R Submission
Pilot 1 – ADaM Extension

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Purpose

Demonstrate the viability of using R for **ADaM dataset creation** in the context of a FDA submission

Provide the industry with an end-to-end example of an R based FDA filling

Intro - Review of Pilot 1

STATISTICAL REVIEW AND EVALUATION

NDA/BLA #:	BLA 111111 (R pilot submission)
Applicant:	R Consortium's R Submission Working Group
Statistical Analyst	Hye Soo Cho, AIS Hye Soo Cho -S Digitally signed by Hye Soo Cho -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Hye Soo Cho -S, 0.9.2342.19200300.100.1.1=2003188359 Date: 2022.03.10 10:26:55 -05'00'
Supervisor	Maria Matilde Kam, AIS Maria Matilde S. Kam -S Digitally signed by Maria Matilde S. Kam -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002402795, cn=Maria Matilde S. Kam -S Date: 2022.03.10 10:46:05 -05'00'
Date(s):	March 10, 2022
Objectives of the submission	To test and support R-based clinical trial application submission
Location of datasets and programs	\\cdsesub3\evsprod\BLA111111\0002
Reviewed tables and figures	Table 14-2.01, Table 14-3.01, Table 14-3.02, Figure 14-1

Summary

- An FDA analyst was able to complete the following tasks:
  - Receive electronic submission package in eCTD format
  - Reconstruct and load the submitted proprietary R package
  - Install and load open-source packages used in this submission
  - Reproduce the analysis results
  - Share potential improvements to the submission deliverable and processes via a written communication
- FDA agrees that the initial phase of the R Pilot submission has been completed.
- For future reference, FDA suggest calculating 95% confidence intervals in a consistent manner.

Scope - Overview of Pilot 1 Extension

Table 14-2.01

Summary of Demographic and Baseline Characteristics

(ADSL)

Protocol: CDISCPILOT01
Population: Intent-to-Treat

	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	77.5	76
Min - Max	52 - 89	51 - 88	56 - 88
Pooled Age Group 1			
<65	14	8	11
65-80	42	47	55
>80	30	29	18
Race			
WHITE	78	78	74
BLACK OR AFRICAN AMERICAN	8	6	9
AMERICAN INDIAN OR ALASKA NATIVE	0	0	1
Baseline Height (cm)			
Mean (sd)	162.57 (11.52)	163.43 (10.42)	165.82 (10.1
Median	162.6	162.6	165.1
Min - Max	137.2 - 185.4	135.9 - 195.6	146.1 - 190.
Baseline Weight (kg)			
Mean (sd)	62.76 (12.77)	67.28 (14.12)	70 (14.65)
Median	60.55	64.9	69.2
Min - Max	34 - 86.2	45.4 - 106.1	41.7 - 108
Baseline BMI (kg/m^2)			
Mean (sd)	23.64 (3.67)	25.06 (4.27)	25.35 (4.16
Median	23.4	24.3	24.8
Min - Max	15.1 - 33.3	17.7 - 40.1	13.7 - 34.5
MMSE Total			
Mean (sd)	18.05 (4.27)	17.87 (4.22)	18.51 (4.16
Median	19.5	18	20
Min - Max	10 - 23	10 - 24	10 - 24

Program: tlf_demographic.Rmd
2022-02-01 17:21:29

Table 14-3.01

Primary Endpoint Analysis: ADAS Cog (11) - Change from Baseline to We

Protocol: CDISCPILOT01
Population: Efficacy

Table 14-3.01
Primary Endpoint Analysis: ADAS Cog (11) - Change from Baseline to Week 24 - 1

	Placebo (N=79)	Xanomeline Low Dose (N=81)	Xanom High (N=
Baseline			
n	79	81	74
Mean (SD)	24.1 (12.19)	24.4 (12.92)	21.3 (11.
Median (Range)	21.0 (5;61)	21.0 (5;57)	18.0 (3;
Week 24			
n	79	81	74
Mean (SD)	26.7 (13.79)	26.4 (13.18)	22.8 (12.
Median (Range)	24.0 (5;62)	25.0 (6;62)	20.0 (3;.
Change from Baseline			
n	79	81	74
Mean (SD)	2.5 (5.80)	2.0 (5.55)	1.5 (4.26)
Median (Range)	2.0 (-11;16)	2.0 (-11;17)	1.0 (-7;13
p-value(Dose Response) [1][2]			0.245
p-value(Xan - Placebo) [1][3]		0.569	0.233
Diff of LS Means (SE)		-0.5 (0.82)	-1.0 (0.86)
95% CI		(-2.1;1.1)	(-2.7;0.7)
p-value(Xan High - Xan Low) [1][3]			0.320
Diff of LS Means (SE)			-0.5 (0.86)
95% CI			(-2.2;1.1)

[1] Based on Analysis of covariance (ANCOVA) model with treatment and site group as factors and baseline value as a covariate.
[2] Test for a non-zero coefficient for treatment (dose) as a continuous variable
[3] Pairwise comparison with treatment as a categorical variable; p-values without adjustment for multiple comparisons.

17:21 Tuesday, February 01, 2022

(ADAS)

Table 14-3.02

Primary Endpoint Analysis: Glucose (mmol/L) - Summary at Week 20 - LOCF

(ADLB)

ANCOVA of Change from Baseline a

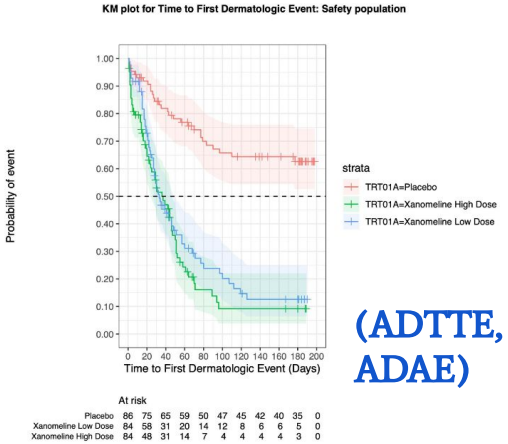
	Baseline[a]		Week 20		
Treatment	N	Mean (SD)	N	Mean (SD)	N
Xanomeline High Dose	84	5.4 (1.34)	31	5.8 (1.61)	31
Placebo	86	5.6 (2.14)	65	5.8 (1.50)	65
Pairwise Comparison				Difference in LS Mean	
Xanomeline High Dose vs. Placebo				0.07 (-0.50, 0.(	
Root Mean Squared Error of Change = 1.30					

[a] Table is based on participants who have observable data at Baseline and Week
[b] Based on an Analysis of covariance (ANCOVA) model with treatment and ba
CI = Confidence Interval, LS = Least Squares, SD = Standard Deviation

Source: [pilot1wrappers: adam-adsl; adl

Figure 14-1

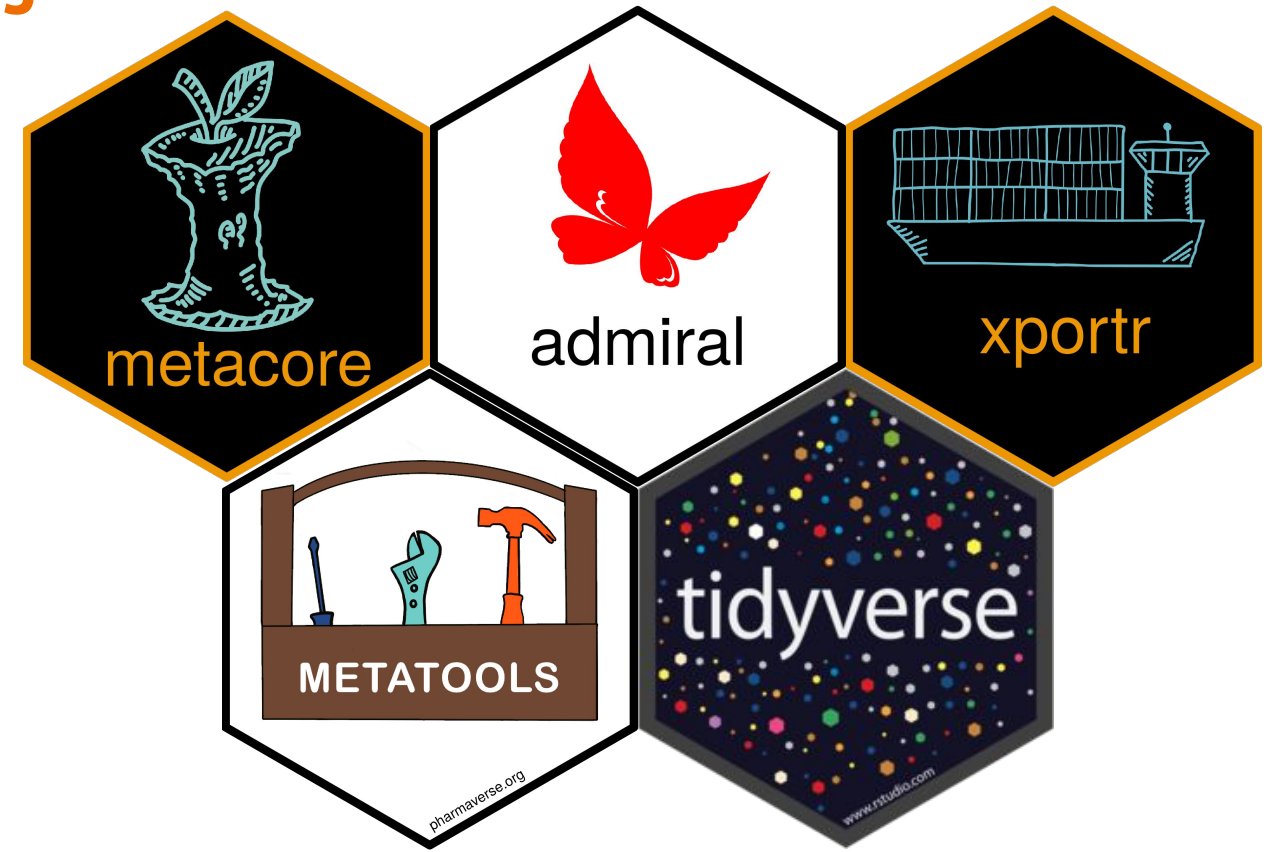
Time to Dermatologic Event by Treatment Group



(ADTTE, ADAE)

Program: tlf_kmplot.Rmd [2022-02-01 17:21:39]

R Packages


metacore
admiral
xportr
METATOOLS
pharmaverse.org
tidyverse
www.rstudio.com

Proposed Running Environment

- **R version**: 4.2.1 (current release)
- **CRAN Snapshot date**: 2022-10-07
- **Snapshot repository**:

  https://mran.microsoft.com/snapshot/2022-07-10

Proposed Timelines

- Finalize Team (2 weeks)
- Admiral mini-workshop/training (1 day)
- Assignments and Development (Start around end of Oct2022)
- Submission (Complete around end of Feb/early Mar2023)

Proposed Timelines

Item	Tentative Date
Finalize Team	End of October 2022
Workshop on pharmaverse tools	Early November 2022
Development in R	Nov 2022 to Feb 2023
Submission	End of February 2023

Call to Action: FDA

- Receive electronic submission package in eCTD format
- Reconstruct and load the submitted proprietary R package
- Install and load open source packages used in this submission
- **Reproduce the ADaM datasets and analysis results**
- **Load the submitted .xpt datasets into SAS**
- Share potential improvements to the submission deliverables and processes via a written communication

Call to Action: Industry

- Finalize Pilot 1 Extension Working Group / Execution Team:
  - Thomas Neitman (Roche: Co-Lead)
  - Joel Laxamana (Roche: Co-Lead)
  - Lei Zhao (Roche)
  - Nicole Jones (Merck)

+ 2-3 collaborators with experience in

- **ADaM**
- **R**
- **GitHub**

Thank you!

Any questions for us?

Questions/Actions for the pilot 1 extension team?

1. CDISC Pilot SDTM has it been updated?
    a. We need to package SDTM, sDRG, with define.xml

       https://github.com/cdisc-org/sdtm-adam-pilot-project

    b. Need to find out what the TRUE dependencies are for ADaMs in slide 4.
2. Submission process - review and feedback of eCTD?
    a. https://github.com/RConsortium/submissions-pilot1-to-fda
3. Proposed package
    a. package SDTM, sDRG, with define.xml
    b. ADaM, ADRG with define.xml (only datasets needed to generate TLFs), & program TOC
        i. Need to convert define to excel, remove the datasets in the define to what we need.
    c. Re-generate the TLFs using the ADaMs generated in R.
        i. Updated R packages potentially
4. Pilot 1 extension wrappers package - will need to follow pilot 1 in the case specific derivations are needed outside of admiral.
5. Send to Ning to review slides.
6. Joel set up working group meetings.