



The R Journey to Submission

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01 Introduction

Introduction

A new chapter in regulatory clinical trial reporting



- Adoption of R
- Upskilling in new tools and systems
- Curated end to end R package solutions
- Submission Pilots with FDA



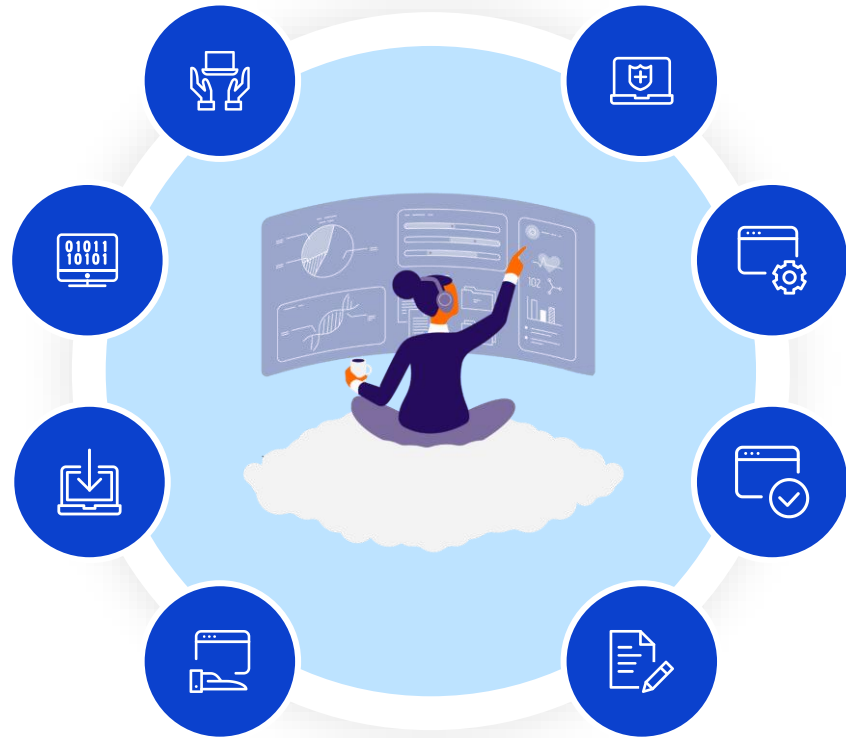
Modernise eSubmission of readable code



OCEAN

Roche PD Data Sciences **Next Gen Tools & System:**

- **OCEAN** (One CEntralised ANalytics platform): a state-of-the-art, cloud-based Analytics & Data platform for both regulatory and exploratory clinical trial work



Early Adopters - The Journey

End users shaping the future tools



Choosing the
Right Study

Consider Study
Timelines



Motivation
Passion

Upskilling
Practice



Programming
Strategy

First Line in R
QC in SAS[®]

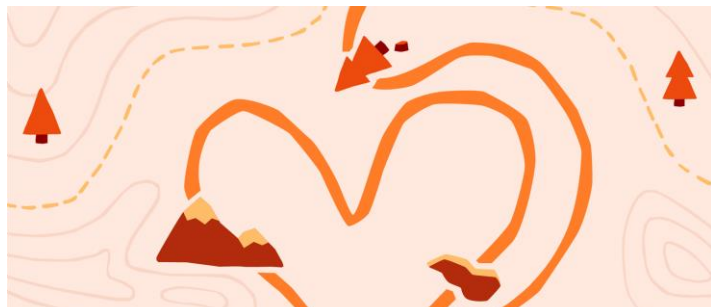


Stakeholder
Management

Health
Authority
Collaborations

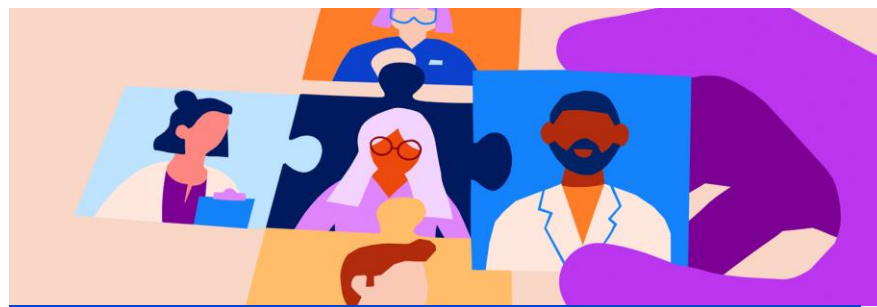


Learning Experience



Learning Curve

- Feels steep
- Increase in confidence, familiarity and delivery over time



Pharmaverse: Positive User Feedback



02 The Regulatory Submissions Journey

Programming Approach

End-to-end in R submission - using primarily open source packages from Pharmaverse

SDTM



ADaM



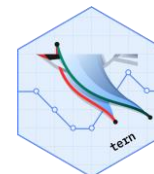
Proprietary



TLGs



**Readable
code**



Regulatory Submission Journey

- Global eSub- FDA, EMA, NMPA.
- HA interactions prior to submission, and related feedback during review period
- How we prepare the eSUB module 5 with limited extra effort.

Interactions with Health Authorities : FDA

Prior to Submission

**June
2023**

Briefing Package :

Propose to include R open source packages for readable code submission for the pivotal Study.

**Aug
2023**

FDA written response:

Agreement.

Please provide appropriate justification and evidence of validation of the package or function used.

Interactions with Health Authorities: FDA

After Submission



- Technical Walkthrough Meeting
- Datasets & supporting documents in module 5
- List and location of the R documents
- Point out different defaults between R and SAS[®]



No Technical Related Information Request Regarding R Submission. FDA approval - 7 weeks ahead of the FDA goal date!

EMA: EU Raw Data Pilot



- EU Raw Data Pilot Meeting
- Similar contents as FDA technical walkthrough
- More details regarding the contents of submitted datasets
- Example of connecting information from the submitted documents



No Technical Questions So Far. Feedback : EMA Replicated analysis is consistent with results provided.

Interactions with NMPA



Some discussion about R submission via R consortium



Had some pre-consultation in other studies

Proposed to **inc. open-source R packages**

June 2023

June 2023

Open-ended responses during **consultation window**

FDA agreed. Requested to provide **justification & evidence of validation**

Aug 2023

Sept 2023

Type III meeting was requested with more comprehensive supportive information

Database Lock

Nov 2023

Jan 2024

CDE written response that **consistent with FDA**

eSUB Contents for E2E R Study

SDTM Package:

- ☐ SDTM data in xpt format from **OAK**
- ☐ Define.xml
- ☐ SDRG
- ☐ aCRF

ADaM Package:

- ☐ ADaMs data in xpt format from **admiral (inc admiralroche)**
- ☐ Define.xml
- ☐ **R Readable code** for ADaMs and Key outputs
- ☐ ADRG

Information for use of R

- ☐ **programTOC** :
 - R specific details
 - Package being used & version
 - Instruction to install R on windows and packages (both open and Proprietary)
- ☐ **Validation reports** for key R packages.

File of ProgramTOC discloses R Packages



Description of eSUB package



List of Analysis Dataset Programs



List of Output Programs



How to use the readable codes



Appendix: Instruction to execute analysis programs in R

File of ProgramTOC discloses R Packages

How to use the Readable code

Proprietary R Analysis Packages

Proprietary R Analysis Package	Package version	Description
<u>admiralroche</u>	0.3.0	Roche-specific extension of admiral. Provides Roche-specific functionality to facilitate ADaM programming using admiral.

Open-source R Analysis Packages

R Packages	Package version	Description
admiral	0.12.1	A toolbox for programming Clinical Data Interchange Standards Consortium (CDISC) compliant Analysis Data Model (ADaM) datasets in R. Analysis derivations are implemented in accordance with the "Analysis Data Model Implementation Guide" (CDISC Analysis Data Model Team, 2021, < https://www.cdisc.org/standards/foundational/adam/adamig-v1-3-release-package >).
<u>admiraldev</u>	0.5.0	Utility functions to check data, variables and conditions for functions used in 'admiral' and 'admiral' extension packages.



Examples in [R Consortium Submission Working Group](#):

File of ProgramTOC discloses R Packages

Include Proprietary R Package

- Convert package of admiralroche to txt file through R package of “pkglite”



[\[link\]](#)

- Include converted txt file to eSUB package along with other readable code for ADaM
- Will be used to install “admiralroche”

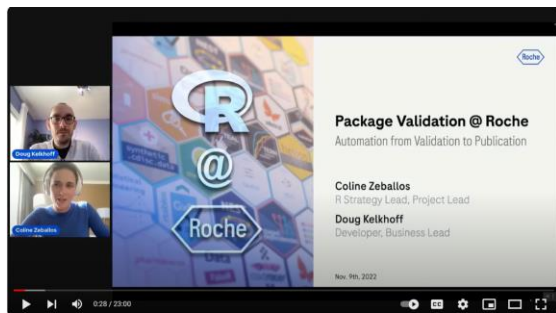
File of ProgramTOC discloses R Packages

Appendix: Instruction to Execute Analysis Program in R

- 1 Install R
- 2 Define Working Directory
- 3 Specify R package repository
- 4 Install open-source R packages
- 5 Install Proprietary R packages
- 6 Update paths to source datasets and execute programs

Internal Validation Process

- Broadly follow the process outlined by the [R Validation Hub's white paper](#)
- Internal R packages Validation process:
 - Autovalidate R is a process of documenting and upholding a set of R package quality expectations.
 - All validation processes are a balance among being thorough, actionable, and fast.
 - [[Roche's approach to software validation.](#)]



R/Pharma 2022 Day 2: Coline Zeballos & Doug Kelkhoff. Roche's approach to software validation



03 Key Takeaways

Key Takeaways



- Health Authorities are open to the usage of R for submission.
- Communicate clearly and align with Health Authorities prior to submission.
- Practical plan within study team
- Disclose the usage of R in submitted package.
- Limited extra efforts to achieve R submission.

Thank you!

Your comments and questions are valued and encouraged. Contact the authors at:

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Doing now what patients need next