



CIMS GLOBAL

PHUSE CONNECT US – 2025 OS06

Generate Clinical Study Report (CSR) document using {quarto} and {shiny}

Telephone
908-557-9366

Address
**285 Davidson Ave.
Suite 504
Somerset, NJ 08873
USA**

Website
www.cims-global.com

Bio



pzhang@cims-global.com

- Peng Zhang, Assistant Director - Innovative Data Sciences
- Ph.D. in Biostatistics, Rutgers School of Public Health
- Research interest in adaptive design and statistical monitoring of clinical trials.
- Lead internal development and production of R package, R Shiny apps and software development.

Agenda

- 01** Introduction
- 02** Statistical validity
- 03** Template-based approach
- 04** Shinyapps production
- 05** Deployment
- 06** Q&A Session

Introduction

- Daily Task: TFL Generation for statistical/Clinical Review
- Special need from CSR: Medical writer generate narratives with inline tables and figures
 - Manually copy, paste, type, regeneration
 - Potential human error, time-consuming
 - Regeneration will take duplicated effort for possible change of raw data
- Proprietary software good for TFLs generation, but not narrative or inline table and figures.
- Propose using Open-source solution with {quarto} and {shiny}:
 - Provide workplace for medical writer to review results and edit tables and narratives
 - Template-based narratives provided and reusable.
 - Generate customized report with user-input with inline table, figures and narratives

Two types of solutions

- There are two common solutions for automation process in R
- The first one is 'one-click' choice:
 - Set up all the options and parameters -> available data -> code run -> expected results
 - {quarto} or Rmarkdown
 - Effort on code process preparation
- The second one is 'by-interaction':
 - Users can review the result
 - Users can simultaneously edit their input and decide what to include (e.g., {shiny})
 - Example: your summary for balanced or imbalanced results between your treatment and control group can be different.
 - Once all the inputs are decided from application, process will be the same as in the first one.

Validation?

- From either way, people worry about validation
 - “Is your application validated”, or, “ what is your validation process”
- Suggest the validation into two parts
 - Statistical Validity (R Package Level)
 - Operational Qualification (OQ, Shiny level)
- Usually a validation report can be a preferred format for the evidence
- Our effort will include statistical validity, template-based narrative, application development and automation process.

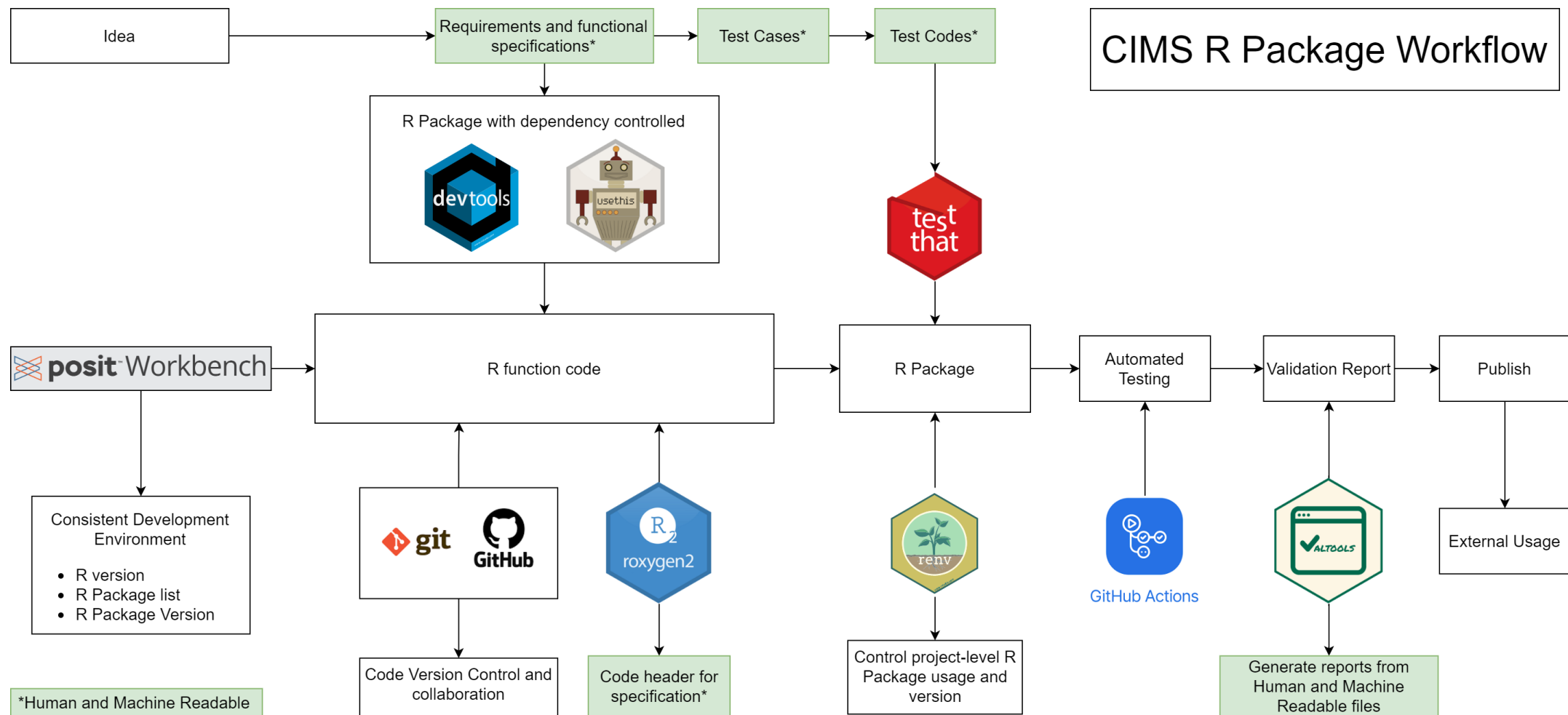
Statistical Validity

- Establish reliable evidence for the results in TFLs in R
- {rtables}, {rlisting} & {tern} approach
 - Easy to use, designed specifically for pharma usage
 - Customized for study-specific usage.
 - Easily connected to docx output with flexible appearance
 - Easily connected to shiny apps
- Shell preparation (e.g., open-source knowledge {tlg-catalog})
 - Similar to Requirement
- Code development & testing for each shell
- Validation & Report

Good Development Practice for R Package

- Good practice: good quality, easy to maintain/update in the future
- Working group {openstatsware} have some white paper about development guides
- Key R Package
 - {roxygen2}: To write function headers and generate comprehensive documentation.
 - {renv}: For managing the package environment and ensuring reproducibility.
 - {devtools} and {usethis}: For streamlined package building and efficient development workflows.
 - {testthat}: For implementing unit tests to validate the functionality of the package.
 - {valtools}: Generate Validation Report with requirement, test cases, test codes and results

Workflow



Unit Testing

- Improve the quality of the package
- Suggest using ARD/ARS from CDISC Standard for validation
 - One Column for numeric values, other columns for value's property
 - Some open-sourced example: {cards}, {cardx}
- Example: AE Table

System Organ Class Preferred Term	Treatment Group (N=xx)	Control Group (N=xx)	Total (N=xx)
At least one AE	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Primary SOC 1			
Preferred Term 1	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Preferred Term 2	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Preferred Term 3	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Primary SOC 2			
Preferred Term 1	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Preferred Term 2	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Preferred Term 3	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

ARDS	group1	group1_level	group2	group2_level	avar_name	trt_var	trt	stat_name	result
						TRT01P	trtA	N	
						TRT01P	trtB	N	
						TRT01P	Total	N	
				At least one AE		TRT01P	trtA	n	
				At least one AE		TRT01P	trtA	pct	
				At least one AE		TRT01P	trtB	n	
				At least one AE		TRT01P	trtB	pct	
				At least one AE		TRT01P	Total	n	
				At least one AE		TRT01P	Total	pct	
	AESOC	<AESOC1>				TRT01P	trtA	n	
	AESOC	<AESOC1>				TRT01P	trtA	pct	
	AESOC	<AESOC1>				TRT01P	trtB	n	
	AESOC	<AESOC1>				TRT01P	trtB	pct	
	AESOC	<AESOC1>				TRT01P	Total	n	
	AESOC	<AESOC1>				TRT01P	Total	pct	
	AESOC	<AESOC1>	AEBODSYS	<AEBODSYS1>		TRT01P	trtA	n	
	AESOC	<AESOC1>	AEBODSYS	<AEBODSYS1>		TRT01P	trtA	pct	
	AESOC	<AESOC1>	AEBODSYS	<AEBODSYS1>		TRT01P	trtB	n	
	AESOC	<AESOC1>	AEBODSYS	<AEBODSYS1>		TRT01P	trtB	pct	
	AESOC	<AESOC1>	AEBODSYS	<AEBODSYS1>		TRT01P	Total	n	
	AESOC	<AESOC1>	AEBODSYS	<AEBODSYS1>		TRT01P	Total	pct	

Validation Report

- PHUSE White paper: R Package Validation Framework
- {valtools} solution
 - A well-written example of R package {drugdevelopeR}
- Good structure for evidence
 - Description
 - Requirement
 - Specification
 - Traceability
 - Test Case
 - Test Result

Validation Report for cimstfl

fyang

2025-01-24

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Medical Narrative

- Template-based approach to generate narrative
- For CSR, Section 9 to 11 are based on the actual results from the trial
- We use variables to be replaced in the template
- ARD Structure provides a good connection between variable and values with {glue} package

```
$var_df
      name      value
1  n_screened      268
2    n_rand      268
3  n_treated      268
4    n_comp      134
5  n_discon       82
6    n_ongo       52
7  name_gp1 A: Drug X
8    n_gp_1      134
9  name_gp2 B: Placebo
10   n_gp_2      134

$header
[1] "Disposition of Participants"

$md
[1] "A total of {n_screened} participants were initially screened for inclusion in the study. Of these, {n_rand} participants were randomized into the study, and {n_treated} participants received medication. The participants were divided into two groups: the {name_gp1} group ({n_gp_1}) and the {name_gp2} group ({n_gp_2}). {n_comp} subjects had completed the study, while {n_discon} subjects discontinued prematurely, and {n_ongo} subjects were ongoing."
```

Disposition of Participants

A total of 268 participants were initially screened for inclusion in the study. Of these, 268 participants were randomized into the study, and 268 participants received medication. The participants were divided into two groups: the A: Drug X group (134) and the B: Placebo group (134). 134 subjects had completed the study, while 82 subjects discontinued prematurely, and 52 subjects were ongoing.

Shiny Application

- Once the method for results and narrative can be available, the functions can be connected through {shiny}
- The working place for medical writer should enable
 - TFLs result review
 - TFLs result filter: to select the desired rows
 - Template Edit: to edit desired narrative template
 - Narrative review: ensure the number is proper in the narrative
- The edit and choice will be saved in the session and for any further reusable purpose.
- Also it should enable report download for further usage

Shiny Example

Section 10.1

t_b_dm_01

Generate the Section

Select Table Rows

- ☒ AGE
- ☒ SEX
- ☒ RACE
- ☒ ETHNIC

	A: Drug X	B: Placebo	Total
	(N=134)	(N=134)	(N=268)
Age			
N	134	134	268
Mean (SD)	33.8 (6.6)	35.4 (7.9)	34.6 (7.3)
Median	33.0	35.0	34.0
Q1 - Q3	28.0 - 39.0	30.0 - 40.0	29.0 - 39.0
(Min, Max)	(21.0, 50.0)	(21.0, 62.0)	(21.0, 62.0)

- The mean (SD) Age was {AGE_mean} ({AGE_sd}) with a median of {AGE_median} (range {AGE_min} to {AGE_max}).
- Of {num_participants} participants enrolled, {SEX1_num} ({SEX1_pop}%) participants were {SEX1_name}, {SEX2_num} ({SEX2_pop}%) participants were {SEX2_name}.
- Of {num_participants} participants enrolled, {RACE1_num} ({RACE1_pop}%) participants were

- The mean (SD) Age was 34.6 (7.3) with a median of 34 (range 21 to 62).
- Of 268 participants enrolled, 161 (60.1%) participants were F, 107 (39.9%) participants were M.
- Of 268 participants enrolled, 135 (50.4%) participants were Asian, 59 (22%) participants were Black or African American, 53 (19.8%) participants were White, 19 (7.1%) participants were American Indian or Alaska Native, 1 (0.4%) participants were Multiple, 1 (0.4%) participants were Native Hawaiian or Other Pacific Islander, 0 (0%) participants were Other, 0 (0%) participants were Unknown.
- Of 268 participants enrolled, 33 (12.3%) participants were Hispanic or Latino, 207 (77.2%) participants were Not Hispanic or Latino, 16 (6%) participants were Not Reported, 12 (4.5%) participants were Unknown.



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CSR Report

- Once the review and edit is completed, the report and corresponding {quarto} file can be generated
- If one has pre-specified template, it can be read into the code and works for the final report.
- Such report can be editable in the future if necessary.



Clinical Study Report

9.1 Disposition of Participants

	A: Drug X (N=134)	B: Placebo (N=134)	Total (N=268)
Number of Patients Screened			268
Number of Randomized Subjects	134 (100%)	134 (100%)	268 (100%)
Number of Treated Subjects	134 (100%)	134 (100%)	268 (100%)
Study Completion Status			
COMPLETED	68 (50.7%)	66 (49.3%)	134 (50.0%)
ONGOING	24 (17.9%)	28 (20.9%)	52 (19.4%)
DISCONTINUED	42 (31.3%)	40 (29.9%)	82 (30.6%)
ADVERSE EVENT	3 (2.2%)	6 (4.5%)	9 (3.4%)
DEATH	25 (18.7%)	23 (17.2%)	48 (17.9%)
LACK OF EFFICACY	2 (1.5%)	2 (1.5%)	4 (1.5%)
PHYSICIAN DECISION	2 (1.5%)	3 (2.2%)	5 (1.9%)
PROTOCOL VIOLATION	5 (3.7%)	3 (2.2%)	8 (3%)
WITHDRAWAL BY PARENT/GUARDIAN	4 (3%)	2 (1.5%)	6 (2.2%)
WITHDRAWAL BY SUBJECT	1 (0.7%)	1 (0.7%)	2 (0.7%)
Treatment Completion Status			
COMPLETED	68 (50.7%)	66 (49.3%)	134 (50.0%)
ONGOING	24 (17.9%)	28 (20.9%)	52 (19.4%)
DISCONTINUED	42 (31.3%)	40 (29.9%)	82 (30.6%)

A total of 268 participants were initially screened for inclusion in the study. Of these, 268 participants were randomized into the study, and 268 participants received medication. The participants were divided into two groups: the A: Drug X group (134) and the B: Placebo group (134). 134 subjects had completed the study, while 82 subjects discontinued prematurely, and 52 subjects were ongoing.

10.2.1 Population at Screening

	A: Drug X (N=134)	B: Placebo (N=134)	Total (N=268)
Age			
N	134	134	268
Mean (SD)	33.8 (6.6)	35.4 (7.9)	34.6 (7.3)
Median	33.0	35.0	34.0
Q1 - Q3 (Min, Max)	28.0 - 39.0 (21.0, 50.0)	30.0 - 40.0 (21.0, 62.0)	29.0 - 39.0 (21.0, 62.0)
Sex			
N	134	134	268
F	79 (59.0%)	82 (61.2%)	161 (60.1%)
M	55 (41.0%)	52 (38.8%)	107 (39.9%)
Race			
N	134	134	268
ASIAN	68 (50.7%)	67 (50.0%)	135 (50.4%)
BLACK OR AFRICAN AMERICAN	31 (23.1%)	28 (20.9%)	59 (22.0%)
WHITE	27 (20.1%)	26 (19.4%)	53 (19.8%)
AMERICAN INDIAN OR ALASKA NATIVE	8 (6.0%)	11 (8.2%)	19 (7.1%)
MULTIPLE	0	1 (0.7%)	1 (0.4%)
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	0	1 (0.7%)	1 (0.4%)
OTHER	0	0	0
UNKNOWN	0	0	0
Ethnicity			
N	134	134	268
HISPANIC OR LATINO	15 (11.2%)	18 (13.4%)	33 (12.3%)
NOT HISPANIC OR LATINO	104 (77.6%)	103 (76.9%)	207 (77.2%)

Application Validation

- Statistical Validity through {vtools} with validation report
- Additional evidence to show the application works per requirement
- Manual screenshot or {shinytest2} should be used for Operational Qualification (OQ)
- Also, similar to statistical validity, a report should be generated

Current Deployment Challenges

- Option 1: Licensed Product including Posit Connect can help deploy application.
- If not: necessary communication with IT and software development
- Option 2: The traditional deployment process requires specialized IT professionals to validate and configure applications using IQ documents before implementing automation. However, this creates a bottleneck due to:
 - Time-consuming and repetitive validation procedures
 - Limited availability of IT professionals due to competing priorities
 - Necessary but restrictive quality control measures that can impact development timelines
- Even with comprehensive documentation and verification processes, manual deployments remain susceptible to human error, potentially affecting application reliability.
- Option 3: Suggest using automation (e.g. Github Action), once setup:
 - Reducing manual effort and associated time investment
 - Minimizing human error risk through standardized processes
 - Increasing deployment frequency and efficiency
 - Enabling faster user feedback and iterative improvements
 - Enhancing overall development cycle and user experience

Automated Deployment Workflow

- Feature Development and Review
 - Code submitted through pull requests
 - Thorough review process ensures stability and reliability
 - Team discussion and approval required
- Quality Assurance
 - Static analysis for code quality
 - Dynamic analysis for runtime behavior
 - Automated test execution
 - Immediate reporting of test failures
- Deployment Process
 - Docker image creation and packaging
 - Push to GitHub Packages Registry
 - Secure deployment to local Shiny server
 - Automated build and parameterization
 - Seamless application release

Discussion

- Propose a way of using R packages and shiny applications:
 - To provide a working station for medical writers to review the results and edit the narratives for section 9 to 11
 - Automated reports by rendering process.
 - Validated Evidence
 - Reliable development process
- On the other hand, some available AI solutions can read the TFLs to generative narrative, however:
 - We believe that the CSR process, as the final step to the regulatory, should be rigorous and fully validated.
 - Concern about results from AI
- We might suggest such a template approach with statistical evidence can be feasible to ensure reliability and flexibility as well in the process.

Thank You!

We welcome any questions or thoughts that you may have.

pzhang@cims-global.com

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