ MEAN	▼	✓	✗
3	SD	✎	✎ STD	▼	✓	✗
4	Min	✎	✎ MIN	▼	✓	✗
5	Q1	✎	✎ Q1	▼	✓	✗
6	Median	✎	✎ MEDIAN	▼	✓	✗
7	Q3	✎	✎ Q3	▼	✓	✗
8	Max	✎	✎ MAX	▼	✓	✗

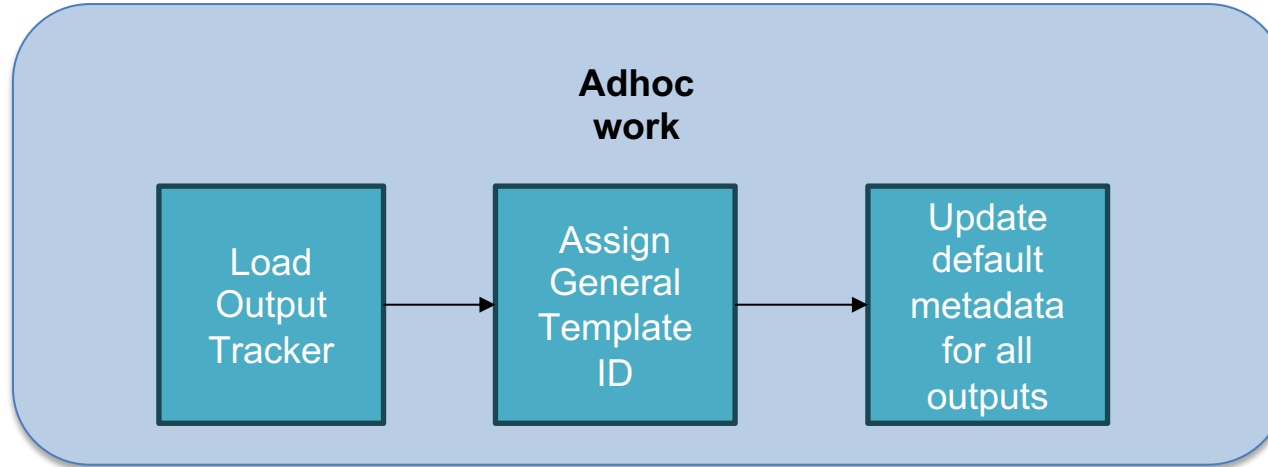
Output Templates – General and Specific

Template ID	Template Category	Template Description
EVENTS1	EVENTS	Events table presenting 1 dictionary variable
EVENTS2	EVENTS	Events table presenting 2 dictionary variables, nested
EVENTS3	EVENTS	Events table presenting 2 dictionary variables, nested, plus additional category variable, e.g., AE severity
EVENTSUM	EVENTS	Summary table presenting counts of subjects per event category
FINDINGA	FINDINGS	Findings table presenting the summary statistics as columns, with column headers containing treatment group labels
FINDINGD	FINDINGS	Findings table presenting the summary statistics as rows, with ID column containing statistics labels
SUMMARY	GENERAL	Summary table presenting frequency counts and/or summary statistics

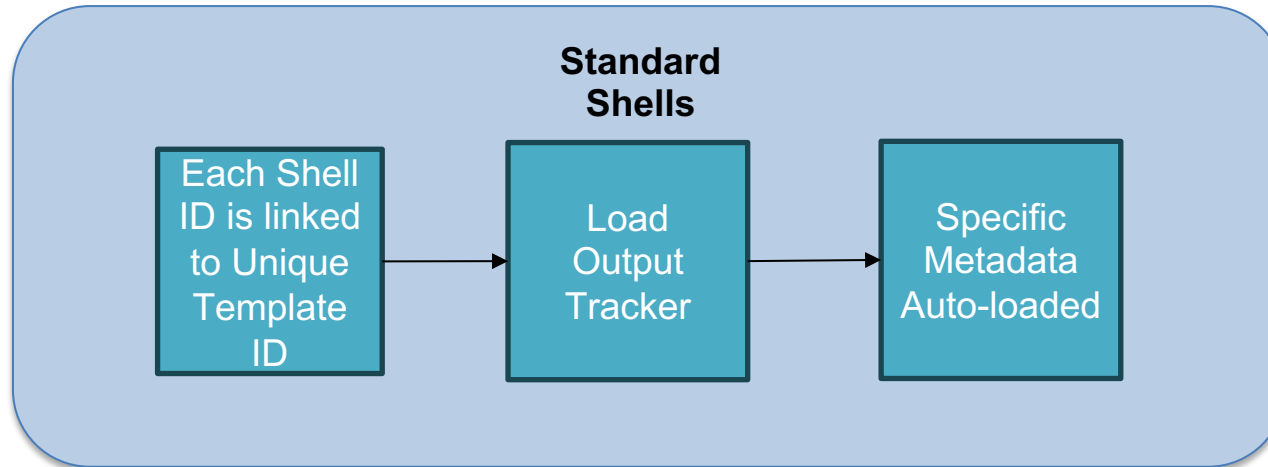
Output Type	Output Number	Title	Output Name	REPIT Template Category	REPIT Unique Template ID
All Adverse Events					
Table	14.3.2.1.1	Overall summary of adverse events - subject count <<-Period>> (Safety set)	ae200	EVENTSUM	PHAE01
Table	14.3.2.1.2	Overall summary of adverse events <<optional text>> - subject count ([[Safety set]])	ae200a	EVENTSUM	PHAE01A
Table	14.3.2.1.3	Overall summary of adverse events <<optional text>> - event count ([[Safety set]])	ae200b	EVENTSUM	PHAE01B
Table	14.3.2.2	Adverse events by system organ class and preferred term <<- Period>> (Safety set)	ae201	EVENTS2	PHAE02A
Table	14.3.2.3.1	Adverse events of special interest by system organ class and preferred term <<- Period>> (Safety set)	ae202	EVENTS2	PHAE02B
Table	14.3.2.4	Adverse events sorted by decreasing frequency on preferred term level <<- Period>> (Safety set)	ae203	EVENTS1	PHAE03
Table	14.3.2.5.1	Adverse events by maximum intensity on preferred term level <<- Period>> (Safety set)	ae204	EVENTS3	PHAE04
Table	14.3.2.5.2	Adverse events by maximum CTCAE grade on preferred term level ([[Safety set]])	ae204a	EVENTS3	PHAE04A

Output Templates – Building versus Loading

Building Outputs



Loading Outputs



Output Templates – Different Views, Same Metadata

Table 14.3.6.1 Haematology and clinical chemistry laboratory variables over time (Safety analysis set)

Lab Parameter	Treatment	Timepoint	Result							
			n	Mean	SD	Min	Median	Max	Q1	Q3
B-Hemoglobin (g/L)	Drug 1 (N=8)	Baseline	8	114.0	14.25	92	113.5	136	104.0	124.5
		Cycle 02	6	123.2	14.44	104	124.5	141	110.0	135.0
		Cycle 03	8	124.9	16.95	106	125.0	150	107.5	139.0

Table 14.3.6.12 Haematology and clinical chemistry laboratory variables over time (Safety analysis set)

		Result							
Parameter	Treatment Timepoint	n	Mean	SD	Min	Median	Max	Q1	Q3
B-Hemoglobin (g/L)	Drug 1 (N=8) Baseline	8	114.0	14.25	92	113.5	136	104.0	124.5
	Cycle 02	6	123.2	14.44	104	124.5	141	110.0	135.0
	Cycle 03	8	124.9	16.95	106	125.0	150	107.5	139.0

Table 14.3.6.11 Haematology and clinical chemistry laboratory variables over time (Safety analysis set)

B-Hemoglobin (g/L)		Result							
Treatment		n	Mean	SD	Min	Median	Max	Q1	Q3
Timepoint									
Drug 1 (N=8)	Baseline	8	114.0	14.25	92	113.5	136	104.0	124.5
	Cycle 02	6	123.2	14.44	104	124.5	141	110.0	135.0
	Cycle 03	8	124.9	16.95	106	125.0	150	107.5	139.0

Output Templates – Stored Metadata

Block Level	Block Order	Block Indent	Block title	Source Table	Source Column	Block Filter	Format	Decimal	Sort By		
1	1	0	&__subjects. screened	ADSL		ENRFL="Y"	DOEVENT_1B			☒	☐
1	2	0	Screen failures	ADSL		SCFFL="Y"	DOEVENT_1B			☒	☐
1	3	1	[STATS]	ADSL	DCSREAS	SCFFL="Y"	DCSREAS_1A			☒	☐
2	1	0	&__subjects. started treatme	ADSL		SAFFL="Y" and TR01SDT ne .	DOEVENT_1A			☒	☐
2	2	0	&__subjects. completed trea	ADSL		EOTSTT="COMPLETED"	DOEVENT_1A			☒	☐
2	3	0	&__subjects. discontinued tr	ADSL		EOTSTT="DISCONTINUED"	DOEVENT_1A			☒	☐
2	4	1	[STATS]	ADSL	DCTREAS	EOTSTT="DISCONTINUED"	DCTREAS_1A			☒	☐
3	1	0	&__subjects. ongoing on trea	ADSL		EOTSTT="ONGOING"	DOEVENT_1A			☒	☐
3	2	0	&__subjects. ongoing in stud	ADSL		EOSSTT="ONGOING"	DOEVENT_1A			☒	☐
4	1	0	&__subjects. completed stud	ADSL		EOSSTT="COMPLETED"	DOEVENT_1A			☒	☐
4	2	0	&__subjects. withdrawn from	ADSL		EOSSTT="DISCONTINUED"	DOEVENT_1A			☒	☐

Block Level	Block Order	Block Indent	Block title	Source Table	Source Column	Block Filter	Format	Decimal	Sort By		
1	1	0	Age (years)	ADSL	AGE		SUMSTAT_1A	0		☒	☐
2	0	0	Age group (years)							☒	☐
2	1	1	n (%)	ADSL	AGE		AGECAT_1A			☒	☐
3	0	0	Sex							☒	☐
3	1	1	n (%)	ADSL	SEX		GENDER_1A			☒	☐
4	0	0	Race							☒	☐
4	1	1	n (%)	ADSL	RACE		RACE_1A			☒	☐
5	0	0	Ethnicity							☒	☐
5	1	1	n (%)	ADSL	ETHNIC		ETHNIC_1A			☒	☐
6	0	0	Country							☒	☐
6	1	1	n (%)	ADSL	COUNTRY		COUNTRY_1A			☒	☐

TFL Code

- Pagination
- Zero filling
- Column width and alignment
- Decimal Precision
- Indentation
- Null reporting

```
*****
*
* Program Name       : ae201.sas
* Protocol / Study   : TESTAREA\REPIT\Development\REPIT Master
* Type               : TFL Generation
* Description        : table 14.3.2.2 adverse events by system organ class and preferred term (safety se
*
* Author            : John McDade
*
* Date Created       : 10SEP2023
* Input Dataset      : ADAM.ADAE, ADAM.ADSL
* Macros Used        : REPIT_DOEVENTS CHECKLOG RSTART RSTOP
* Files Used         :
* Status:            : in progress
*****
* Change History
* Changed By        :
* Reason for Change :
* Date Changed      :
*****;
```

```
** Proc report to generate output **;

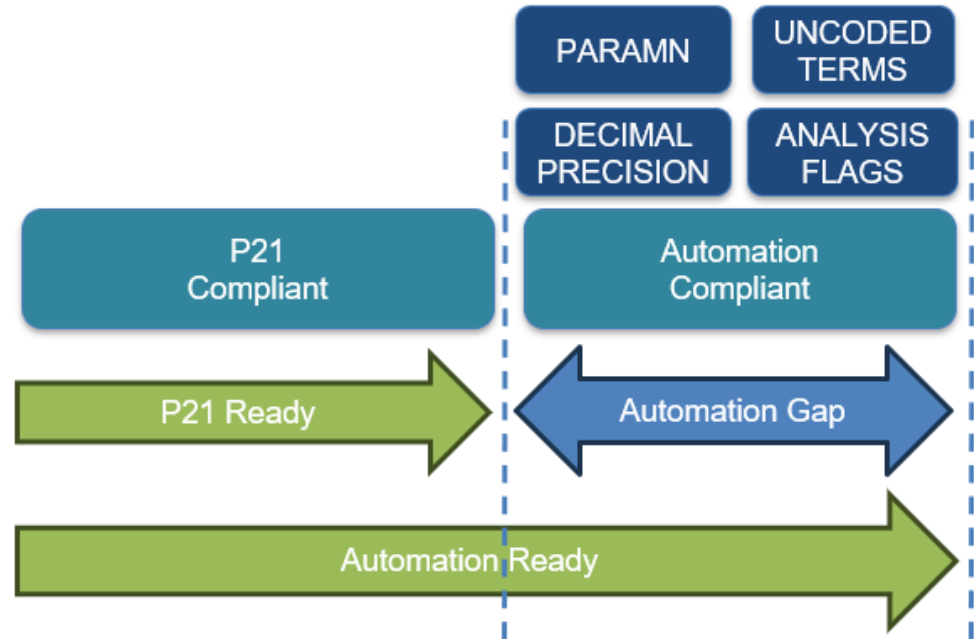
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ods escapechar='^';

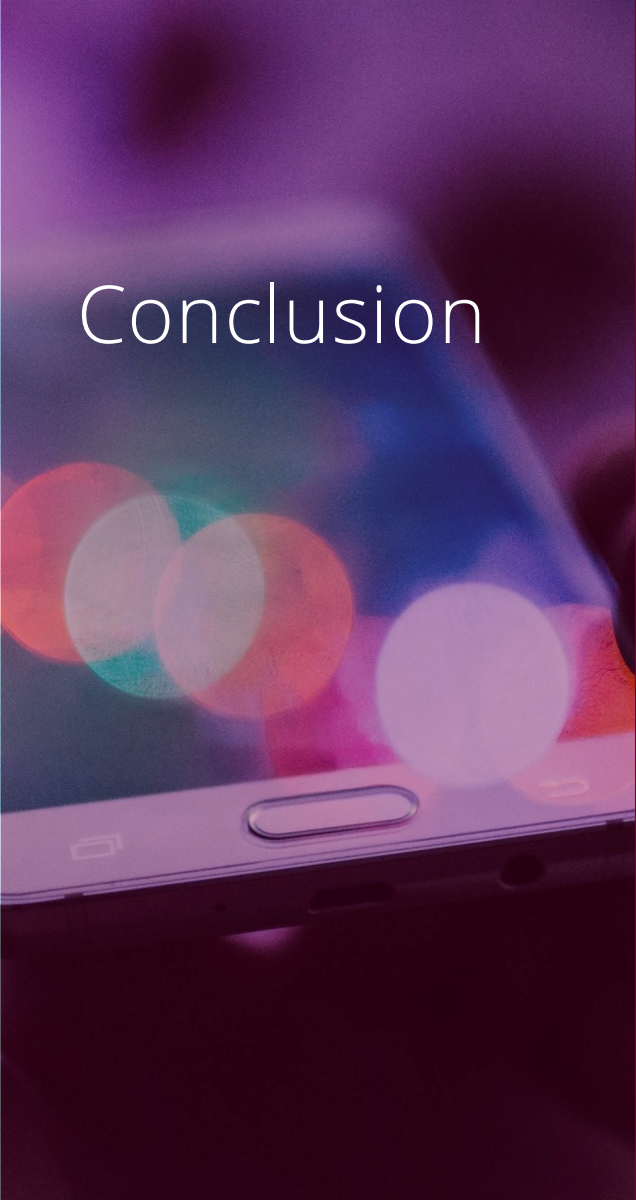
%if & repit_nobs > 0 %then %do;
% proc report data = tab_l4_3_6_1 missing spanrows split='~'
    style(report)=[asis=on protectspecialchars=off cellspacing=0]
    style(column)=[asis=on protectspecialchars=off]
    style(header column)=[asis=off protectspecialchars=off rules=none fontsize=9pt];

    column rowblk rowidl rowtitel col101 col102 col103;
    define rowblk / order order=internal noprint;
    define rowidl / order order=internal noprint;
    define rowtitel / group id "Specific adverse event of interest" style(header column)=[just=1] style(column)=[just=1]
    define col101 / display style(column)=[just=1 asis=on cellwidth=20% pretext=""] flow style(header)=[asis=on];
    define col102 / display style(column)=[just=1 asis=on cellwidth=20% pretext=""] flow style(header)=[asis=on];
    define col103 / display style(column)=[just=1 asis=on cellwidth=20% pretext=""] flow style(header)=[asis=on];
    compute after rowblk;
        line ' ';
    endcomp;
run;
%end;
```

ADaM Quality

- Analysis Ready
- Early Compliance checking
- Specification / Define.xml process





Conclusion

By breaking TFLs into modular components aligned with CDISC 360 vision, we can create a very fluid workflow allowing us to automate outputs efficiently.

Key benefits from this approach are:

- TFL creation time
- Analysis Results Metadata creation
- Ease of global updates
- ADaM quality and consistency

Future Development

- Integration of R code automation
- ADaM specification and code generation
- Interactive outputs
- Additional tools to interact with metadata

Acknowledgements:

- Application Developer – Rajwanur Rahman
- Code Automation Developer – Spencer Renyard
- Testing, Training and Support – Nuala Gallagher, Scott Kosten

Thank You!

Questions?

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Web: www.PHASTAR.com