OPEN PROBLEMS FOR ANALYSIS AND REPORTING IN CLINICAL TRIALS USING R

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Feb. 2021

BBSW Feb Meetup

Disclaimer

This presentation reflects the views of the author and does not represent a company position for Merck

Challenges

An end-to-end solution for clinical trial analysis and reporting is critical to fit business need.

- System and process:
    - Programming environment shall be regulatory compliant
        - Our solution: Collaborate with IT to build a GxP compliance platform
    - R packages used for analysis and reporting shall be qualified
        - Our solution: following risk-based approach suggested by R Validation hub
    - Internal software development life cycle (SDLC)
        - Our solution: following existing workflow if possible.
    - Prepare submission package (i.e. eCTD submission)
- R Community Growth within an Organization
    - Training
        - Our solution: peer-review learning approach
    - Proof-of-concept projects

How Did We Start?

- Merck has a set of pre-specified table format standards.
  - We built an R package (r2rtf) to streamline the process https://merck.github.io/r2rtf/index.html

Summary of Adverse Events
All Subjects as Treated

	Xanomiline High Dose	Xanomiline Low Dose	Placebo
	N	N	N
Participants in population	84	84	86
Participants with at least one adverse events	79	77	69
Participants with drug-related[a] adverse events	48	44	26
Participants with serious adverse events	0	2	1
With serious drug-related[a] adverse events	0	0	1
Who died	0	1	2

[a] Determined by the investigator to be related to the drug.

Source: [Study MK9999P001: adam-adsl; adae]

Analysis and Reporting Demo

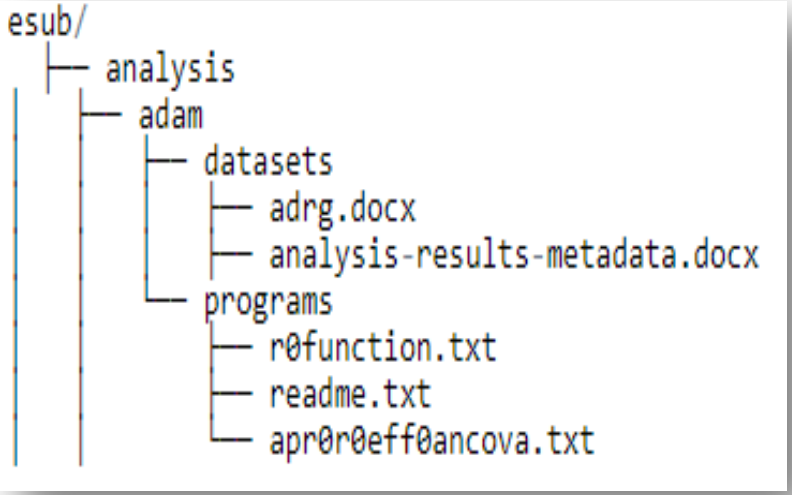
- Assumptions: Analysis datasets (SDTM/ADaM) are created by SAS
- R is used for selected table and figure generation in RTF format (using r2rtf)
- Demo project:
  - Completed typical analysis in clinical trial using R following internal SDLC process
  - Open-source project created by Atorus Research (CDISC Pilot Replication)

```
── DESCRIPTION
── NAMESPACE
── mk9999p001.Rproj
── R
    ├── continous_by.R
    ├── count_by.R
── man
    ├── continous_by.Rd
    ├── count_by.Rd
── tests
    ├── testthat
    │   ├── test-continous_by.R
    │   ├── test-count_by.R
    │   ├── test-independent-test-tfl_001_apr0ds.R
    │   ├── test-independent-test-tfl_002_apr0base.R
    │   ├── test-independent-test-tfl_003_apr0eff0ancova.R
    └── testthat.R
── vignettes
    ├── tlf_001_apr0ds.Rmd
    ├── tlf_002_apr0base.Rmd
    ├── tlf_003_apr0eff0ancova.Rmd
```

Prepare Submission

4.1.2.10 Software Programs

"Sponsors should provide the software programs used to create all ADaM datasets and generate tables and figures associated with primary and secondary efficacy analyses. Furthermore, sponsors should submit software programs used to generate additional information included in Section 14 CLINICAL STUDIES of the Prescribing Information (PI)26 if applicable. The specific software utilized should be specified in the ADRG. The main purpose of requesting the submission of these programs is to understand the process by which the variables for the respective analyses were created and to confirm the analysis algorithms. Sponsors should submit software programs in ASCII text format; however, executable file extensions should not be used."



https://www.fda.gov/media/88173/download

Proof-of-Concept Project: Interactive Visualization

- Interactive safety data exploration:
  - Related open-source project: safetyGraphics