



Track: Biostatistics

17th Annual Conference
**Transformations in Clinical Research
for Better Patient Outcomes**
Novotel Hyderabad Convention Centre, Hyderabad | 01-03 February 2024

Indian Society for Clinical Research
ISCR Conference 2024
Transformations in Clinical research for Better Patient Outcomes
02-03 Feb 2024

SESSION: Biostatistics and Statistical Programmer

02-February 2024

Topic: Traverse the "Pharmaverse": ouR insights

Speaker : Pooja Kumari

Traverse the "Pharmaverse": ouR insights

- Disclaimer

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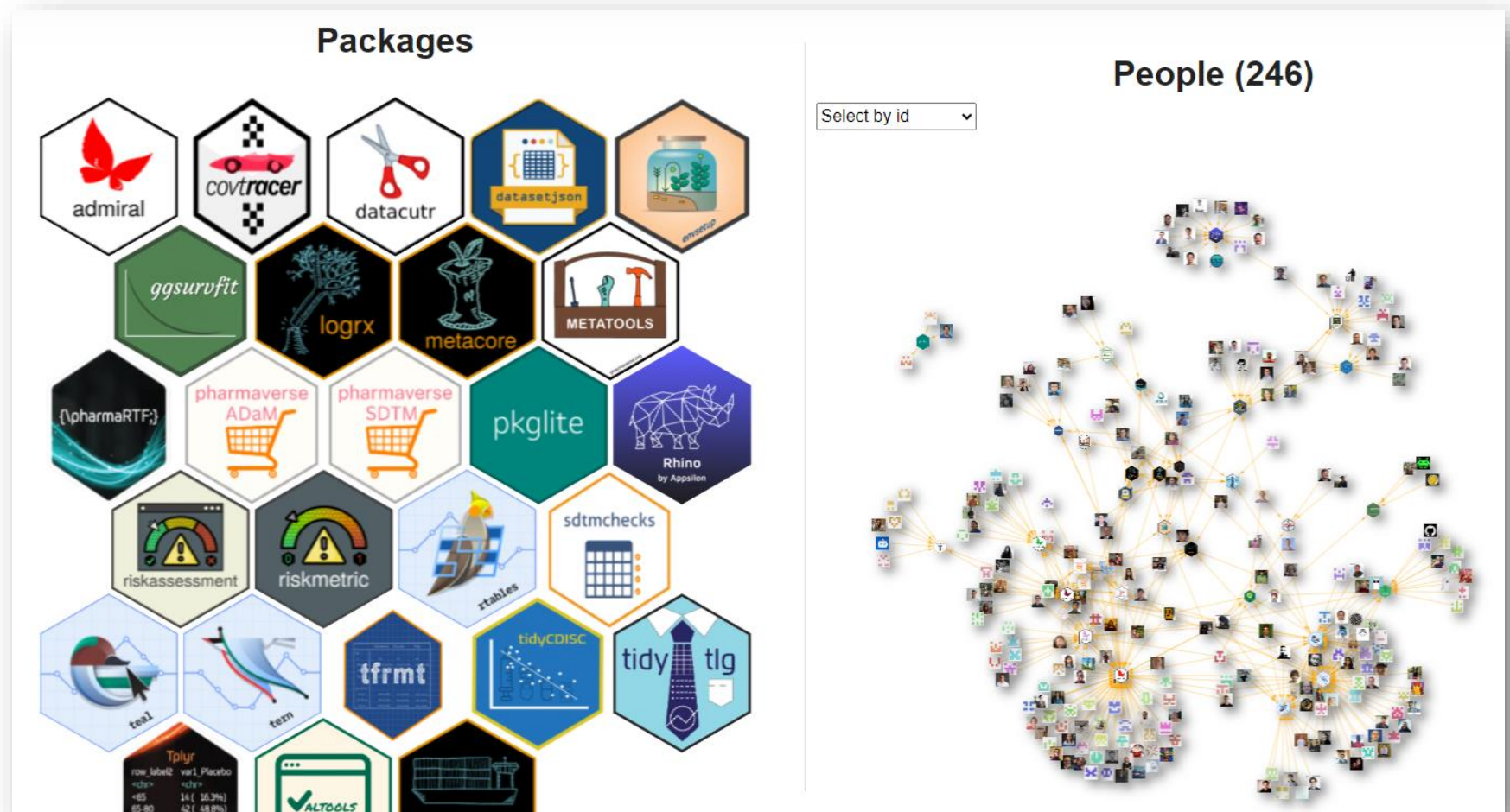
Traverse the "Pharmaverse": ouR insights

- Introduction to Pharmaverse



- Intrigued by this revolutionary concept of **tidyverse**, the origin of Pharmaverse was seeded into the minds of some R enthusiast.

- Source: [pharmaverse \(github.com\)](https://pharmaverse.github.com/)



Traverse the "Pharmaverse": ouR insights

- Understanding Pharmaverse



- Source: [pharmaverse](https://pharmaverse.org/)

Traverse the "Pharmaverse": ouR insights

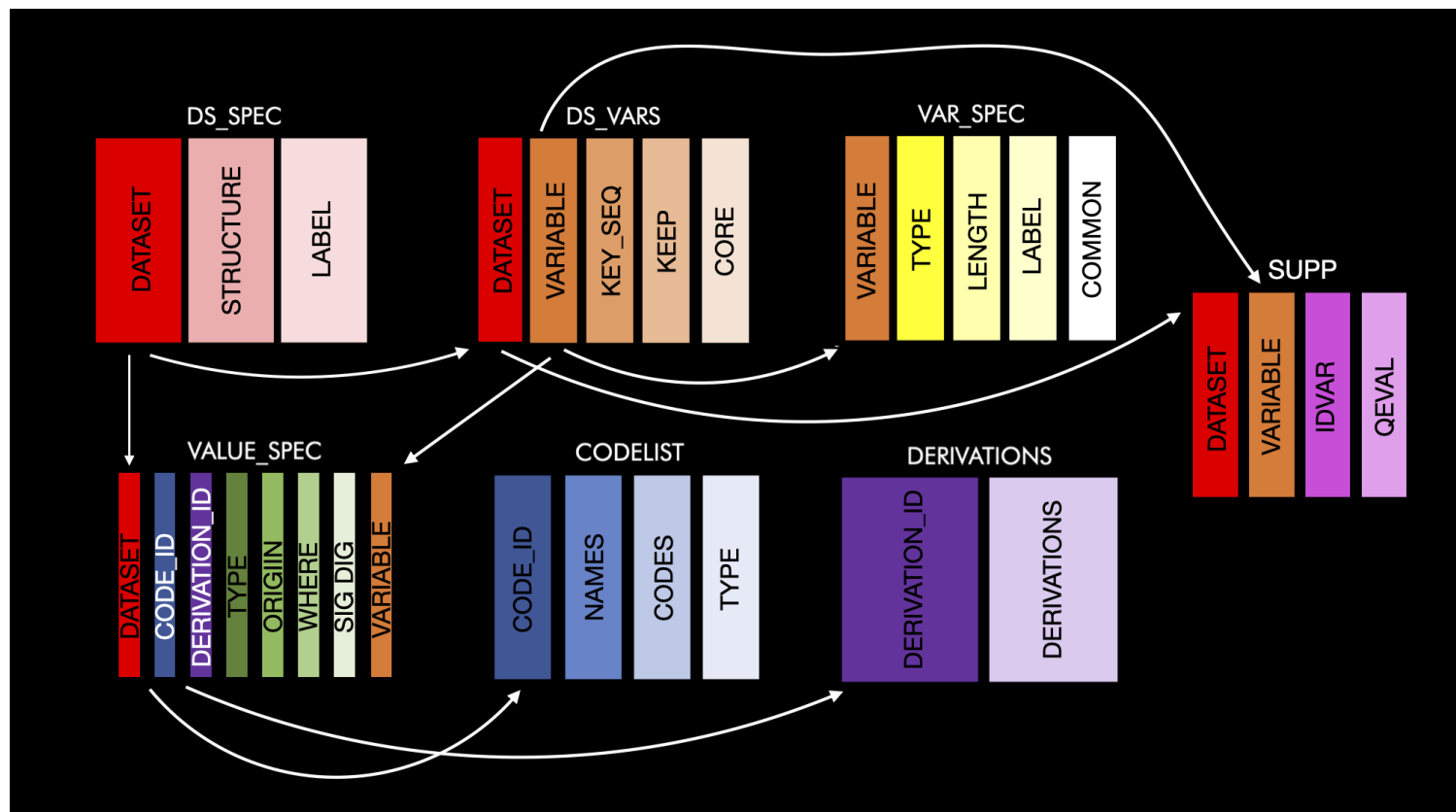
- Understanding metacore

PURPOSE

To establish a common foundation for the use of metadata within an R session. This is done by creating an R object that can hold the necessary data in a standardized, immutable structure (using R6) that makes it easy to extract out necessary information when needed.



Load specification file
and create "metacore"
object



- [metacore \(atorus-research.github.io\)](https://github.com/atorus-research/metacore)

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- Understanding metatools



PURPOSE

The goal of metatools is to enable the use of metacore objects. Metatools can be used to build datasets or enhance columns in existing datasets as well as checking datasets against the metadata in metacore.

- [metatools \(pharmaverse.github.io\)](https://pharmaverse.github.io/metatools)

Create categorical
Variable from codelist
(e.g.: AGEGR1)

Create
"Predecessor"
variables

Combine Domain
and Supplemental
Qualifier

Compare Planned
and Actual
dataset
values/attributes

Create numeric version
of variables from
codelist (e.g.: TRT01PN)

Traverse the "Pharmaverse": ouR insights

- Understanding admiral

PURPOSE

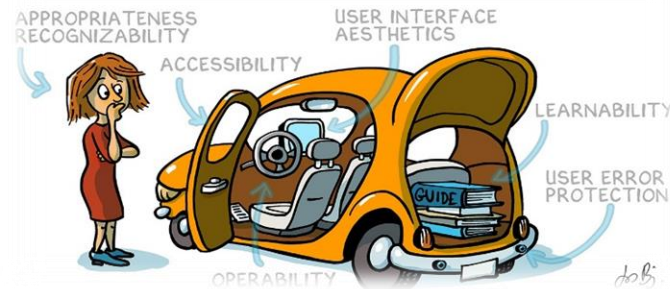
To provide an open source, modularized toolbox that enables the pharmaceutical programming community to develop ADaM datasets in R.

admiral

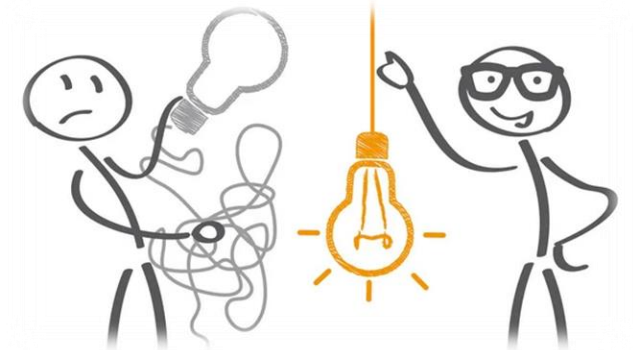
- [admiral \(pharmaverse.github.io\)](https://pharmaverse.github.io)

Derive
Assigned/Derived
variables

Usability



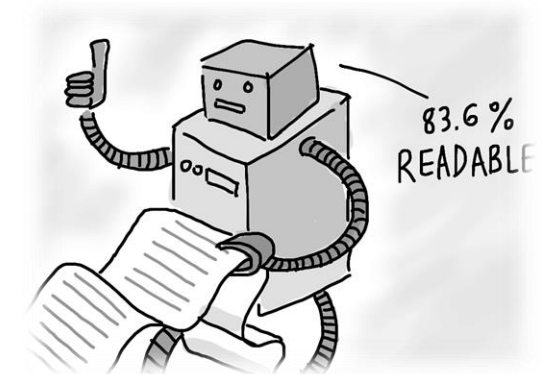
Simplicity



Findability



Readability



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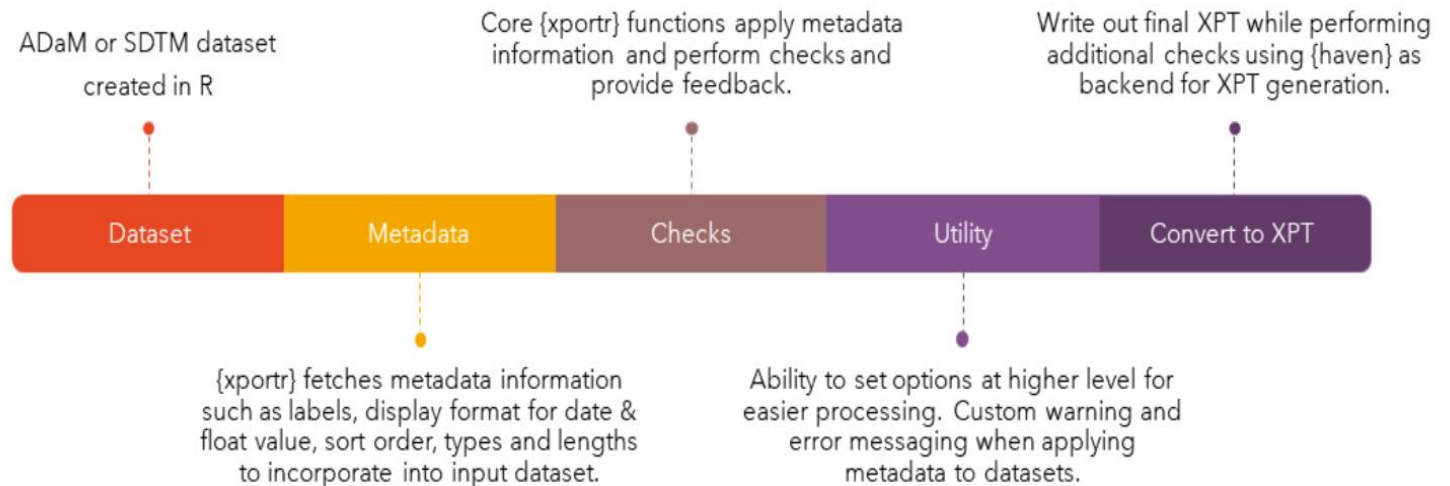
- Understanding xportr



PURPOSE

This package has the functionality to associate metadata information to a local R data frame, perform data set level validation checks and convert into a [transport v5 file\(xpt\)](#).

Final transportable file
creation and validation

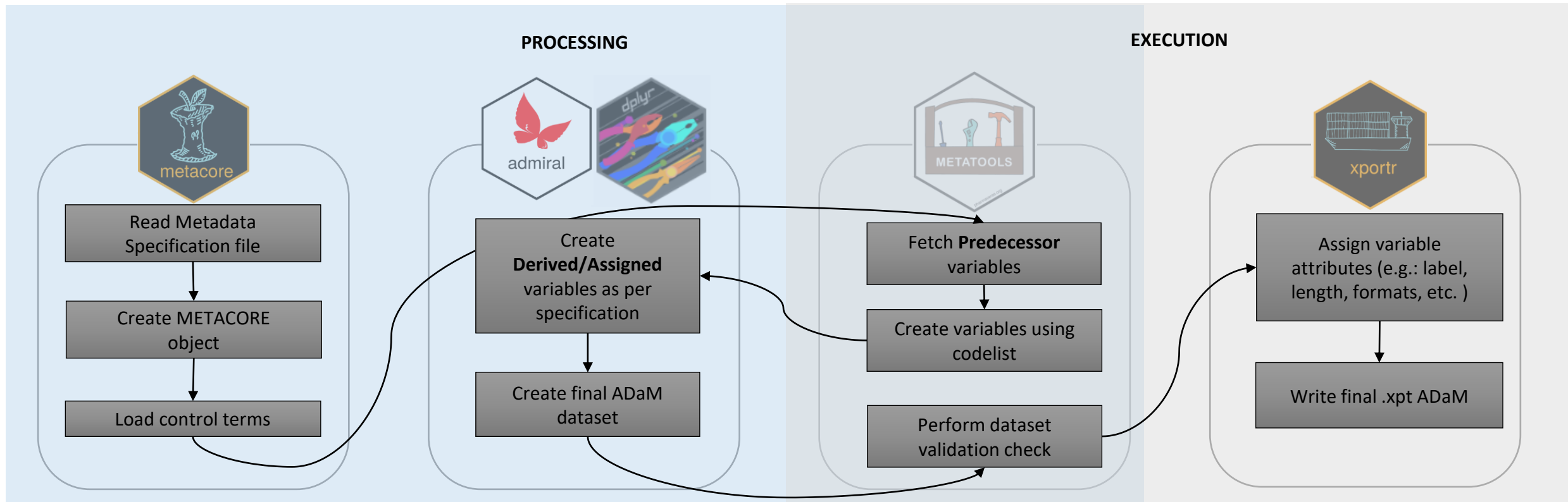


- [xportr \(atorus-research.github.io\)](https://atorus-research.github.io/xportr/)

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- Workflow

INITIALIZE : Load libraries and required input datasets



Traverse the "Pharmaverse": ouR insights

- R Pilot submission story

pilot3 3.3.3

Project Background/Setup ▾ Deliverables ▾ Conferences ▾ Feedback from FDA ▾

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Project Background

Below we discuss the scope of the project and how we worked as a team. All submission materials and communications from this pilot are publicly available, with the aim of providing a working example for future R language based FDA submissions.

The Scope

The team landed on developing five ADaM datasets in R with a focus on using the R package [admiral](#). These five ADaMs supported the already developed [Submission Pilot 1](#) TLFs that were delivered to the FDA in 2021. A Cover Letter and ADRG were also created as part of this submission.

The submission package is small and makes use of a modernized version of the [CDISC Pilot data](#). The CDSIC Pilot was developed to demonstrate that the CDSIC standards met the requirements of FDA Reviewers. The R-based Pilots are more interested in the delivery process and use of R. Therefore, it was decided that only a subset of the [CDISC Pilot data](#) was needed to accomplish our goals.

The Team

The Pilot 3 team met weekly over the course of 2022 and 2023 comprising of individuals across the Pharma Industry. We used [pharmaverse slack](#) and [GitHub](#) to communicate on blockers and ideas in between meetings.

We would report back monthly to the R Submission Core Team on progress and blockers. The [Submissions Working group website](#) houses some additional discussion and supporting documentation on Pilots 1, 2, 3 and now 4!

We kept minutes and recordings of our meetings, which can be found here: [‘STAND-UP’ MINUTES](#)

The Results

Please take a look at the Deliverable Tab to see our Cover Letter to the FDA, TLFs, ADaMs and a R-based ADRG. All done in R!

On this page

The Scope

The Team

The Results

Developed by Joel Laxamana-Roche, Robert Devine-J&J, Benjamin Straub-GSK, Kangjie Zhang-Bayer, Thomas Neitmann-Roche, Phanikumar Tata-Syneos, Steven Haesendonckx-J&J, Rikimaru Nishimura-J&J, Yutong Liu-Moderna, Lei Zhao-Roche, Nicole Jones-Merck, Benjamin Wang-Merck, Ryan Johnson-Posit, Dadong Zhang-Illumina, Declan Hodges-GSK.

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[Project Background • pilot3 \(rconsortium.github.io\)](#)

Deliverables ▾ Conferences ▾ Feedback from FDA ▾

Cover Letter

Displays

Summary of Demographic and Baseline Characteristics

Efficacy Tables

Kaplan-Meier Plot for Time to First Dermatologic Event

ADAS Cog Change from Baseline to Week 24 - LOCF

Datasets and ADRG

ADSL - Subject Level Analysis

ADAE - Adverse Event Analysis

ADLBC - Laboratory Results Chemistry Analysis

ADTTE - AE Time to 1st Derm. Event Analysis

ADADAS - ADS-COG Analysis

ADRG - Analysis Data Reviewer's Guide

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- R Pilot submission story

pilot3 3.3.3 Project Background/Setup ▾ Deliverables ▾ Conferences ▾ Feedback from FDA ▾

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Feedback: January 2024

Overview

The [R Consortium Submissions Working Group](#) meets monthly to discuss progress on the various pilots being submitted to the FDA as well as receive feedback from the FDA reviewers. Pilot 3 was submitted in October 2023 and has started to receive feedback from the reviewers.

The following is a summary of the January 2024 meeting that pertains to the Pilot 3 Submission

- The FDA Review indicated that using the R generated ADaM data sets in Pilot3, the reviewers were able to replicate the results of the four analyses used in Pilot 1. The FDA Reviewer (Hye Soo) did identify (so far) several issues and presented observations and questions for response from the Pilot3 Team.
- Items [1] through [3] are Actionable. Items [4] and [5] are Non-Actionable.

On this page

- Item 1
- Item 2
- Item 3
- Item 4
- Item 5

Item 1

- FDA Reviewer observed no statistical analysis plan (SAP) was included with the Pilot3 submission.

Action Item: Confirm with FDA Reviewers that the SAP should be included if a re-submission is requested. Given Question 1(b) inclusion of the SAP may provide clarity regarding correctness.

Item 2

- The Primary output in Pilot 3 was different from the Pilot 1 result due to the QC findings. QC findings in the ADRG include all of the discrepancies between the original ADaM datasets.

Action Item: Respond to FDA Review Question #1: How did you know this was an issue from the CDISC ADaM (Pilot1) and how did you correct them? FDA Reviewer shared an example using USUBJID 01-705-1292

Question 1(a): Why was LOCF required when there was no missing data in the QS?

Observation: FDA Reviewer (Hye Soo) noted in the primary results (i)slight difference in rounding and (ii)quite different p-values. [Appears to be due to QC Findings discrepancies.] **Action Item:** Respond to FDA Review Question 1(b): Which primary analysis output is correct? Hye Soo noted lack of clarity regarding determination of correctness due to unavailable SAP.

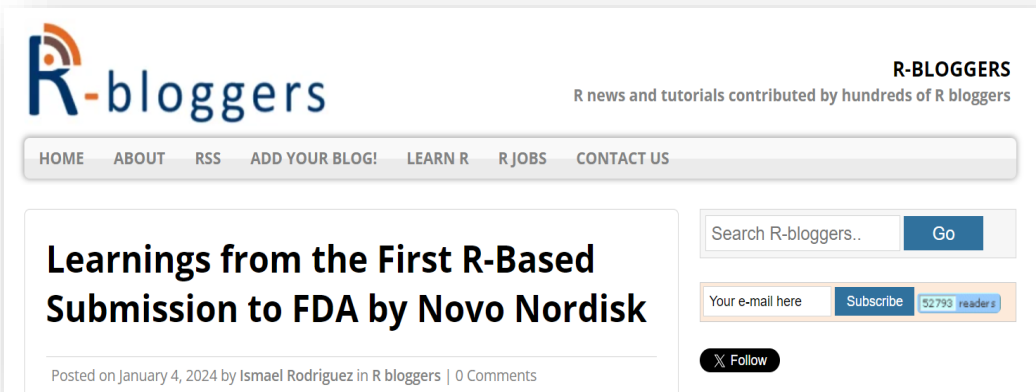
Item 3

- FDA Review also presented an observation noting that in the Pilot3 Summary Tables and Figures Report you noted that different open-source packages were used when generating each of the 4 analysis outputs to test wider use case scenarios. However, the R packages and scripts seem identical to Pilot1.

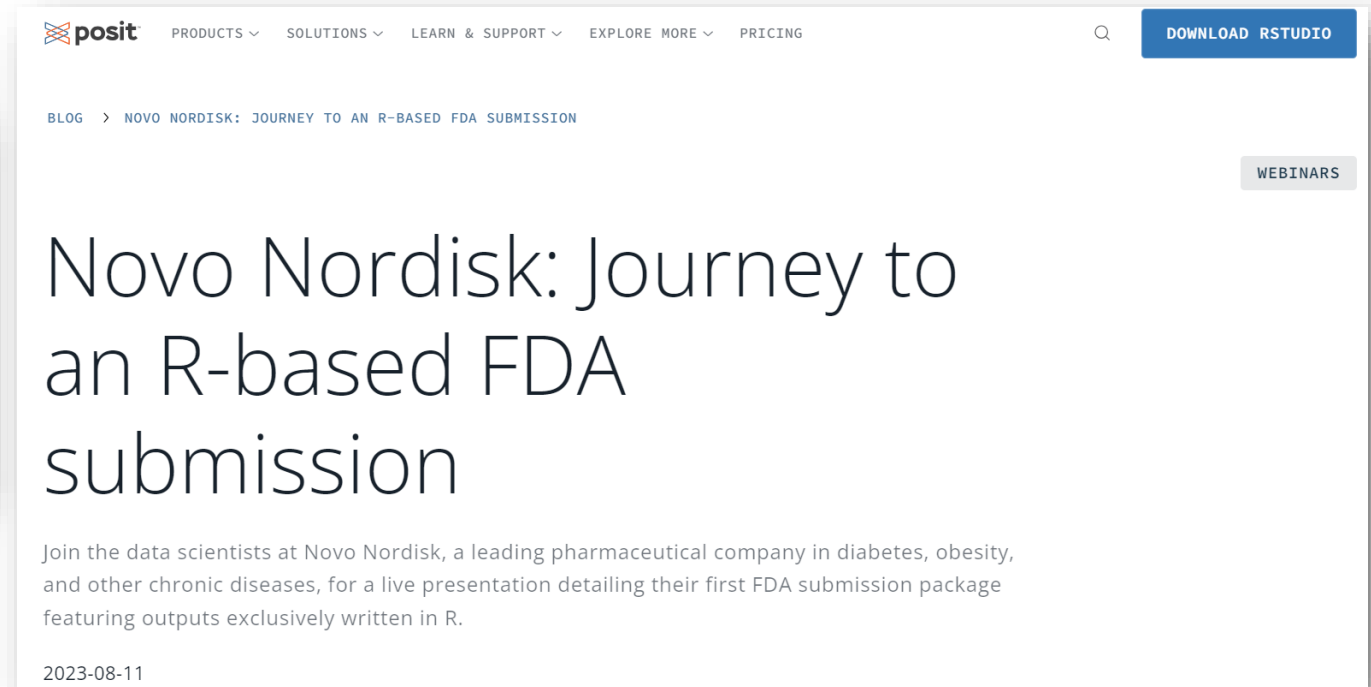
Action Item: Respond to FDA Review Question #2: What exactly has changed? *This was discussed at the R Consortium WG and Ning responded to the question by stating the language used in the Pilot3 submission was carried over from Pilot1 to Pilot3. The Pilot3 response should confirm Ning's response to Hye Soo.

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- R Submission success stories



- [Learnings from the First R-Based Submission to FDA by Novo Nordisk | R-bloggers](#)
- Gives a nice summary of past projects as well, talks about Pilot 1,2,3,4



- [Novo Nordisk: Journey to an R-based FDA submission – Posit](#)
- You Tube link: [Novo Nordisk's Journey to an R based FDA Submission - YouTube](#)

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- References

- pharmaverse : <https://pharmaverse.org/>
- {metacore}: <https://atorus-research.github.io/metacore/>
- {metatools}: <https://pharmaverse.github.io/metatools/>
- {admiral}: <https://pharmaverse.github.io/admiral/cran-release/>
- {xportr}: <https://atorus-research.github.io/xportr/>

I would like to acknowledge Ben Straub and all the contributors of above-mentioned packages for their support and kind contributions to R for clinical programming open-source community. My colleague Tanisha Gupta for helping me with the presentation. Also, ISCR organizing committee for providing us the opportunity to share our experience.

Thank You!!!

- Don't Keep calm and explore Pharmaverse.

