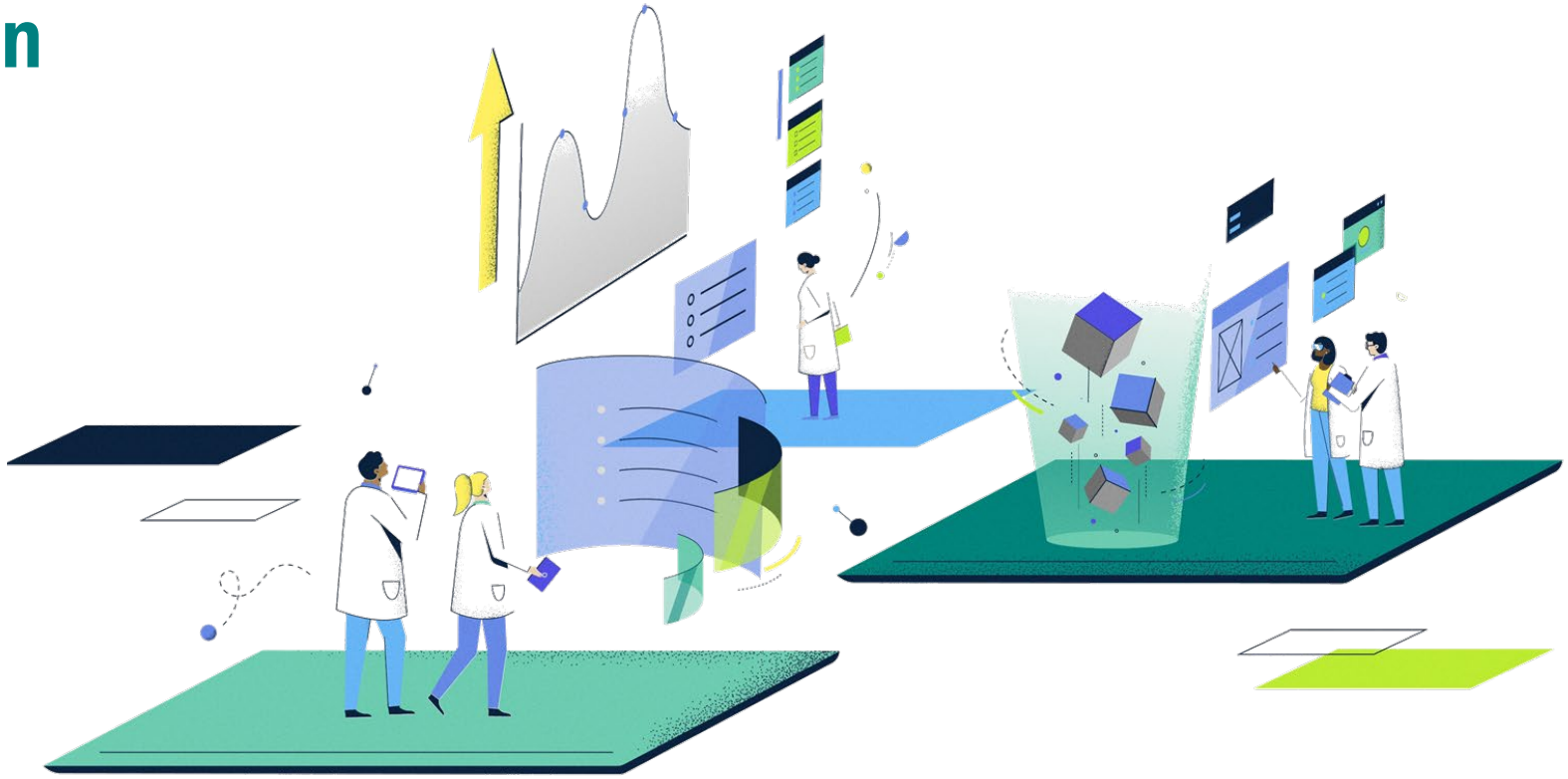
R and Shiny in Regulatory Submission



Gregory Chen

Biostatistics and Research Decision Sciences (BARDS), MSD, Switzerland

Ning Leng

Product Development Data Sciences (PDDS), F. Hoffmann-La Roche, USA

on behalf of R Consortium Submission Working Group

present to Swissmedic in Bern, Switzerland

Jan 30, 2024

Outline

1. Introduction: R Consortium Submission Working Group
2. Open-Source Software (OSS) for Regulatory submission
    - What is important in a regulatory submission
    - Why consider adopting open-source statistical software
    - Key Challenges
3. Using R and Shiny in Regulatory Submission
    - R, Its suitability and current landscape
    - Pilots of R Consortium Working Group
    - Can Shiny bring opportunity for easier and faster review?
    - OSS challenges in the context of R
4. Acknowledgement
5. Discussion

Declaration

This presentation only reflects personal view or understanding of the presenter, not representing company's position.

Introduction:

R Consortium Submission Working Group

The R Consortium, announced in 2015 useR! Conference, is a non-profit organization with an open-source governance and foundation model to support the worldwide community of users, maintainers and developers of R software.

Central Mission:

Work with and provide support to the R Foundation and key organizations and groups developing, maintaining, distributing and using R software. Its activities and programs include:

- Promoting the growth and development of R as a leading platform for data science and statistical computing
- Supporting and collaborating with the R Foundation, the governing body of the R Project
- Funding projects to enhance R and support its users
- Fostering the continued growth of R community and the data science ecosystem *(sponsors R-related conferences, meetings, and local user groups worldwide)*

Current Members

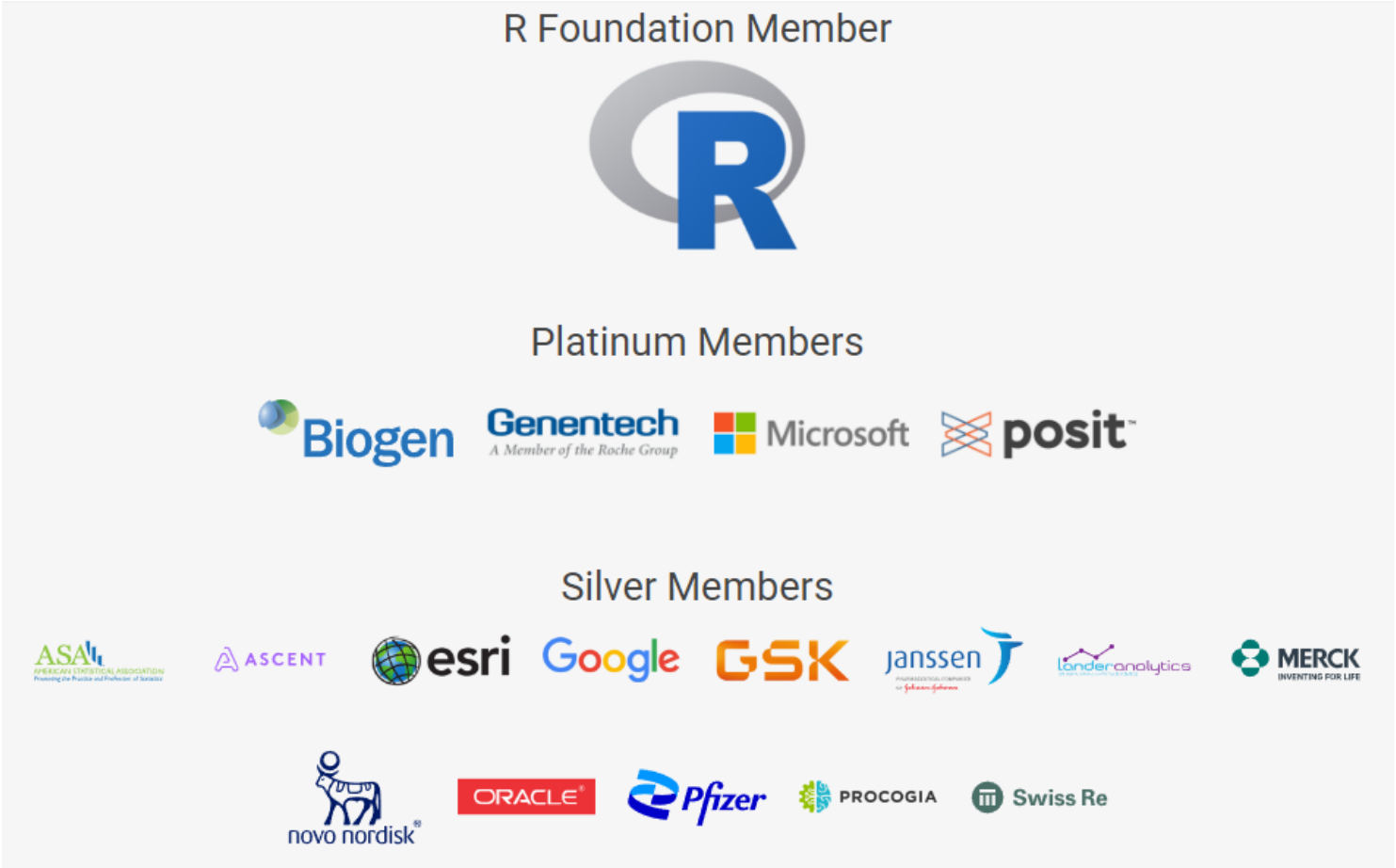
(Associate Members are not displayed)

See Governance here

See Bylaw here

See Infrastructure Steering Committee* here

** ISC working groups provide the mechanism through which the ISC can explore, fund, and manage large collaborative projects.*



Cited from: https://www.r-consortium.org/members

Current Active Working Groups

Active Working Groups

Census: Is developing package recommendations, and other materials for working with census data.

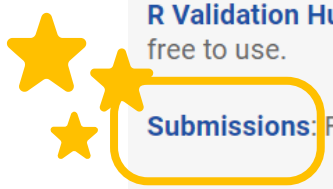
R7 Package: Object-Oriented Programming. The R7 package is a new OOP system designed to be a successor to S3 and S4. It has been designed and implemented collaboratively by the R Consortium Object-Oriented Programming Working Group, which includes representatives from R-Core, BioConductor, RStudio/tidyverse, and the wider R community.

R Certification: Is working to establish a common certification program for proficiency in R.

R Repositories: Collaboratively exploring how to support, maintain, and improve the tooling for R package distribution.

R Tables for Regulatory Submission (RTRS): Develop standards for creating tables that meet the requirements of FDA submission documents

R Validation Hub: Working to devise a standard for validating packages for the regulated Pharmaceutical industry and create a online repository that will be free to use.



Submissions: Focus on IT and platform challenges that must be addressed in order to make "all R" regulatory submissions.

Active working groups have public mailing lists to facilitate discussions.

Cite from: https://www.r-consortium.org/all-projects/isc-working-groups

Submission Working Groups

See details here and our public GitHub repo here

The R submission working group is a cross-industry working group in pharma, focusing on improving practices of R-based clinical trial regulatory submissions. The working group has

- ca. 75 participants in total, out of which ca. 15 are active in an average month
- from 20+ companies (incl. pharma, CROs, Posit) and FDA
- monthly joint meeting, open to everyone and records are available on YouTube

Our mission is to make R-based clinical trial regulatory submissions easier today and tomorrow by

- sharing pilot examples of using current regulatory submission portals on public repository (github),
- collecting feedback and influencing future industry and agency decisions on system/process setup regarding R based submission

Open-Source Software (OSS)

For Regulatory Submission

- What is important in a regulatory submission
- Why consider adopting open-source statistical software
- Key Challenges

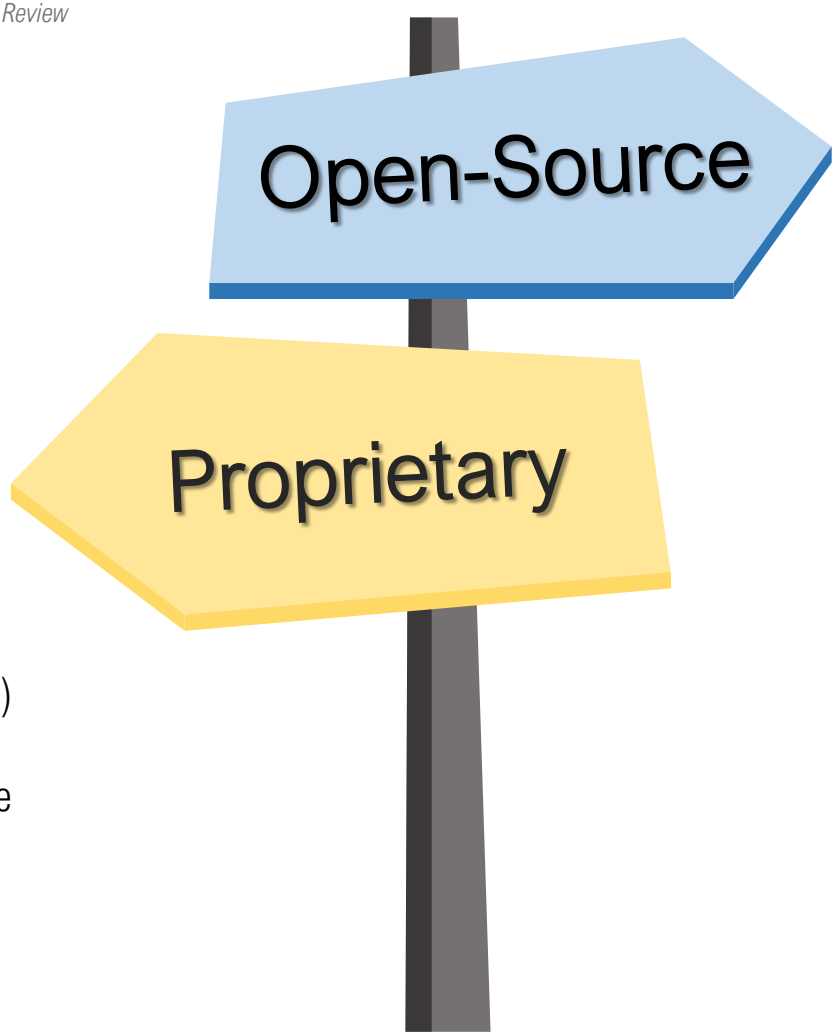
Open-Source Software (OSS)

For Regulatory Submission

- What is important in a regulatory submission
- Why consider adopting open-source statistical software
- Key Challenges

What are Proprietary and Open-Source Software (OSS)

See more discussion on R Adoption Series – Using R in Regulatory Review
https://www.youtube.com/watch?v=dtdd_jc1ybw&t=1979s



- Publicly accessible with no fee
- Distributed with its source code, making it available for inspection, modification and enhancement
- Example: R, Python

- Non-free or closed-source software
- Can be expensive
- Source code of a (modeling or plotting) function can only be examined and modified by the original owner(s) of the software exclusively
- Example: SAS, STATA

What is important to a regulatory submission:

Analysis should be done in a specific programming language? **No!**

For example, here is FDA's Statistical Software Clarifying Statement

”
“

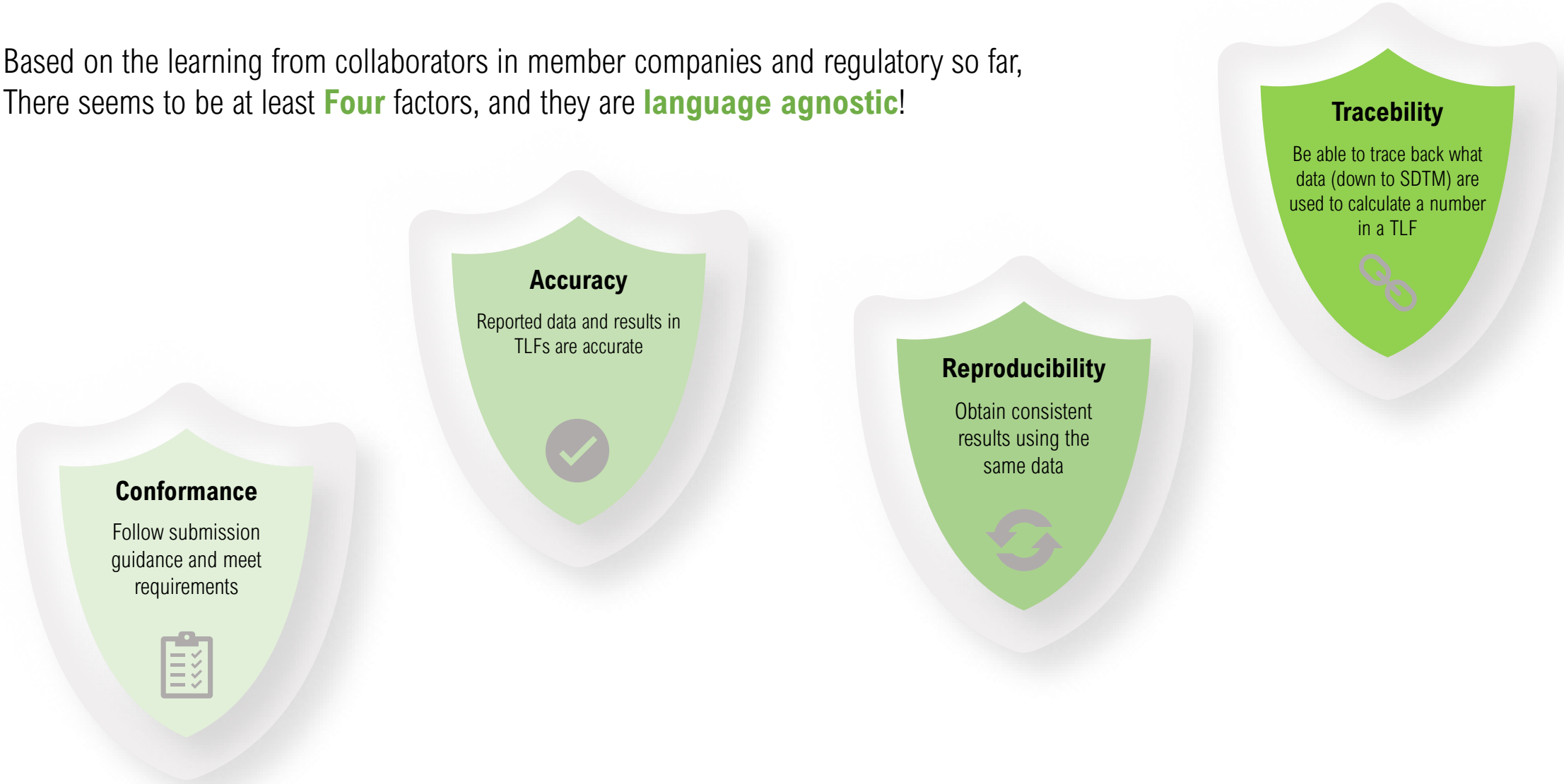
May 6, 2015

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.

As noted in the FDA guidance, *E9 Statistical Principles for Clinical Trials* (available at this link), "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.

What could be important ?

Based on the learning from collaborators in member companies and regulatory so far,
There seems to be at least **Four** factors, and they are **language agnostic**!



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Open-Source Software (OSS)

For Regulatory Submission

- What is important in a regulatory submission
- Why consider adopting open-source statistical software
- Key Challenges

Why Consider Open-Source Software (OSS)

Just to name a few …

New advance or practical methods typically become available in OSS much quicker than in Proprietary Software

New graduates (also your future talents in regulatory) are likely much more familiar with OSS (e.g. R, Python) nowadays than some proprietary software

OSS makes cross-pharma collaboration easier, stimulate discussion and effort towards "cross-industry" solutions on various topics

tested by unpredictable use cases in reality, by pharma practitioners, academia and even practitioners in other industries, quality of the product can improve quickly

all source code and documentations are publicly accessible (for collaboration and for inspection), including issues/bugs reported by user and what is fixed when, full transparency

Open-Source Software (OSS)

For Regulatory Submission

- What is important in a regulatory submission
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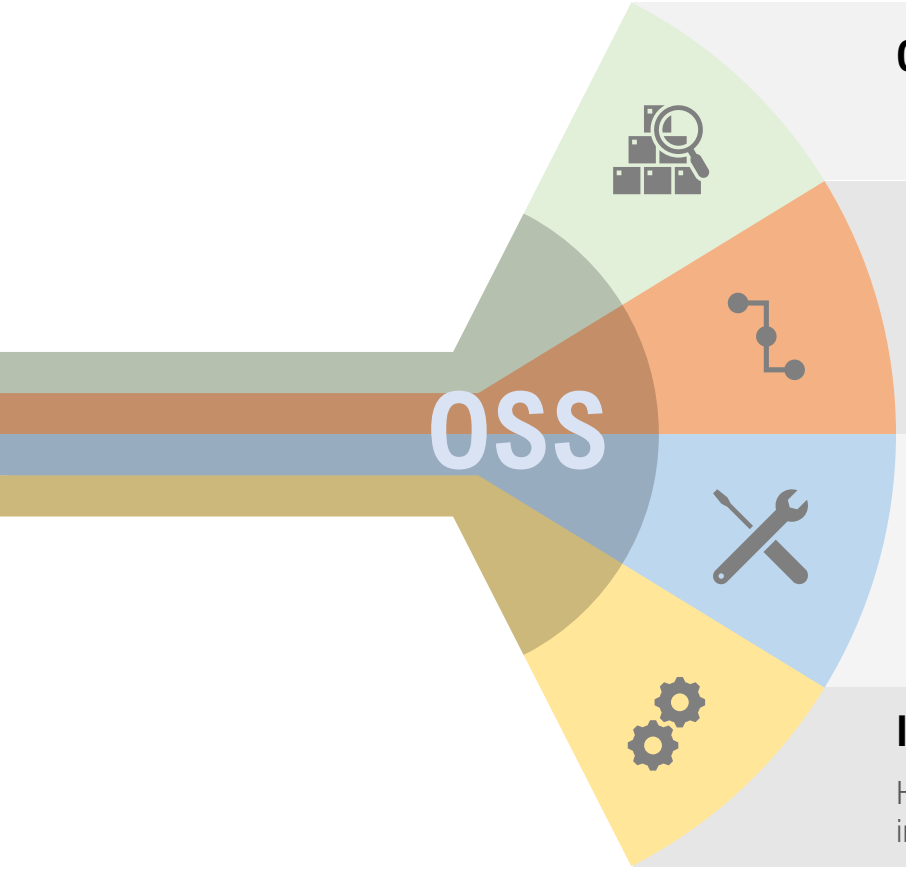
Challenges with Open-Source Software (OSS)



Qualiy and Validation

For one model, there are usually many OSS solutions, which one to be trusted?

Version Control for Reproducibility

Rate of change could be a two-side sword. An OSS solution or its dependency could be upgraded many version within a short time frame to pursue higher quality. A program using such OSS may work for a past version but not for the new version (backward compatibility). Even the program remains executable, the result might be different. This calls for good documentation and version control

Maintain and Support

Will the trusted OSS solution be maintained over time? Who to call when there is a bug?

Implementation and Deployment

How can reviewers on the regulatory side run the submitted files using OSS? Will In-house IT support needed for infrastructure related issues?

Using R and Shiny in Regulatory Submission

- R, Its suitability and current landscape
- Pilots of R Consortium Working Group
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R, Its suitability and current landscape

Introduction

A free programming language and software environment that is used for statistical computing. R was first created in 1993, and it is now supported by the R Foundation for Statistical Computing.

Although R is open source, its updates, maintenance and releases are tightly controlled by the R Core Team to ensure stable development.

Main repositories of OOS R packages developed by broad R communities are Comprehensive R Archive Network (CRAN), GitHub, and Bioconductor.

Current Landscape in Submission Usage

FDA has yet to experience a completely R based submission, but hybrid submissions and hybrid workflows are reported. See more discussion on this YouTube link.

Full submission based on R to other agencies is also yet to happen. **Pilot in partner with different agencies to experiment how to make it work and give examples and guidance to pharma companies** is the key mission of our working group.

Suitability

In response to federal regulations, the R Foundation released R: Regulatory Compliance and Validation Issues. A Guidance Document for the Use of R in Regulated Clinical Trial Environments. This document relates to both Base R and recommended R packages.

This document relates to both Base R and recommended R packages. The R Foundation addresses the validation of R, and includes the following information:

- Relevance of 21 CFR Part 11 to R
- R's definition of validation*
- Organizations are responsible for validating their R installations
- R Foundation's System Development Life Cycle (SDLC)**
- Responses to various sections of 21 CFR Part 11

* The R Foundation uses the FDA's Glossary of Computer System Software Development Terminology definition of "validation", namely, Establishing documented evidence which provides a high degree of assurance (accuracy) that a specific process consistently (reproducibility) produces a product meeting its predetermined specifications (traceability) and quality attributes.

** see more details here.

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R submission Pilots to FDA

- Collaboration between the R consortium R submission Working Group and FDA

	Pilot 1	Pilot 2	Pilot 3	Pilot 4
Focus	TLF	Shiny	ADaM	Shiny in Container
Main Purpose	To test an R-language based submission package can meet the needs and expectations of the FDA	To test a Shiny application created with the R-language can be bundled into a submission package and transferred to FDA	To re-test the pilot 1 with ADaM datasets generated using R	To test a potential solution (container-based) in delivering a regulatory shiny app with easier deployment on the regulator side
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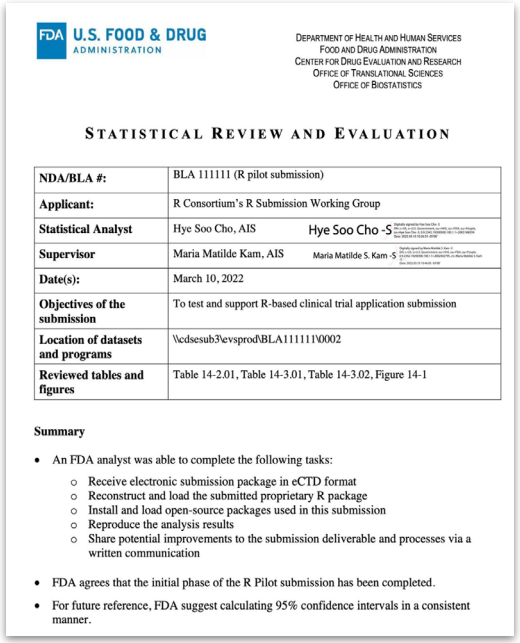
Pilot 1 Submission to FDA:

Successful open pilot that showcased R based FDA submission



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CENTER FOR DRUG EVALUATION AND RESEARCH
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OFFICE OF BIOSTATISTICS

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
Supervisor	Maria Matilde Kam, AIS Maria Matilde S. Kam -S
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:
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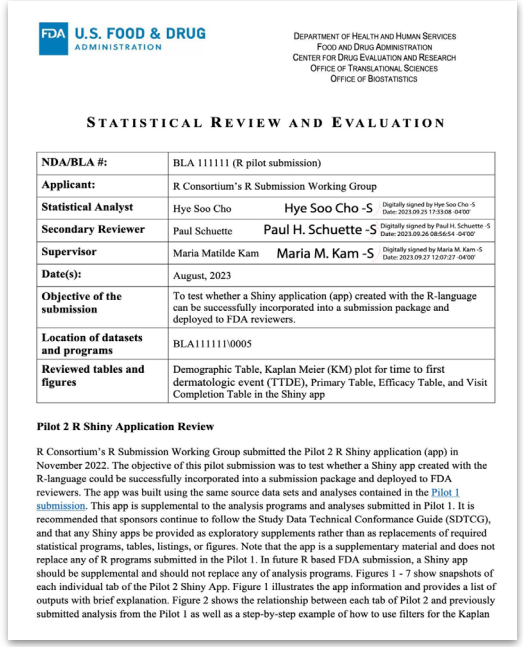
  - Install and load open-source packages used in this submission
  - Reproduce the analysis results
  - Share potential improvements to the submission deliverable and processes via a written communication
- FDA agrees that the initial phase of the R Pilot submission has been completed.
- For future reference, FDA suggest calculating 95% confidence intervals in a consistent manner.

Pilot 2 Submission to FDA:

Successful open pilot that showcased shiny based FDA submission



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Key Links

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- Pilot 3: https://github.com/RConsortium/submissions-pilot3-adam-to-fda

All materials are open to the public
Anyone is welcome to join the working groups! (info@r-consortium.org)

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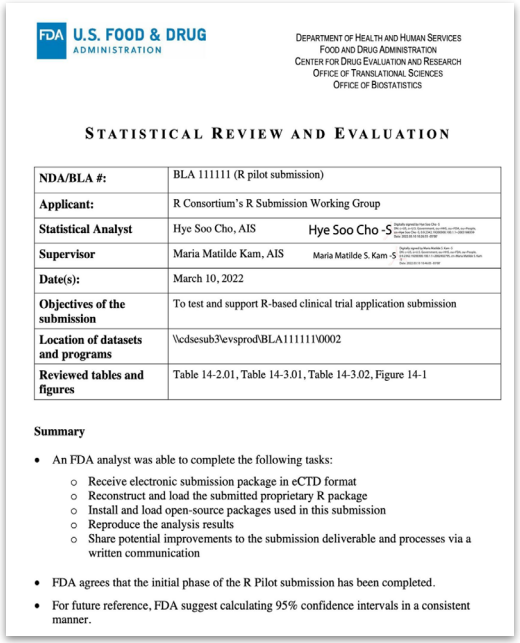

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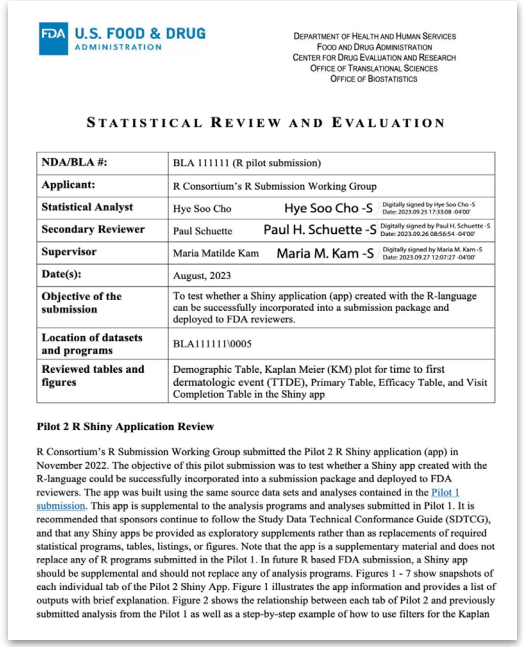

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- Pilot 3: https://github.com/RConsortium/submissions-pilot3-adam-to-fda

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Anyone is welcome to join the working groups! (info@r-consortium.org)

R Pilot 1 Submission: What were submitted

- ADaM datasets (.xpt files)
- A pdf report with 4 analyses outputs
- Analysis Data Reviewer's Guide (ADRG), link here
- Analysis output programs (.r files)
- Sponsor developed R package (.txt file)

Adhered to the specification of Electronic Common Technical Document (eCTD*) portal.

* eCTD: the standard format for submitting applications, amendments, supplements, and reports to FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER).

R Pilot 1 Submission: A peek into ADRG

7. Submission of Programs

Description

The sponsor has provided all programs for analysis results. They are all created on a Linux platform using R version 4.1.0.

Proprietary R Analysis Package	Package version	Analysis Package Description
pilot1wrappers	0.1.0	A collection of R functions for this pilot project. Functions include wrappers for ANCOVA modeling and data/tableformatting.
cowplot	1.1.1	Arrange figure
dplyr	1.0.7	Manipulate dataset.
emmeans	1.6.3	Calculate least square mean
ggplot2	3.3.5	Create figure
haven	2.4.3	Read in SAS dataset.
huxtable	5.4.0	Style data into presentation ready table
pharmaRTF	0.1.3	Write out a styled table to RTF format
pkglite	0.2.0	Prepare submission package
r2rtf	0.3.0	Create RTF table

Appendix: Instruction to Execute Analysis Program in R

1. Install R

Download and install R 4.1.2 for Windows from https://cran.r-project.org/bin/windows/base/old/4.1.2/R-4.1.2-win.exe.

2. Define Working Directory

Create a temporary working directory, For example, "C:\tempwork". Copy all submitted R programs into the temporary folder. All steps below should be executed in this working directory represented as "." in the example R code below.

3. Specify R package repository

The R packages are based on CRAN at 2021-08-31. To install the exact R package versions used in this project, run the code below to set the snapshot repository.

```
options(repos = "https://mran.microsoft.com/snapshot/2021-08-31")
```

4. Install open-source R packages

In the same R session, install the required packages by running the code below.

```
install.packages(c("haven", "dplyr", "emmeans", "pkglite" , "r2rtf", "rtables", "ggplot2",
                   "cowplot", "visR", "Tplyr", "pharmaRTF", "huxtable"))
```

5. Install Proprietary R packages

The proprietary R package "pilot1wrappers" is packed in the file r0pkg.txt. In the same R session, restore the package structures and install them by running the code below. Adjust the output path as needed to use a writable local directory.

```
pkglite::unpack("r0pkg.txt", output = ".", install = TRUE)
```

6. Update path to dataset and TLFs

R Pilot 1 Submission: 4 analysis outputs (1/2)

Table 14-2.01

Summary of Demographic and Baseline Characteristics

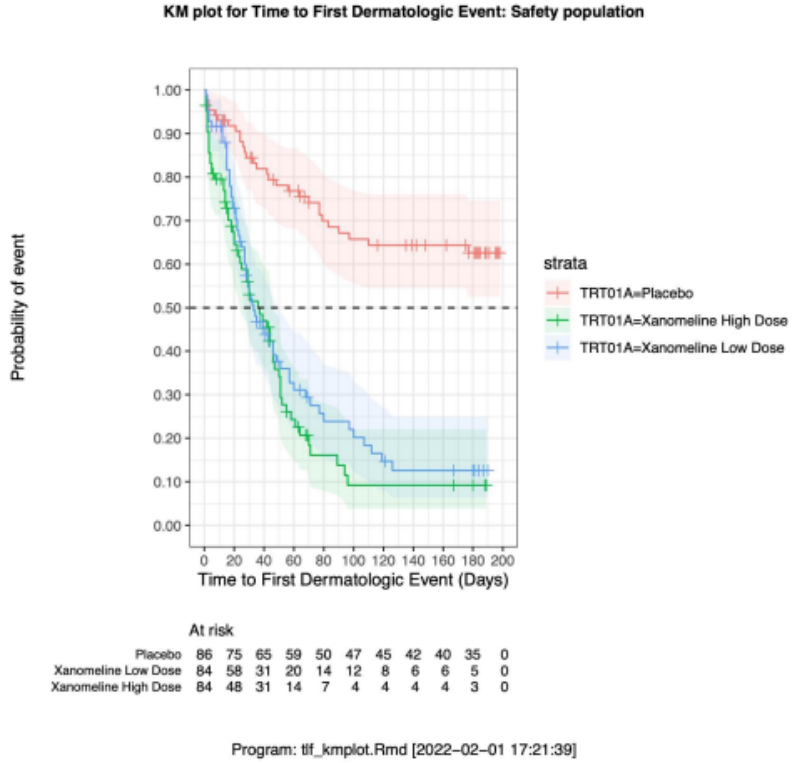
Protocol: CDISCPILOT01
Population: Intent-to-Treat

	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 (10.13)
Median	162.6	162.6	165.1
Min - Max	137.2 - 185.4	135.9 - 195.6	146.1 - 190.5
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

Figure 14-1

Time to Dermatologic Event by Treatment Group



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

R Pilot 1 Submission: 4 analysis outputs (2/2)

Table 14-3.01

Primary Endpoint Analysis: ADAS Cog (11) - Change from Baseline to Week 24 - LOCF

Protocol: CDISCPILOT01 *Page 1 of 1*
Population: Efficacy

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

	Placebo (N=79)	Xanomeline Low Dose (N=81)	Xanomeline High Dose (N=74)
Baseline			
n	79	81	74
Mean (SD)	24.1 (12.19)	24.4 (12.92)	21.3 (11.74)
Median (Range)	21.0 (5;61)	21.0 (5;57)	18.0 (3;57)
Week 24			
n	79	81	74
Mean (SD)	26.7 (13.79)	26.4 (13.18)	22.8 (12.48)
Median (Range)	24.0 (5;62)	25.0 (6;62)	20.0 (3;62)
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 (0.84)
95% CI		(-2.1;1.1)	(-2.7;0.7)
p-value(Xan High - Xan Low) [1][3]			0.520
Diff of LS Means (SE)			-0.5 (0.84)
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

Table 14-3.02

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

ANCOVA of Change from Baseline at Week 20

	Baseline[a]		Week 20		Change from Baseline		
Treatment	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	LS Mean (95% CI)[b]
Xanomeline High Dose	84	5.4 (1.34)	31	5.8 (1.61)	31	0.2 (1.47)	0.16 (-0.31, 0.63)
Placebo	86	5.6 (2.14)	65	5.8 (1.50)	65	0.1 (2.08)	0.09 (-0.23, 0.42)
Pairwise Comparison			Difference in LS Mean (95% CI)[b]				p-Value
Xanomeline High Dose vs. Placebo			0.07 (-0.50, 0.63)				0.822
Root Mean Squared Error of Change = 1.30							

[a] Table is based on participants who have observable data at Baseline and Week 20.
[b] Based on an Analysis of covariance (ANCOVA) model with treatment and baseline value as covariates
CI = Confidence Interval, LS = Least Squares, SD = Standard Deviation

Source: [pilot1wrappers: adam-adsl; adlbc]

R Pilot 1 Submission: Summary from FDA

- Using R version 4.1.1, FDA was able to run the submitted code and confirm the applicant's tables and the submitted figure in report-tlf pdf file.
- Using FDA developed code, a statistical analyst was able to independently generate tables using the submitted data. There are some minor issues with some of the tables that were submitted.
    - Minor issues:
        1) A few values are slightly off. This could potentially be a rounding issue.
        2) Column headers are switched in Table 14-3.01.
        3) Important information, such as a specification of the ANCOVA model, is not given for Table 14-3.02.

*See full FDA's review and evaluation response https://github.com/RConsortium/submissions-pilot1/blob/main/vignettes/fda/fda-response-2021-11-22.pdf

Using R and Shiny in Regulatory Submission

- R, Its suitability and current landscape
- Pilots of R Consortium Working Group
- Can Shiny bring opportunity for easier and faster review?
- OSS challenges in the context of R

What is Shiny

Toy App to give initial taste of Shiny: Kmeans example (posit.co)

Shiny provides a framework to statisticians to quickly build niche web-based apps in R

- App should be small and to-the-point (well-defined scope and audience)
- Development lifecycle is shorter than regular software
- Statisticians are developers (self-sufficient)
- Almost all needed interactivity/reactivity, flexibility and automation can be realized by design

Typically, Shiny is used to

- Make automation and guided analysis
- Extract insights from massive statistical outputs via designed interactivities and visualization
- Understand complicated methods and models

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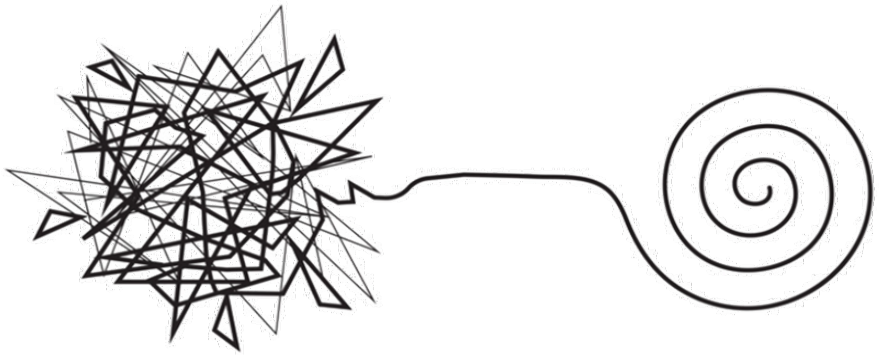

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→ *Shiny apps for regulatory submission*

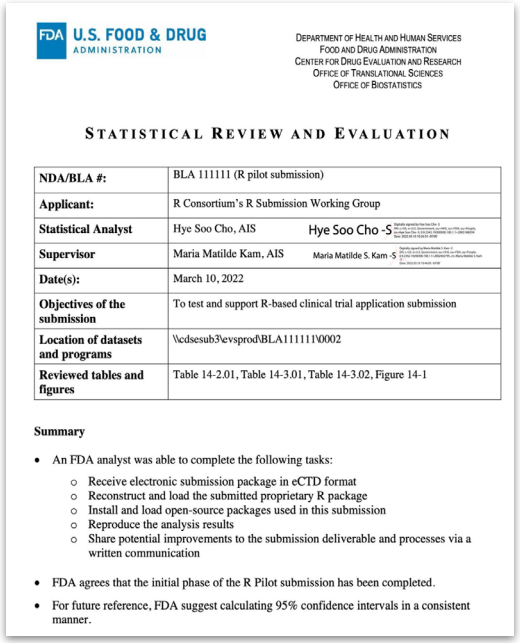
R submission Pilots to FDA

- Collaboration between the R consortium R submission Working Group and FDA

	Pilot 1	Pilot 2	Pilot 3	Pilot 4
Focus	TLF	Shiny	ADaM	Shiny in Container
Main Purpose	To test an R-language based submission package can meet the needs and expectations of the FDA	To test a Shiny application created with the R-language can be bundled into a submission package and transferred to FDA	To re-test the pilot 1 with ADaM datasets generated using R	To test a potential solution in delivering a regulatory shiny with easier deployment on the regulator side
Status	Completed	Completed	In Review by FDA	On-going

Pilot 1 Submission to FDA:

Successful open pilot that showcased R based FDA submission



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CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF TRANSLATIONAL SCIENCES
OFFICE OF BIOSTATISTICS

STATISTICAL REVIEW AND EVALUATION

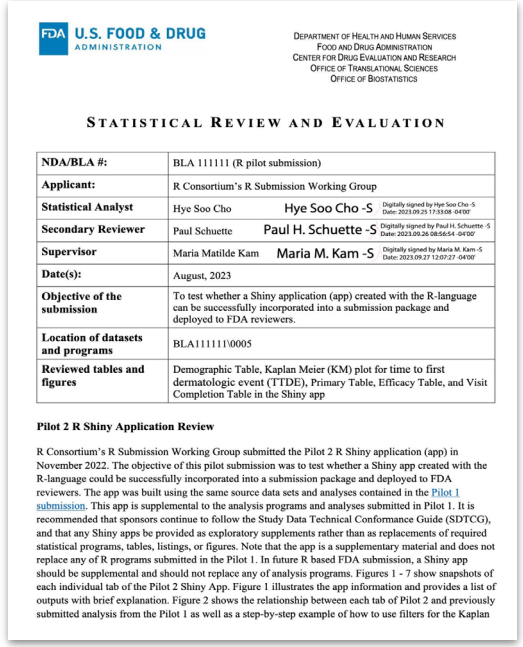
NDA/BLA #:	BLA 111111 (R pilot submission)
Applicant:	R Consortium's R Submission Working Group
Statistical Analyst	Hye Soo Cho, AIS Hye Soo Cho -S
Supervisor	Maria Matilde Kam, AIS Maria Matilde S. Kam -S
Date(s):	March 10, 2022
Objectives of the submission	To test and support R-based clinical trial 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.

Pilot 2 Submission to FDA:

Successful open pilot that showcased shiny based FDA submission



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STATISTICAL REVIEW AND EVALUATION

NDA/BLA #:	BLA 111111 (R pilot submission)
Applicant:	R Consortium's R Submission Working Group
Statistical Analyst	Hye Soo Cho Hye Soo Cho -S
Secondary Reviewer	Paul Schuette Paul H. Schuette -S
Supervisor	Maria Matilde Kam Maria M. Kam -S
Date(s):	August, 2023
Objective of the submission	To test whether a Shiny application (app) created with the R-language can be successfully incorporated into a submission package and deployed to FDA reviewers.
Location of datasets and programs	BLA111111\0005
Reviewed tables and figures	Demographic Table, Kaplan Meier (KM) plot for time to first dermatologic event (TTDE), Primary Table, Efficacy Table, and Visit Completion Table in the Shiny app

Pilot 2 R Shiny Application Review

R Consortium's R Submission Working Group submitted the Pilot 2 R Shiny application (app) in November 2022. The objective of this pilot submission was to test whether a Shiny app created with the R-language could be successfully incorporated into a submission package and deployed to FDA reviewers. The app was built using the same source data sets and analyses contained in the Pilot 1 submission. This app is supplemental to the analysis programs and analyses submitted in Pilot 1. It is recommended that sponsors continue to follow the Study Data Technical Conformance Guide (SDTCG), and that any Shiny apps be provided as exploratory supplements rather than as replacements of required statistical programs, tables, listings, or figures. Note that the app is a supplementary material and does not replace any of R programs submitted in the Pilot 1. In future R based FDA submission, a Shiny app should be supplemental and should not replace any of analysis programs. Figures 1 - 7 show snapshots of each individual tab of the Pilot 2 Shiny App. Figure 1 illustrates the app information and provides a list of outputs with brief explanation. Figure 2 shows the relationship between each tab of Pilot 2 and previously submitted analysis from the Pilot 1 as well as a step-by-step example of how to use filters for the Kaplan

Key Links

- Webpage: https://rconsortium.github.io/submissions-wg/
- Pilot 1: https://github.com/RConsortium/submissions-pilot1-to-fda
- Pilot 2: https://github.com/RConsortium/submissions-pilot2-to-fda
- Pilot 3: https://github.com/RConsortium/submissions-pilot3-adam-to-fda

All materials are open to the public
Anyone is welcome to join the working groups! (info@r-consortium.org)

R Pilot 2 Submission: Summary and Demo

Pilot 2 (R Shiny App) was submitted in November 2022.
Use this link to access the app.

The objective of this pilot submission was to test whether a Shiny app (created in R language) could be successfully incorporated into a submission R package and deployed to FDA reviewers. Pilot 2 was not to demonstrate how Shiny techniques could facilitate regulatory review.

The app was built using the same source datasets and analyses contained in the Pilot 1 submission.

This app is provided as an exploratory supplemental to the submission in Pilot 1

FDA noted in their statistical review and evaluation: see link here

" In future R based FDA submission, a Shiny app should be supplemental and should not replace any of analysis programs."

Screenshot from FDA's statistical review and evaluation Aug, 2023

- Receive the electronic submission package in eCTD approved formats.
- Install and load open-source packages used in this submission and the submitted pilot2wrappers R package.
- Review Analysis Data Reviewer's Guide (ADRG) and execute a Shiny app.
- Identify issues and provide potential solutions.
- Review re-submissions.
- Share potential improvements to the submission deliverable and processes via a written communication.

The Pilot 2 submission materials and communication are publicly available.

R Pilot 2 Submission: One question emerged in the process

Should the submission App support free exploratory subpopulation analysis or not? (One step further from the KM module in the demo)

Two schools of thoughts at the moment below. What do you think? (Defer to Discussion section)

Shiny app for regulatory submission need to be fully validated. Hence totality of content should be predefined, fully checked and aligned with the static clinical study report.

The final version of pilot 2 took the view of this school

VS

Shiny app is ultimately for acceleration of review. Other than regular interactivity to jump among TLFs, it should give certain degrees of freedoms to make exploratory analysis, which in turn may greatly shorten back-and-forth inquiry between regulator and drug developer. (may be start with the descriptive ones)

A shared concern of statisticians on both the drug developer and the regulatory sides:
Interactive features of a shiny app may be inappropriately used to enable p-hacking and for cherry picking.

See more in: R adoption series in 2023 Dec

What more can Shiny offer in regulatory space

Small automation to streamline process, see several examples from how FDA uses Shiny

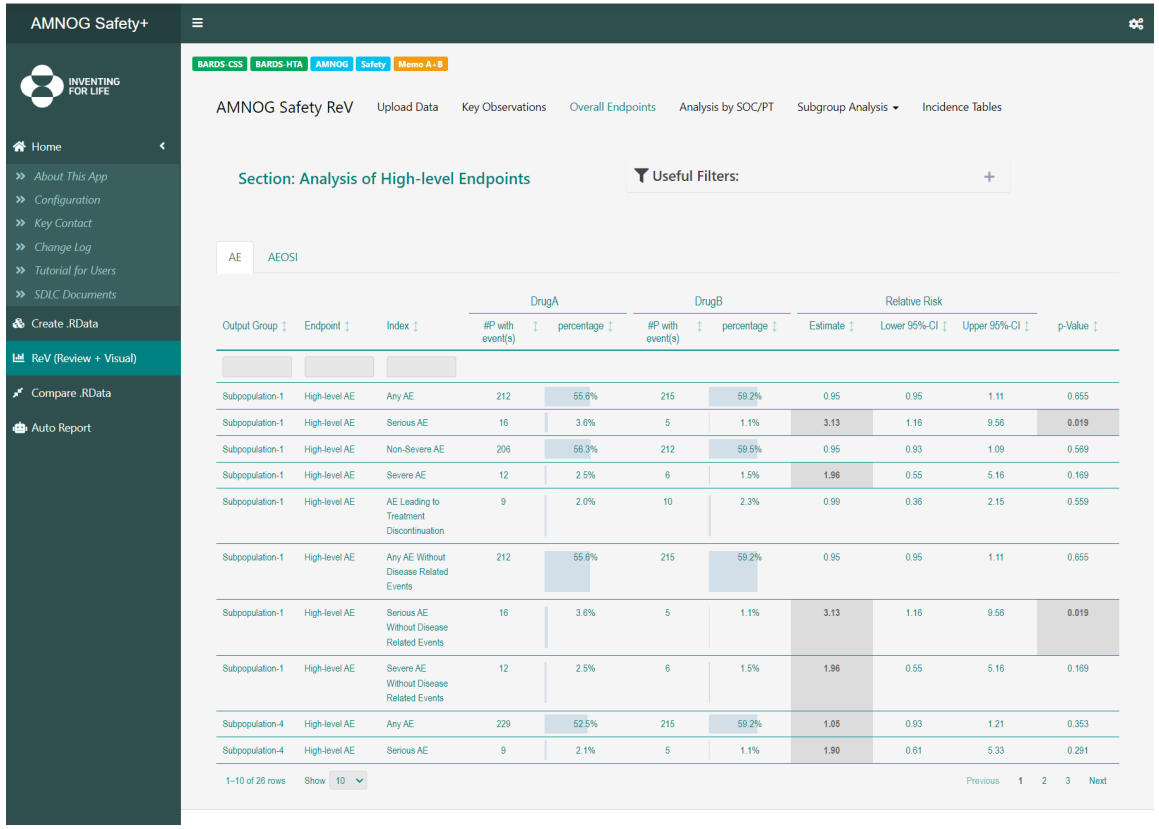
- sendigR: Cross-study analysis of the standard for exchange of nonclinical data (SEND) (link)
- MCDA app: multiple criteria decision analysis for quantitative benefit risk assessment (link)
- Several Shiny-based mobile tools to aid regulatory decisions and program evaluation, e.g. economically optimized sampling calculator (link)
- An app to facilitate evaluating the effect of dosage modification on safety and efficacy (link)

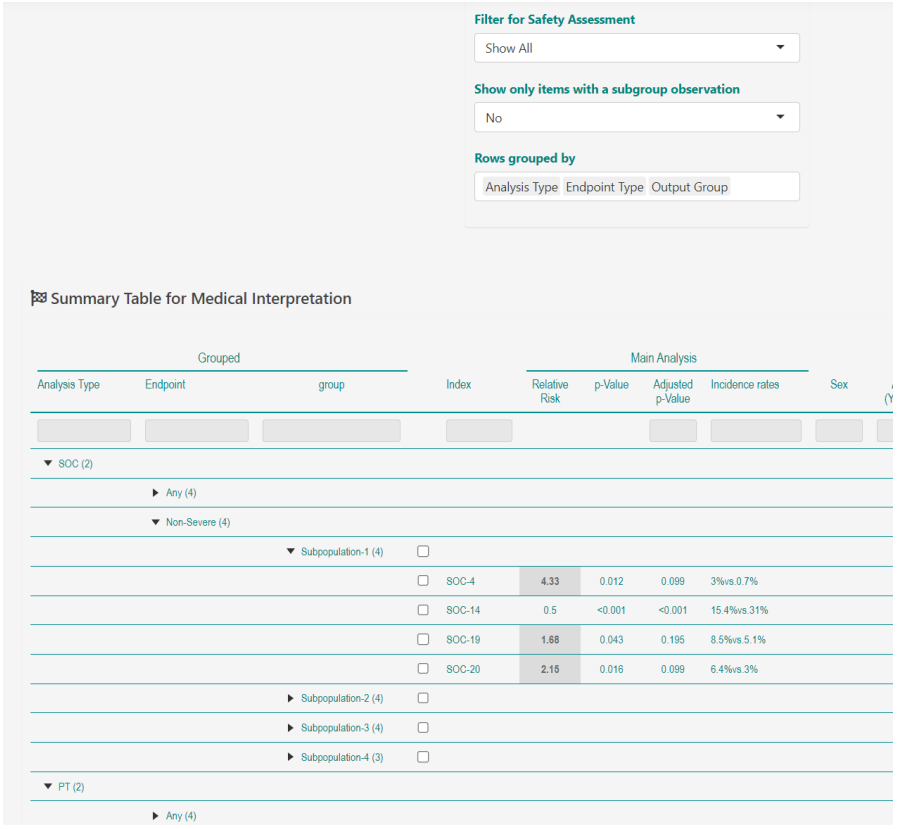
Insight extraction (the focus of a submission Shiny App)

Use designed interactivity features to enable reviewers to quickly find the information and data that they need, and moving from spot to spot in the spectrum between very abstract (e.g. some graph) and very detailed (e.g. some listing) to depending on the phase of their decision making

Example of Shiny interactivity (1/2)

Groupable, Expandable, Designed Filter, Visual-aid

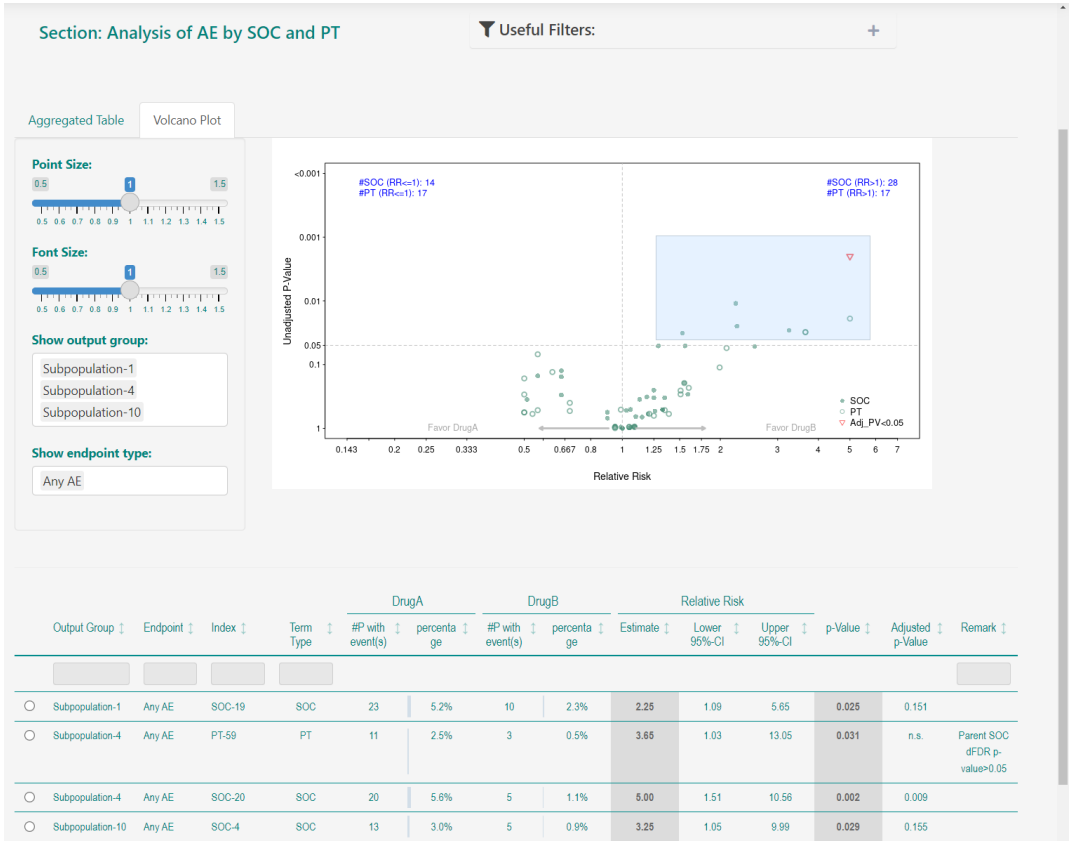




** Screenshot is from an internal app in MSD for stat. review safety data in the preparation of a German HTA dossier. Note, only simulated data are used here*

Example of Shiny interactivity (2/2)

Jump from table to table, table to figure, figure to table



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Using R and Shiny in Regulatory Submission

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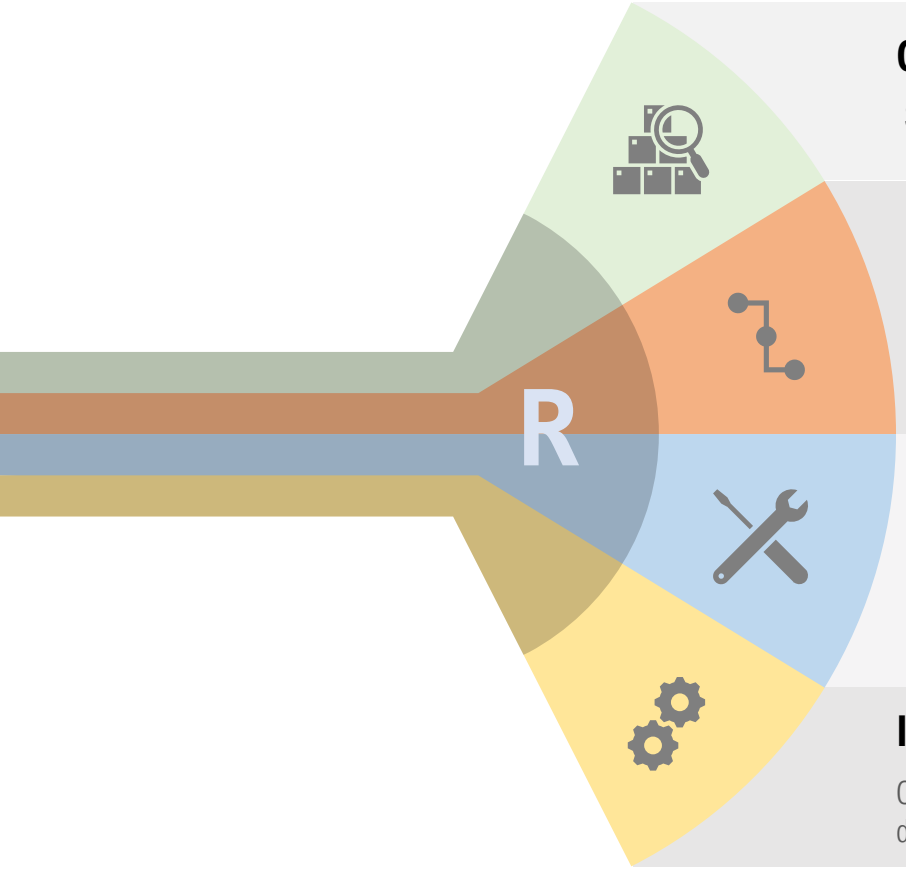
Open-Source Software Challenges in context of R



Qualiy and Validation

Several R packages for one model, which one to be trusted?

Version Control for Reproducibility

Upversion rate is different from package to package, because they are developed and maintained by different individuals or teams. Each R package may have dependency on multiple other R packages.

Maintain and Support

Will the trusted R package be well maintained when base R version has an upgrade? Who to call when there is a bug?

Implementation and Deployment

Operating systems (file path, warning message and more could be different between linux and windows) may lead to small difference based on the same code and data. In-house IT support might be needed

R Consortium Submission Working Group presentation,
Chen & Leng 2024

Could These Challenges be Addressed ?

Quality and Validation

Some good initiatives are in place: R Validation hub, CAMIS.

The goal is to built up a pool of validated R packages that are suitable for regulatory submission via cross-industry collaboration

Version Control For Reproducibility

Documentation (e.g. ADRG) and Startup file (e.g. use renv) in the source file of submission, or leverage more innovative submission format (e.g. container-based solution, rmarkdown/quarto)

Maintain and Support

Many company and cross-industrial initiatives make open source now. A package has now an active team or community behind it, not relying on one or few individuals, stronger sustainability and continuity (e.g. pharmaverse, openpharma, openstatware)

Implementation And Deployment

Particularly for shiny app, there may be two options

- Regulator relies on their own IT (pilot 2 and 4)
- Company create and maintain a safe and secure environment while regulators get access.

R Consortium Submission Working Group presentation, Chen & Leng 2024

Acknowledgement

(alphabetically by last name)

- Beverly Chin (Roche)
- Hye Soo Cho (FDA)
- Tae Hyun (Ryan) Jung (FDA)
- Eric Nantz (Eli Lilly)
- Eli Miller (Atorus)
- Tim Powell (Biogen)
- Paul Schuette (FDA)
- Mike Stakehouse (Atorus)
- Heng Wang (Roche)
- Peikun Wu (R&G US)
- Yilong Zhang (Meta)

and to our R Consortium Submission Working Group

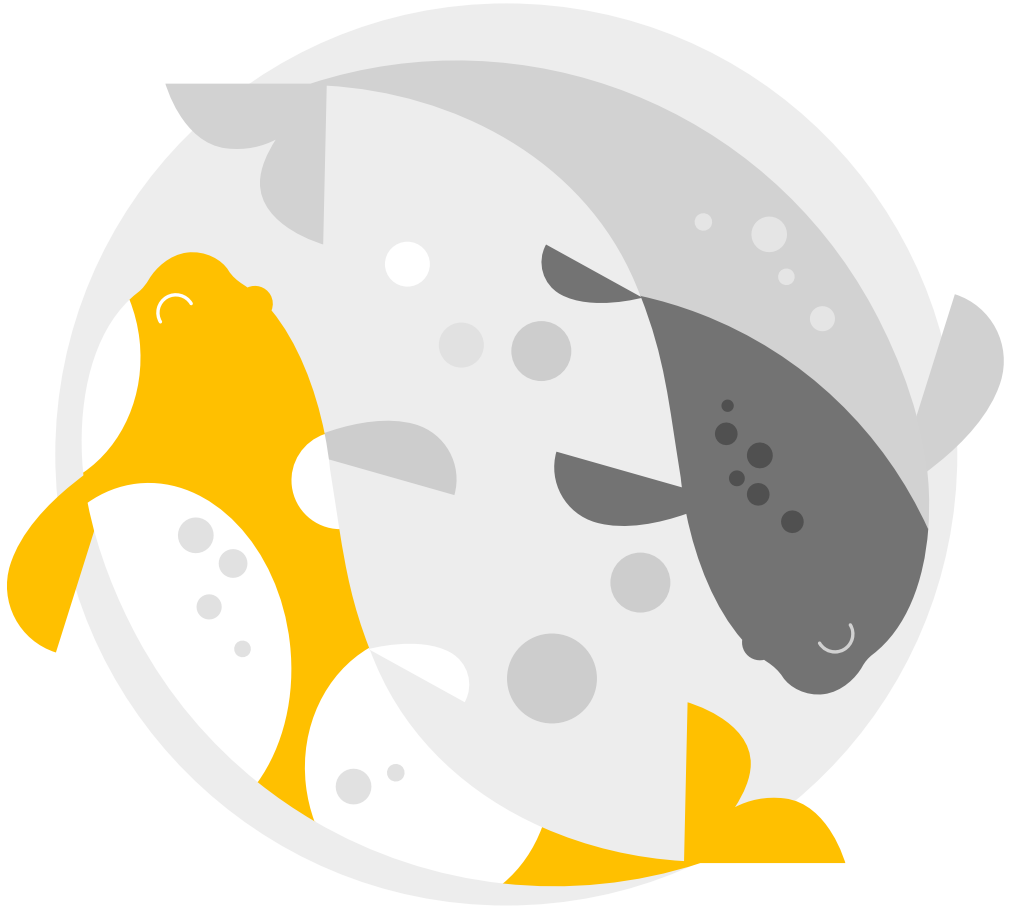
Discussion

and Q&A

Two questions to Kick Off

- Any key aspect that Swissmedic would want to test out with R Consortium Submission Working Group via collaborating on a tailor-made pilot?

- Which school of submission Shiny App does Swissmedic lean more into at the moment? What features of a submission App should have in order to be value-added for regulatory review?



Thank You

Contact: xiangyi.gregory.chen@msd.com