



OPTIMIZING OUTPUT REVIEW: A TARGETED AND SCALABLE RTF VALIDATION FRAMEWORK

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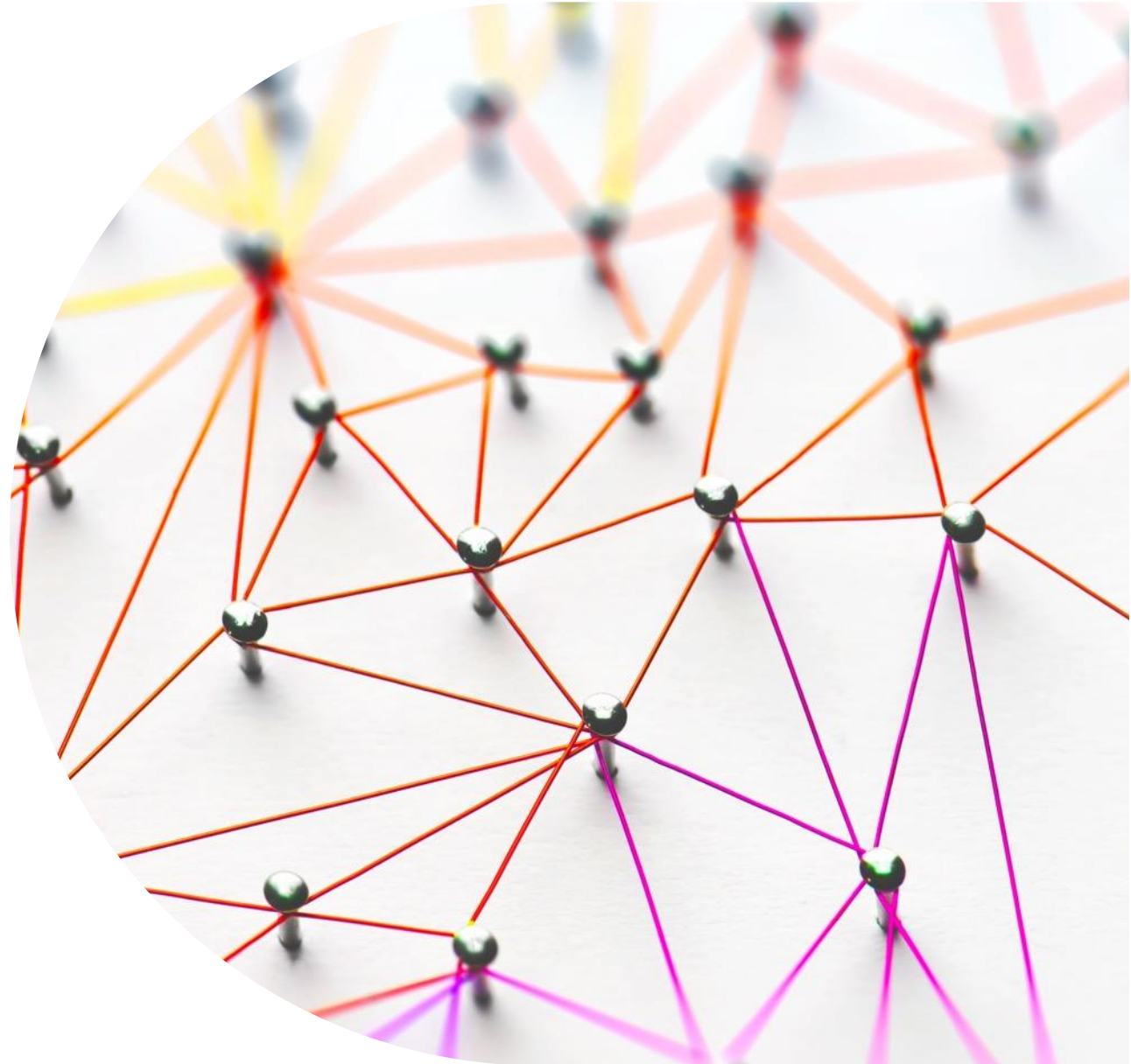
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SUMMARY

VALIDATION OF TLF RTF OUTPUT

- Clinical Programming and Biostatistics teams operate under tight timelines while delivering accurate, submission-ready Tables, Figures, and Listings (TFLs).
- Traditionally, TLF outputs undergo independent QC through double programming, including re-creation of final SAS datasets.
- While this approach is effective for data validation, review of the final RTF outputs remains largely manual
- Manual TFL review is resource-intensive and prone to oversight, particularly in large or complex studies with frequent data cuts.
- This challenge becomes more pronounced when TLF packages are delivered by a CRO, where sponsors are expected to perform a sanity check and QC within a very short timeline (typically 3–5 days).
- Deliverables in these scenarios are almost always RTF outputs, and a common workaround is to convert RTF outputs back into SAS datasets and perform a tertiary PROC COMPARE, which is:
- Time-consuming, Resource-intensive, Ineffective at detecting formatting and presentation issues

Selective QC

- Focuses on a subset of outputs, often topline tables only
- situational QC approach driven by practical constraints
- Phase 1 studies, ISS Component studies
- Commonly used during CRO-to-sponsor handoffs
- Selection based on:
 - Tight timelines (e.g., 3 - 5 days)
 - Limited reviewer resources
 - Large volume of outputs
- Relies heavily on manual review and reviewer judgment
- Validation depth may vary across studies and reviewers
- Higher risk of missed presentation or formatting issues
- Key Message: Selective QC helps manage time pressure but introduces variability and residual quality risk.

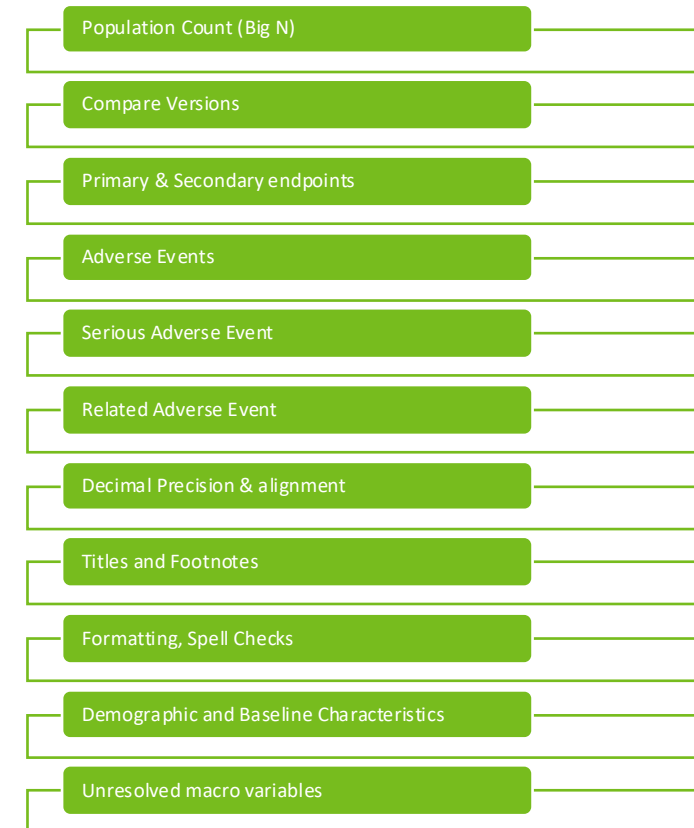
Target QC

- In many studies, full independent QC is not required, and a targeted QC approach is adopted by directly reviewing high-risk outputs.
- Result: Reviewers spend significant effort validating outputs, yet key presentation risks remain.
- Challenge: There is no efficient, scalable, and automated approach to directly validate RTF outputs within tight delivery timelines.
- Manual Review Burden - Manually reviewing hundreds of RTF outputs requires significant time and resources, creating bottlenecks in tight submission timelines.
- Reviewers must verify, across numerous files:
 - Population counts and row consistency
 - Decimal precision
 - Alignment and formatting
 - Spelling, titles, footnotes, and page breaks

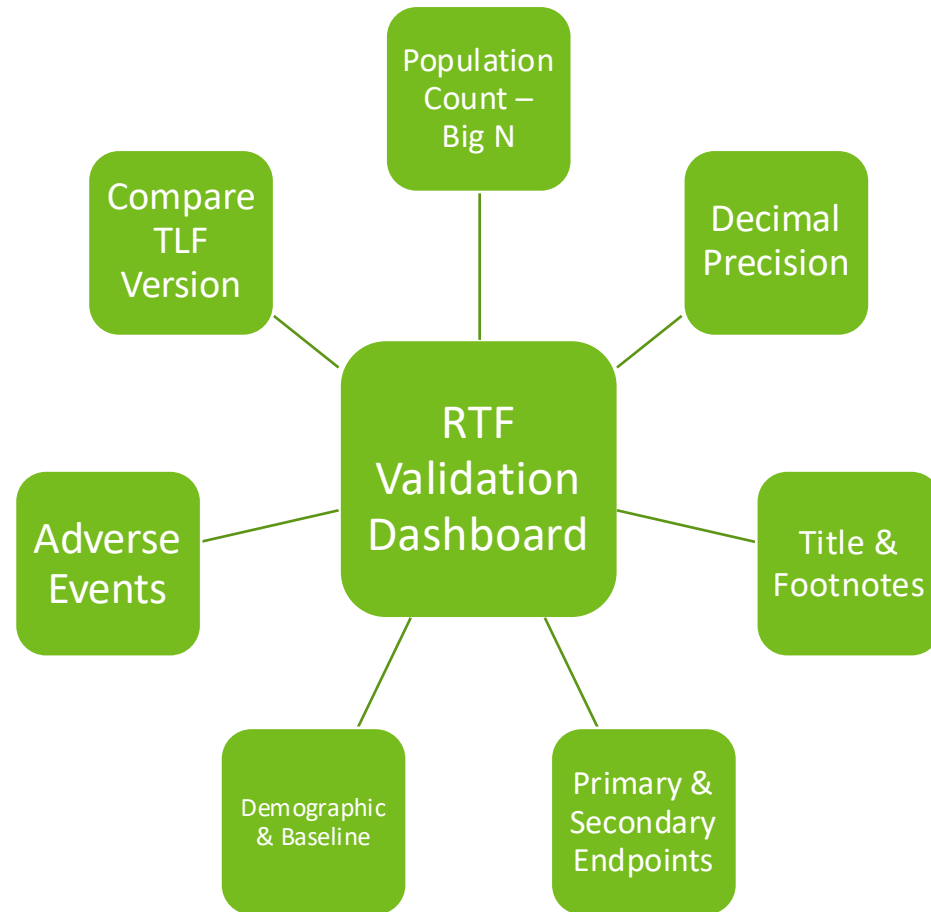
RTF VALIDATION FRAMEWORK

Objectives of the Framework

- Automatically detect and summarize row-level changes between TFL version
- Minimize the number of TFL pages requiring human review
- Provide traceable, reproducible, and audit-ready reviewer artifacts
- Reduced manual review cycles
- Improved traceability and audit readiness
- Seamless integration into existing SAS/R workflows
- a practical, reproducible workflow that leverages R, Python & SAS for automated change detection for interactive review.
- By identifying and surfacing only meaningful differences between TFL cuts, the approach reduces manual rework, improves review efficiency, and provides an auditable framework suitable for regulated clinical environments.



RTF VALIDATION FRAMEWORK

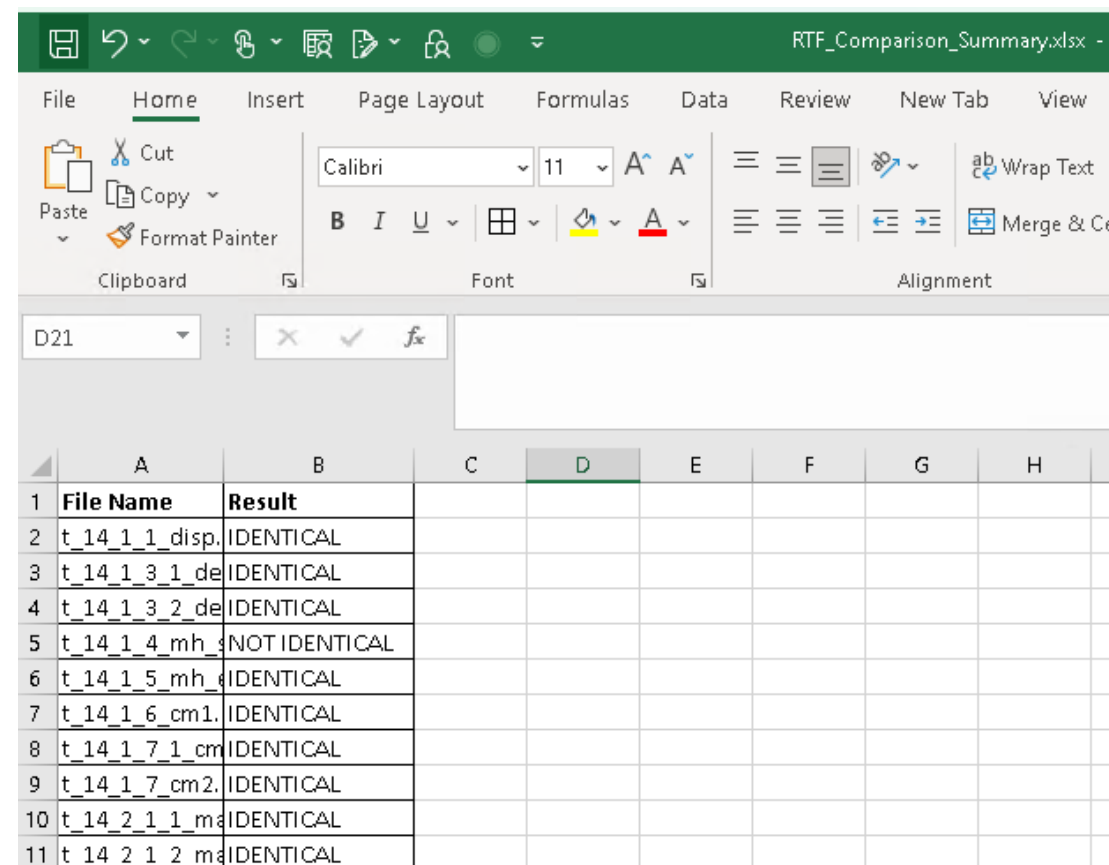


- The proposed approach integrates automated data and metadata validation using R, Python, SAS
- Provides with independent cross-validation of statistical summaries through interactive Smartsheet dashboards.
- These dashboards enable reviewers to rapidly identify discrepancies, trends, and anomalies across outputs.
- The framework supports reproducible validation, reduces manual review cycles, and improves collaboration and communication among programming, statistics, and study teams.
- Examples based on typical clinical trial deliverables demonstrate how these workflows can be incorporated into existing processes without disrupting established standards.

RTF COMPARISON – PYTHON USE CASE

Automatically detect differences between two TLF deliveries by comparing RTF outputs directly.

- Approach
- Read RTF files from two delivery folders and perform line-by-line comparison
- Capture differences in:
 - Content
 - Formatting-related text
- Generate:
 - Text-based diff files
 - Excel summary for reviewers
- Key Python Libraries
- striprt – extract readable text from RTF
- difflib – detect line-level differences
- openpyxl – generate reviewer-friendly Excel summaries
- This helps eliminate manual side-by-side RTF review
- Scales to hundreds of outputs
- Works directly on CRO delivered files



	A	B	C	D	E	F	G	H
1	File Name	Result						
2	t_14_1_1_disp.	IDENTICAL						
3	t_14_1_3_1_de	IDENTICAL						
4	t_14_1_3_2_de	IDENTICAL						
5	t_14_1_4_mh_s	NOT IDENTICAL						
6	t_14_1_5_mh_s	IDENTICAL						
7	t_14_1_6_cm1.	IDENTICAL						
8	t_14_1_7_1_cm	IDENTICAL						
9	t_14_1_7_cm2.	IDENTICAL						
10	t_14_2_1_1_ma	IDENTICAL						
11	t_14_2_1_2_ma	IDENTICAL						

POPULATION COUNTS – BIG N

Table 14.1.1
Summary of Participant Disposition and Analysis Sets
ITT Analysis Set



	Treatment (N=236)	Placebo (N=237)	Overall (N=473)
Analysis Populations			
ITT Analysis Set [1]	236 (100%)	237 (100%)	473 (100%)
Safety (SAF) Analysis Set [2]	201 (85.16%)	204 (85.73%)	405 (85.73%)
mITT Analysis Set [3]	199 (84.32%)	200 (84.31%)	399 (85.33%)

Table 14.1.3.2
Summary of Demographic and Baseline Characteristics
Safety (SAF) Analysis Set



Variable Statistics	Treatment (N=201)	Placebo (N=204)	Overall (N=405)
Age as reported at time of consent (years)			
n	201	234	435
Mean (SD)	68.3 (9.29)	68.9 (8.12)	68.6 (8.72)
Median	69.0	70.0	70.0
Min, Max	28, 85	26, 85	26, 85
Gender			
Female	101 (45.49%)	103 (43.16%)	204 (44.33%)
Male	100 (54.51%)	101 (56.84%)	201 (55.67%)

R SHINY USE CASE

```
library(shiny)
library(dplyr)
library(readxl)
library(writexl)
library(striprtf)
library(stringr)

ui <- fluidPage(
  titlePanel("RTF Population (Big N) Extractor"),
  sidebarLayout(
    sidebarPanel(
      fileInput("folder", "Select Folder Containing RTF Files", multiple = TRUE, accept = ".rtf"),
      textInput("treatment1", "Enter Treatment 1 Name", value = "Treatment"),
      textInput("treatment2", "Enter Treatment 2 Name", value = "Placebo"),
      downloadButton("downloadData", "Download Excel")
    ),
    mainPanel(
      tableOutput("extractedData")
    )
  )
)

server <- function(input, output) {
  extract_big_n <- function(file_path, treatment1, treatment2) {
    rtf_text <- read_rtf(file_path)
    extracted_T1 <- na.omit(str_extract(rtf_text, paste0(treatment1, "[^]*\\)")))
    extracted_T2 <- na.omit(str_extract(rtf_text, paste0(treatment2, "[^]*\\)")))
    data.frame(File = basename(file_path), T1 = ifelse(length(extracted_T1) > 0, extracted_T1[1], NA),
  )
}
```

RTF Population (Big N) Extractor

Enter Folder Path Containing RTF Files

Enter Treatment 1 Name

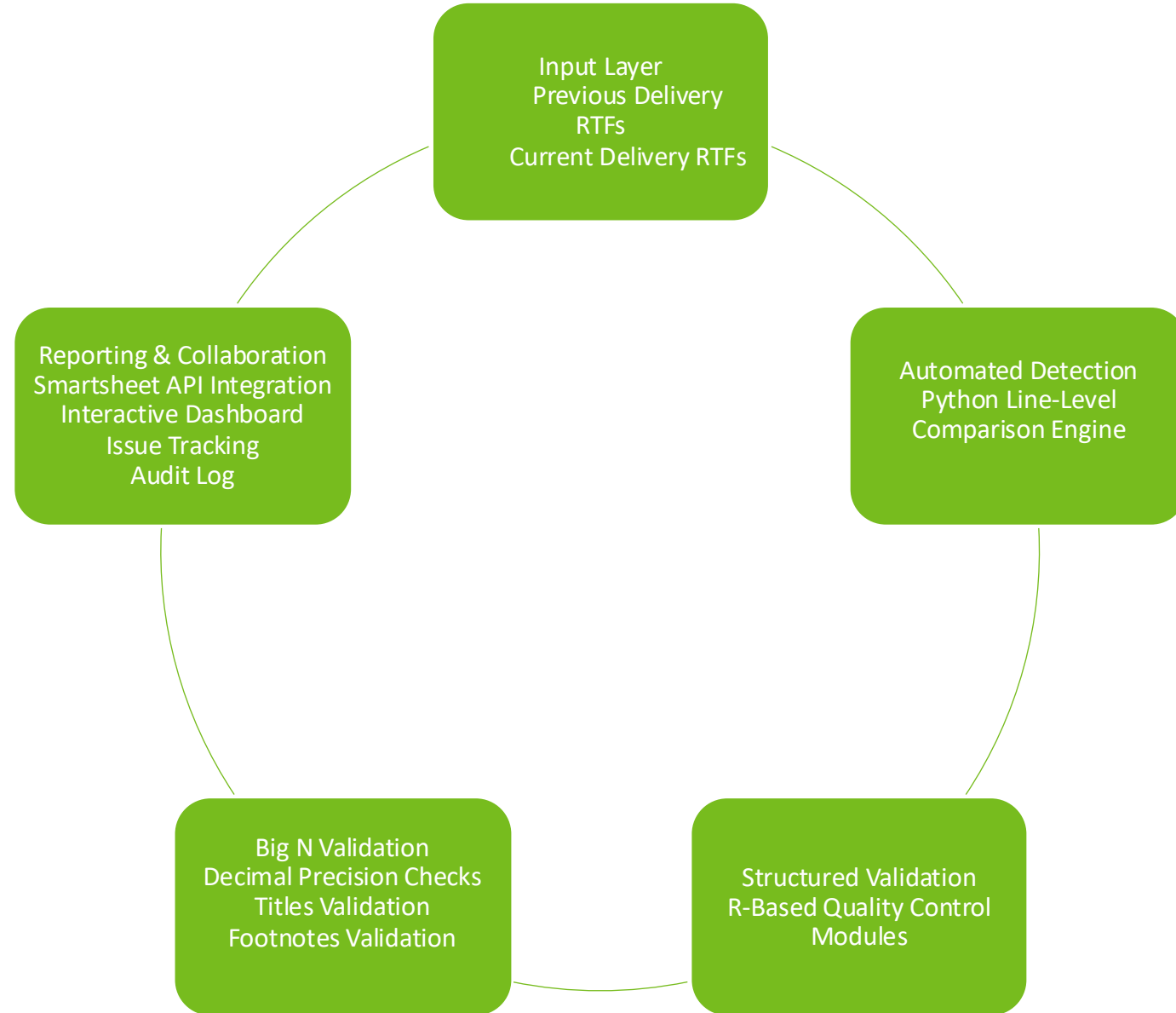
Enter Treatment 2 Name

 Download Excel

 Download Excel

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WORKFLOW - AUTOMATED DELIVERY VALIDATION FRAMEWORK



REVIEW OF RTF OUTPUTS

Sponsor
Protocol:

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Table 14.1.6
Summary of Prior Medications by ATC Level 3 and Preferred Term
Safety (SAF) Analysis Set

+	Anatomic Therapeutic Class (ATC) Level 3 Preferred Term [n (%)]	Treatment (N=201)	Placebo (N=204)	Overall (N=405)
	Participants taking at least 1 Prior Medication	62 (26.61%)	72 (30.77%)	134 (28.69%)
	Adrenergics For Systemic Use	0	1 (0.43%)	1 (0.21%)
	Epinephrine	0	1 (0.43%)	1 (0.21%)
	Adrenergics, Inhalants	1 (0.43%)	1 (0.43%)	2 (0.43%)
	Fluticasone Propionate;salmeterol Xinafoate	1 (0.43%)	0	1 (0.21%)
	Salbutamol	0	1 (0.43%)	1 (0.21%)
	All Other Therapeutic Products	0	1 (0.43%)	1 (0.21%)
	All Other Therapeutic Products	0	1 (0.43%)	1 (0.21%)
	Angiotensin Ii Receptor Blockers (Arbs), Plain	3 (1.29%)	2 (0.85%)	5 (1.07%)
	Losartan	0	1 (0.43%)	1 (0.21%)
	Olmesartan	1 (0.43%)	1 (0.43%)	2 (0.43%)
	Valsartan	2 (0.86%)	0	2 (0.43%)



Table 14.3.1.1
Overview of Adverse Events
Safety (SAF) Analysis Set

Category [n (%)]	Treatment		
	Placebo		
Category [n (%)]	Treatment	Placebo	Overall
	(N=201)	(N=204)	(N=405)
Participants with any adverse event	200 (97.00%)	191 (81.62%)	391 (89.29%)
Participants with TEAEs	199 (94.85%)	177 (75.64%)	376 (85.22%)
Participants with			
Severe TEAEs	14 (6.01%)	10 (4.27%)	24 (5.14%)
Moderate TEAEs	109 (46.78%)	78 (33.33%)	187 (40.04%)
Mild TEAEs	98 (42.06%)	89 (38.03%)	187 (40.04%)

Table 14.3.1.2
Summary of TEAE by System Organ Class and Preferred Term
Safety (SAF) Analysis Set

System Organ Class Preferred Term	Treatment		
	Placebo		
System Organ Class Preferred Term	Treatment	Placebo	Overall
	(N=201)	(N=204)	(N=405)
Participants with at least 1 TEAE	201 (94.85%)	177 (75.64%)	378 (85.22%)
Blood And Lymphatic System Disorders	6 (2.58%)	5 (2.14%)	11 (2.36%)
Anaemia	3 (1.29%)	0	3 (0.64%)
Leukopenia	1 (0.43%)	0	1 (0.21%)
Lymphadenopathy	1 (0.43%)	1 (0.43%)	2 (0.43%)
Lymphocytosis	0	1 (0.43%)	1 (0.21%)
Thrombocytopenia	1 (0.43%)	1 (0.43%)	2 (0.43%)
Thrombocytosis	0	2 (0.85%)	2 (0.43%)

Forms Connections Dynamic View

RTF Validation Dashboard ☆

Line ID	Unique / Repeated	ProglID	TLF Number	Title 1	Title 2	Footnote 1	Footnote 2	Footnote 3	Footnote 4	Footnote 5	Footnote 6
	Table	14.1.1	Table 14.1.1	Summary of Participant Disposition and Analysis Sets	ITT Analysis Set	All percentages are based on the ITT analysis set.	[1] All participants who are randomized to this study. Participants in this analysis set will be analyzed according to their randomized treatment arm.	[2] All participants who received at least 1 dose of study drug. The safety analysis set will be the primary analysis set for all safety analyses and participants will be analyzed according to the actual treatment received on Study Day 1.	[3] All the participants in the ITT analysis set who received at least one dose of study drug and have one post-baseline efficacy measurement. The mITT analysis set will be the primary analysis set for all efficacy analyses and participants in the mITT analysis set will be analyzed according to their randomized treatment arm. Also referred to as the Evaluable Analysis Set.	[4] All the participants included in mITT analysis set without any major protocol deviations potentially affecting efficacy. Participants in Per-protocol analysis set will be analyzed according to their randomized treatment arm.	[5] All participants who received at least 1 dose of study drug and have at least 1 reportable plasma concentration.

ions Dynamic View

RTF Validation Dashboard ☆

RTF Comparison Summary	Title Check	Footnotes	Page Break	Order of Treatment Column	Population - Big N - Treatment	Big N - Placebo	Decimal Precision
Identical	OK	!error	OK	OK	Treatment (N=201)	Placebo (N=204)	OK

R SHINY - DECIMAL PRECISION

COUNTS

- Ensuring decimal consistency across all outputs, as defined in the SAP, is essential.
- The lead programmer is responsible for verifying that all outputs adhere to the specified decimal precision.
- The program captures actual decimal precision in outputs, compares it against SAP-defined precision, and flags discrepancies.
- The R package Striprtf is used to read RTF files, with further processing using stringr, dplyr, dt, and Shiny.
- The Shiny interface allows users to input file locations and review flagged inconsistencies efficiently.



RTF Decimal Precision Checker

Enter Folder Path:

Show entries
Search:

	FileName	Content	ConsistentDecimalPlaces
318	t_14_3_2_4_1_eg_visit.rtf	* Mean (SD) 69.0 69.0	false
324	t_14_3_2_4_1_eg_visit.rtf	* Mean (SD) -5.0 -5.0	false
696	t_14_3_2_4_1_eg_visit.rtf	* Mean (SD) 135.0 135.0	false
702	t_14_3_2_4_1_eg_visit.rtf	* Mean (SD) 6.0 6.0	false
1074	t_14_3_2_4_1_eg_visit.rtf	* Mean (SD) 93.0 93.0	false
1080	t_14_3_2_4_1_eg_visit.rtf	* Mean (SD) 6.0 6.0	false
1452	t_14_3_2_4_1_eg_visit.rtf	* Mean (SD) 390.0 390.0	false
1458	t_14_3_2_4_1_eg_visit.rtf	* Mean (SD) 2.0 2.0	false
1830	t_14_3_2_4_1_eg_visit.rtf	* Mean (SD) 409.0 409.0	false
1836	t_14_3_2_4_1_eg_visit.rtf	* Mean (SD) -7.0 -7.0	false

Showing 1 to 10 of 28 entries

Previous
1
2
3
Next

R SHINY - TITLE & FOOTNOTES

TLF METADATA

- Ensuring that titles and footnotes in RTF outputs are consistent, accurate and error-free
- Identifying discrepancies such as unresolved macros, spell checks, formatting inconsistencies are key during manual review.
- additional R package hunspell used
- Parsing Data – Extract and parse data from the RTF files for further analysis.



RTF Footnote Extractor

Enter Folder Path Containing RTF Files

C:\Users\kumars\Documents\TLFVAP\AE_Table

 Download Excel

R SHINY TITLE & FOOTNOTES



File	Content	SpellCheck
t_14_3_1_1_ae_overall.rtf	AE: Adverse Event; AESI: Adverse Event of Special Interest; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary of Regulatory Activities; NCI: National Cancer Institute;	AE, AESI, CTCAE, MedDRA, NCI
t_14_3_1_1_ae_overall.rtf	TEAE: Treatment-Emergent Adverse Event; SAE: Serious Adverse Event.	TEAE, SAE
t_14_3_1_1_ae_overall.rtf	N represents the number of participants in the corresponding cohort.	No errors
t_14_3_1_1_ae_overall.rtf	All AEs were coded using MedDRA Version 24.0.	AEs, MedDRA
t_14_3_1_1_ae_overall.rtf	The severity of All AEs are graded using NCI-CTCAE Version 5.0: Grade 1=Mild; Grade 2=Moderate; Grade 3=Severe; Grade 4=Life-threatening; Grade 5=Death.	AEs, NCI, CTCAE
t_14_3_1_1_ae_overall.rtf	TEAEs are classified as study drug-related if they have an investigator determination of related to study treatment.	TEAEs
t_14_3_1_1_ae_overall.rtf	A TEAE is defined as an AE that starts or worsens on or after the first dose of study treatment is taken, including those occurring or increasing in severity up to 30 days after the last dose of study treatment.	TEAE, AE
t_14_3_1_1_ae_overall.rtf	A TEAE is defined as leading to a dose modification if the action taken with study treatment for a TEAE was having a dose interruption, dose reduction or dose increase.	TEAE, TEAE
t_14_3_1_1_ae_overall.rtf		No errors

SUMMARY

○ Accelerated output review

Automated RTF validation enables reviewers to assess outputs significantly faster

Enables rapid cross-review – Standardized programmatic checks ensure consistent findings across study team

○ Improves collaboration with study teams

○ Shared, structured results eliminate back and forth and aligns team on the findings.

○ Delivers live actionable insights. Dashboard and automated summaries provide near real-time visibility into output quality and review status.

○ This approach is scalable, repeatable and study agnostic. Supporting large TLF packages without increasing manual review effort.