Open-Source Software for Regulatory Submissions and Regulatory Environments: an FDA perspective.

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Disclaimer

This presentation reflects the views of the author and should not be construed to represent the FDA's views or policies.

Statistical Software Clarifying Statement

https://www.fda.gov/media/109552/download

FDA does not require use of any specific software for statistical analyses, and statistical software is not explicitly discussed in Title 21 of the Code of Federal Regulations [e.g., in 21CFR part 11]. However, the software package(s) used for statistical analyses should be fully documented in the submission, including version and build identification.

Statistical Software Continued

As noted in the FDA guidance, *E9 Statistical Principles for Clinical Trials*, "The computer software used for data management and statistical analysis should be reliable, and documentation of appropriate software testing procedures should be available."

Sponsors are encouraged to consult with FDA review teams and especially with FDA statisticians regarding the choice and suitability of statistical software packages at an early stage in the product development process.

May 6, 2015

Which programs should be submitted?

"4.1.2.10 Software Programs (Study Data Technical Conformance Guide) (SDTCG)

Sponsors should provide the source code used to create all ADaM datasets, tables, and figures associated with primary and secondary efficacy analyses. Sponsors should submit source code in single byte ASCII text format. Files with MS Windows executable extensions (.cmd, .com, and .exe) should NOT be submitted. **For a list of acceptable file extensions, refer to the document entitled Specifications for File Format Types Using eCTD Specifications.**

Furthermore, sponsors should submit the source code used to generate additional information included in Section 14 CLINICAL STUDIES of the Prescribing Information,32 if applicable. **The specific software utilized (version and operating system) should be specified in the ADRG."**

Which file formats are accepted ?

- A text file does not have to be a .txt file.
- For CDER, as of 2021, .c, .cpp, .m, .mat, .rmd, .py, .jl are accepted in M5, while .sas and .r are acceptable in M3-M5.

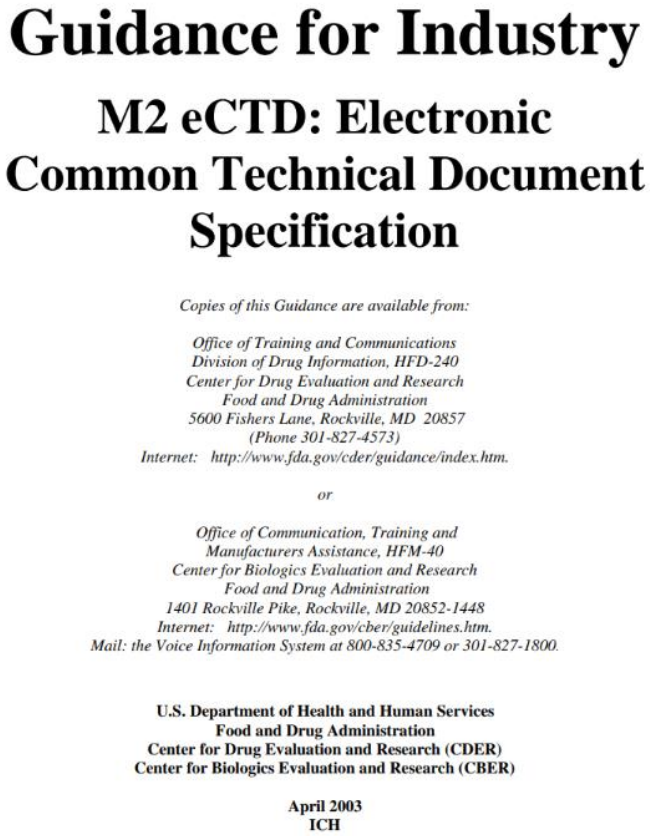
https://www.fda.gov/media/85816/download, *Specifications for File Format Types Using eCTD Specifications*

Caveats from the SDTCG

3.3.5 Special Characters: Variables and Datasets

“Variable names, as well as variable and dataset labels should include American Standard Code for Information Interchange (ASCII) text codes only. Variable values are the most broadly compatible with software and operating systems when they are restricted to ASCII text codes (printable values below 128). Use UTF-8 for extending character sets; however, the use of extended mappings is not recommended. Transcoding errors, variable length errors, and lack of software support for multi byte UTF-8 encodings can result in incorrect character display and variable value truncations. Ensure that LBSTRESC and controlled terminology extensions in LBTEST do not contain byte values 160-191 as some character mappings in that range may interfere with agency processes.”

M2 eCTD Guidance



Guidance for Industry

M2 eCTD: Electronic Common Technical Document Specification

Copies of this Guidance are available from:

Office of Training and Communications
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, Rockville, MD 20857
(Phone 301-827-4573)
Internet: http://www.fda.gov/cder/guidance/index.htm.

or

Office of Communication, Training and
Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
Internet: http://www.fda.gov/cber/guidelines.htm.
Mail: the Voice Information System at 800-835-4709 or 301-827-1800.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

April 2003
ICH

Restrictions on file names

- lower case file names only
- Files names can only have letters, numerals, hyphens, along with an extension
- No spaces in file names
- No UPPERCASE, no_underscore

Additional restrictions for directory names

- No extensions in directory/folder names

R Programming Language

- Based on S, which was originally developed at Bell Labs, by Chambers et al, 1976
- R, Ihaka and Gentleman, 1993
- Comprehensive R Archive Network (CRAN) for R packages, GitHub, Bioconductor, etc.
- RStudio is a widely used IDE, (2011)
- Governance: R Core Team, R Foundation

R Consortium Efforts

- R Consortium (https://www.r-consortium.org/)
  - Supports the R Foundation, members include pharma, tech companies, and the ASA
- R Consortium Working Groups
  - R Validation Hub
  - R Repositories
  - R Tables for Regulatory Submissions
  - R Submissions

R Submissions WG

Pilots:

- Pilot 1: R based submission of tables, graphs and analyses for CDER using ADaM datasets. (completed)
- Pilot 2: CDER submission with an interactive Shiny component (completed)
- Pilot 3: R based CDER submission, derivation of ADaM datasets from SDTM. (completed)
- Pilot 4: R based CDER submission with a container or WebAssembly (Wasm) component (in development)

https://github.com/RConsortium/submissions-wg

Data: CDISC Pilot Submission

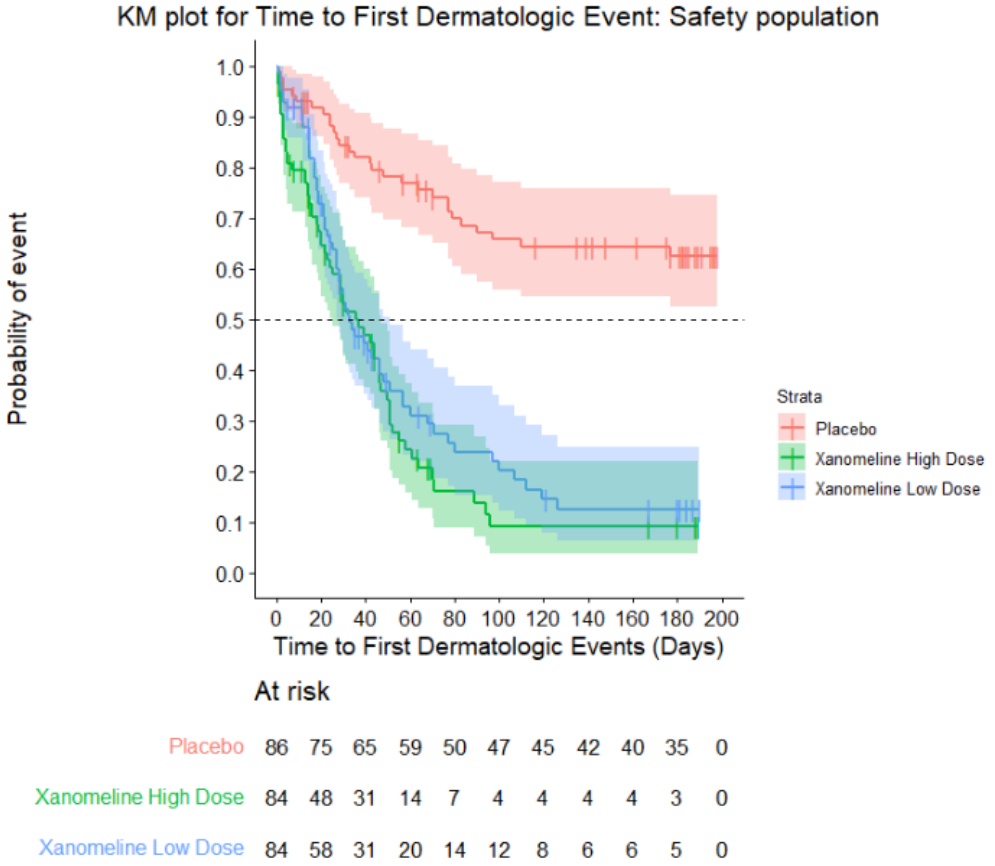
Demographics Table, Pilot 1

Table 14-2.01 Summary of Demographic and Baseline Characteristics

	Placebo N=86	Xanomeline Low Dose N=84	Xanomeline High Dose N=84
Age			
Mean (SD)	75.21 (8.59)	75.67 (8.29)	74.38 (7.89)
Median	76.00	77.50	76.00
Min, Max	52.0, 89.0	51.0, 88.0	56.0, 88.0
Pooled Age Group 1			
<65	14 (16)	8 (10)	11 (13)
65-80	42 (49)	47 (56)	55 (65)
>80	30 (35)	29 (35)	18 (21)
Race			
White	78 (91)	78 (93)	74 (88)
Black or African American	8 (9)	6 (7)	9 (11)
American Indian or Alaska Native	0 (0)	0 (0)	1 (1)
Baseline Height (cm)			
Mean (SD)	162.57 (11.52)	163.43 (10.42)	165.82 (10.13)
Median	162.60	162.60	165.10
Min, Max	137.2, 185.4	135.9, 195.6	146.1, 190.5
Baseline Weight (kg)			
N	86	83	84
Mean (SD)	62.76 (12.77)	67.28 (14.12)	70.00 (14.65)
Median	60.55	64.90	69.20
Min, Max	34.0, 86.2	45.4, 106.1	41.7, 108.0
Missing	0	1	0
Baseline BMI ($kg/m^{2)}$			
N	86	83	84
Mean (SD)	23.64 (3.67)	25.06 (4.27)	25.35 (4.16)
Median	23.40	24.30	24.80
Min, Max	15.1, 33.3	17.7, 40.1	13.7, 34.5
Missing	0	1	0
MMSE Total			
Mean (SD)	18.05 (4.27)	17.87 (4.22)	18.51 (4.16)
Median	19.50	18.00	20.00
Min, Max	10.0, 23.0	10.0, 24.0	10.0, 24.0

Source: adsl.xpt
2021-12-01 13:26:33

Pilot 1, KM Plot



Pilot 2, Interactive KM Plot

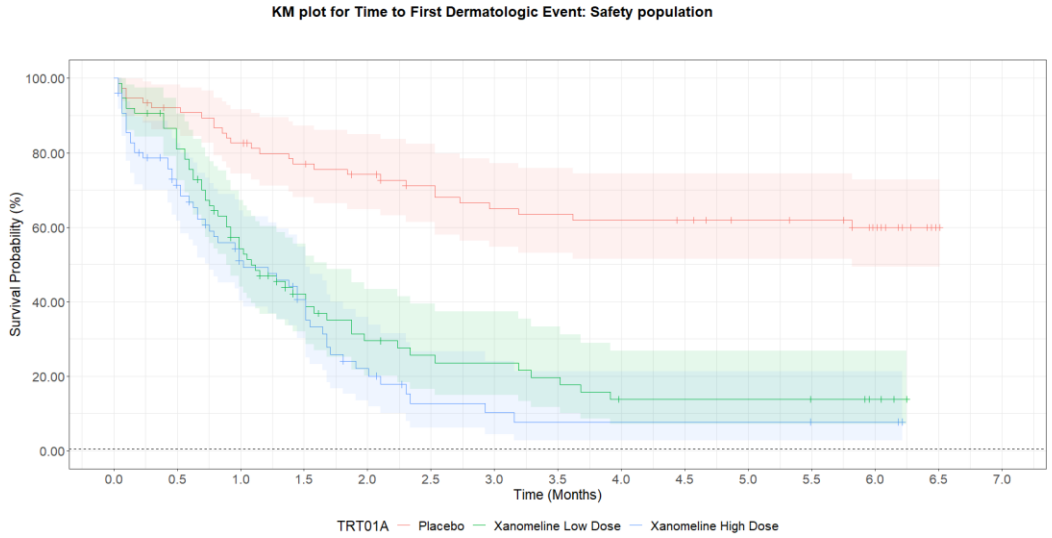
Pilot 2 Shiny Application

App Information | Usage Guide | Demographic Table | **KM plot for TTDE** | Primary Table | Efficacy Table | Visit Completion Table

Important Information:
The analyses performed when utilizing subgroups or other subsets of the source data sets are considered **exploratory.**

- Treatment information variables from the **ADTTE** data set are excluded from the variable list. Use the treatment variables present in the **ADSL** set to perform treatment-related filters.
- In rare situations, applying filters with variables from both **ADSL** and **ADTTE** that overlap in content could result in an invalid data subset. When possible, select variables with distinct content.

Figure 14-1
Time to Dermatologic Event by Treatment Group



Active Filter Summary

	Obs	Subjects
ADSL	227/254	227/254
ADTTE	227/254	227/254

Active Filter Variables

ADSL

AGE

51 57 85 89
51 55 59 63 67 71 75 79 83 87 89

ADTTE

Add Filter Variables

Add ADSL filter
Select variable to filter

Add ADTTE filter
Select variable to filter

Exploratory Analyses

Some sponsors have suggested interactive exploratory analyses

However, ICH E9 section 5.7 states:

"In most cases, however, subgroup or interaction analyses are *exploratory* and *should be clearly identified as such*; they should explore the uniformity of any treatment effects found overall."

"When exploratory, these analyses should be interpreted cautiously. *Any conclusion of treatment efficacy (or lack thereof) or safety based solely on exploratory subgroup analyses is unlikely to be accepted*." (Italics added).

Any exploratory analyses should be clearly labelled as exploratory and be distinguished from the prespecified primary and secondary analyses.

Other Groups Supporting R

- R in Pharma conference, end of October 2024, https://rinpharma.com/
- R in Medicine conference, June 10-14, 2024
- Pharmaverse, https://pharmaverse.org/
- useR! The R User Conference, July 8-11, 2024
- R Foundation

What about Python?

- Natural Language Processing (NLP)
- Text modelling, OCR, machine learning
- Data Science applications
- Less focus on statistics and visualization
- Some commercial packages use Python
- Shiny apps for Python in development

Challenges with Open-Source

- Rate of change
- “Who are you going to call?”
- Support by IT (open-source isn’t always free)
- Plethora of Packages
  - Which ones can be trusted?
  - Dependencies and version control issues

Reflections & Observations

- CDER has just begun to deal with completely R based submissions
- Hybrid submissions and hybrid workflows are reported
- Recent graduates tend to have more experience with open-source tools than proprietary alternatives.
- Recommend that sponsors reach out to review division(s) Consider the perspective of FDA staff with your submissions
- FDA Windows environments do not behave the same way as sponsor's Linux environments (e.g. relative paths)

More Reflections & Observations

- Open-source tools are popular for smaller scale AI/ML.
- Digital Health Technologies (DHTs), while not specifically open-source, have the potential to be a disruptive technology.
- “With great power comes great responsibility” (Stan Lee, 1962). Open-source tools and methods don’t necessarily promote good statistical practices. Avoid p-hacking and cherry picking.

Acknowledgements

- DAI colleagues: Hye Soo Cho, Youn Kyeong Chang
- R Consortium members: Ning Leng, Joe Rickert, Eric Nantz, Joel Laxamana, (and many others)

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