An Overview of Regulatory Submission by using R Language

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- Overall 12+ years of industry experience
- I am passionate towards the innovations that helps organization and better patient care

Disclaimer

The content presented in this presentation is based on my personal knowledge and research. All information and materials used are sourced from the public domain, and proper references have been shared at the end of the presentation.

The opinions expressed are my own and do not represent the views or responsibility of any company or organization.

Agenda

- Introduction to Regulatory Submission
- Evolution of R
- R packages used
- Validate and Manage Risks
- Pilot projects submitted to FDA
- Benefits and Challenges
- Future possibilities for Clinical Industry

Introduction

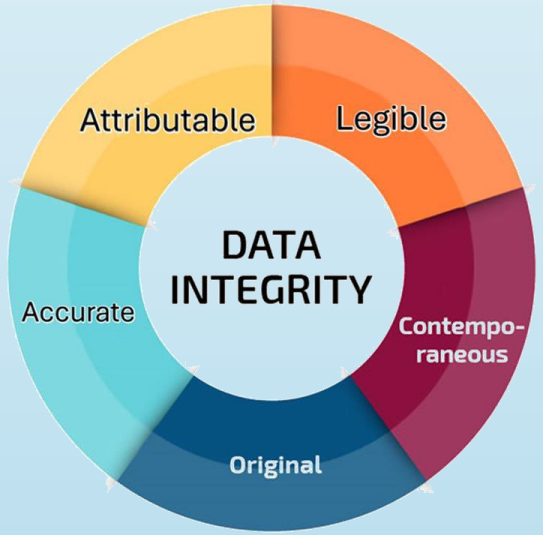
Regulatory Submission

What it includes:

- Clinical trial protocol details
- Investigator information
- Study drug information
  (chemistry, manufacturing, controls)
- Patient recruitment criteria
- Safety and efficacy endpoints
- Statistical analysis plan
- Clinical trial data and reports

Introduction

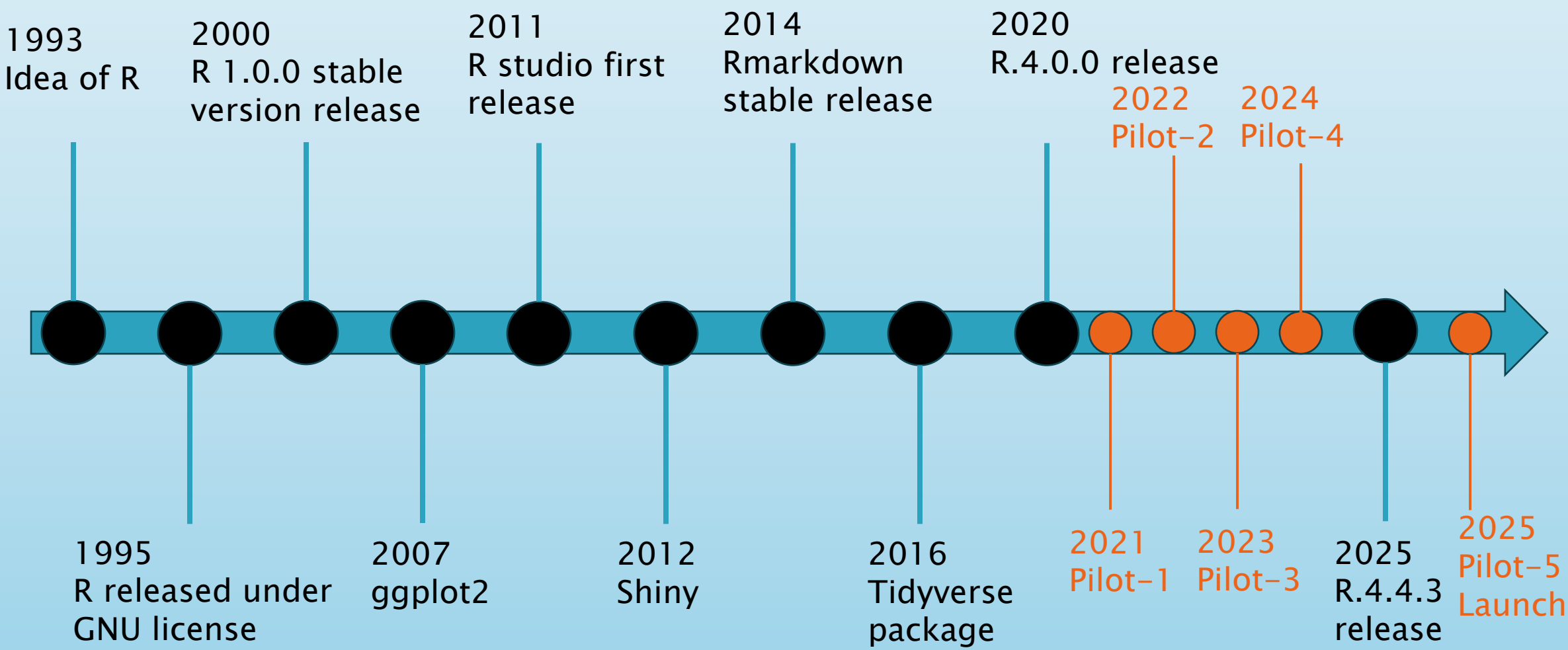
WHY?



Global
Market
Access

COMPLIANCE

Evolution of R



R Packages


readr
dplyr
tidyverse
www.rstudio.com
ggplot2
pkglite
r2rtf
R
pharmaverse
admiral
riskmetric
lubridate
stringr
Shiny

Validate and Manage Risks

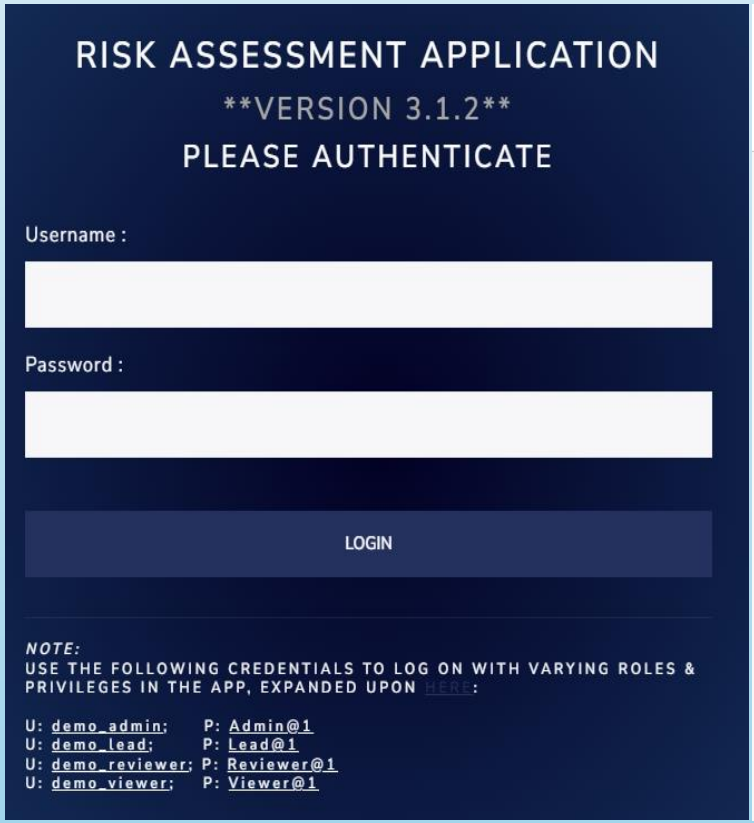
TWO TOOLS

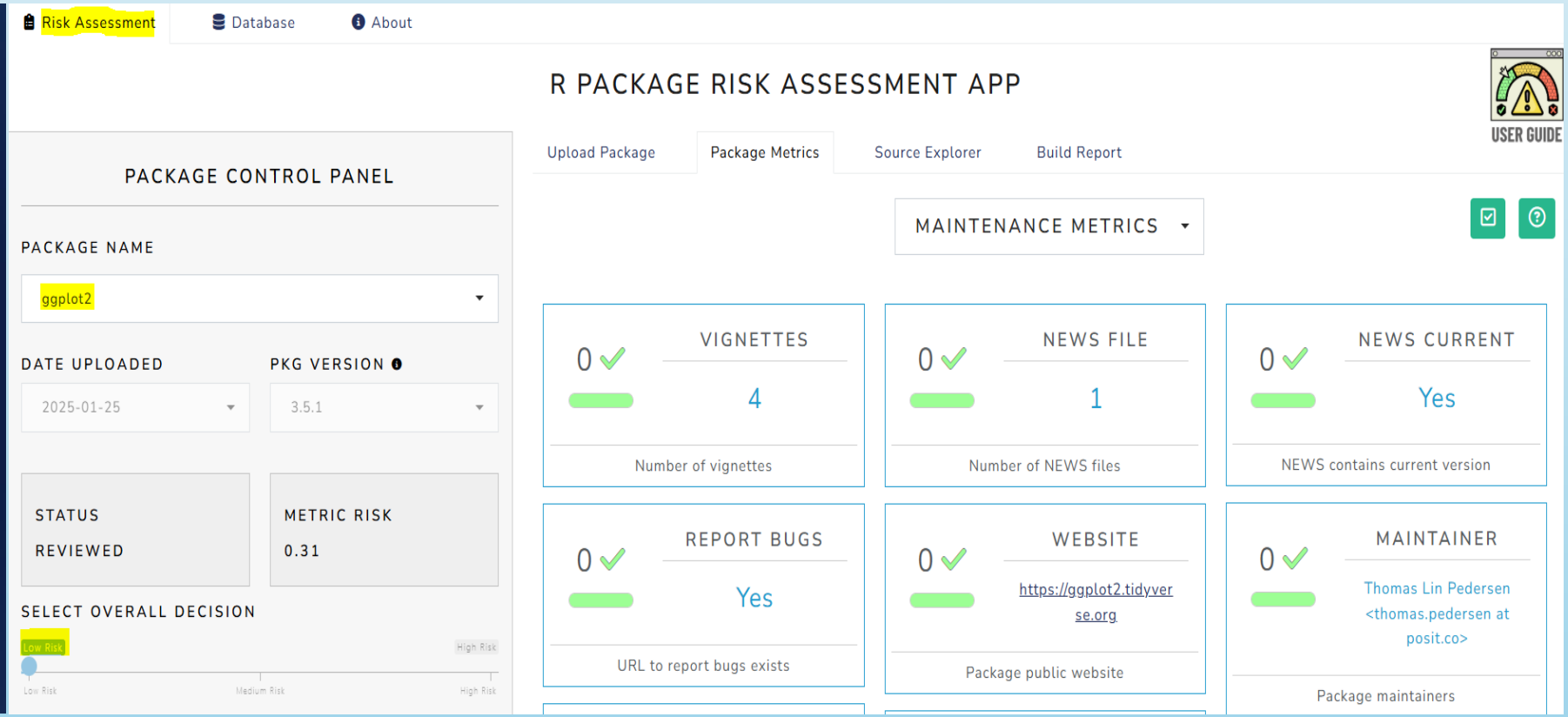
Quantify Risk Programmatically

Interactive app for an Organization

Validate and Manage Risks

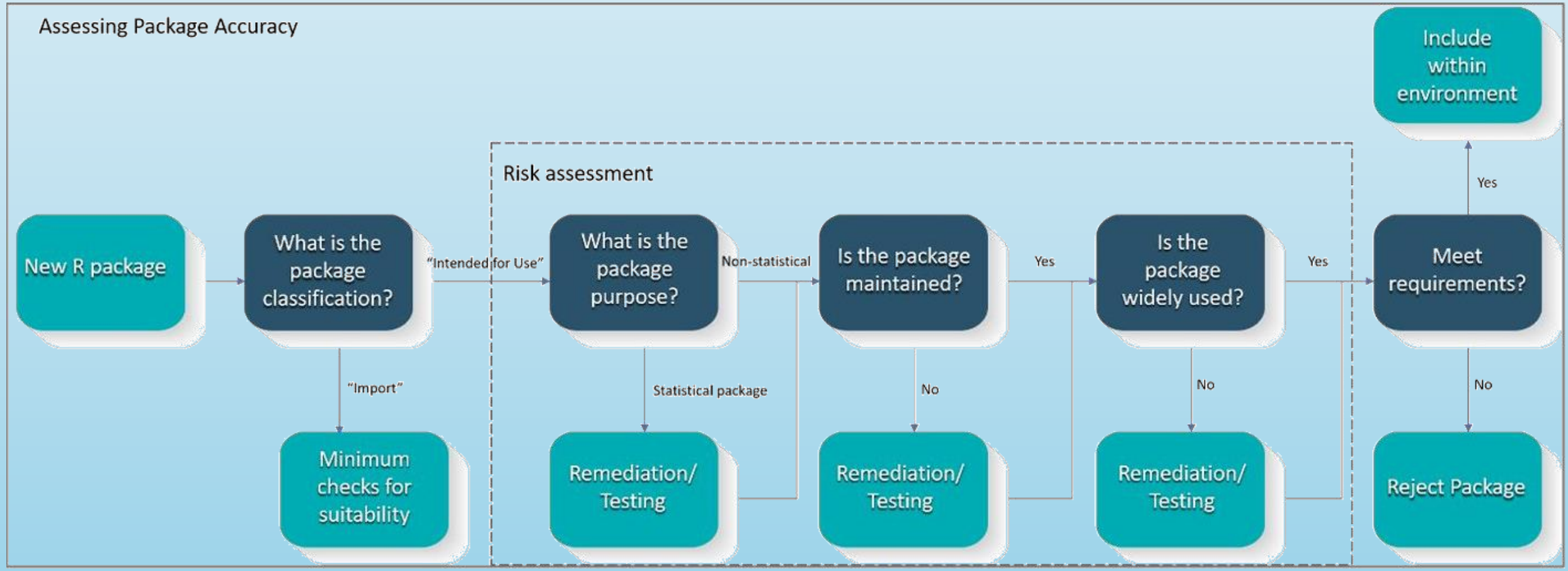
Login page





Validate and Manage Risks

Proposed process for risk-based approach



Pilot projects submitted to FDA

Pilot 1

To showcase the feasibility of submitting data and analyses to the FDA using R and following eCTD specifications

Objective

Focus on an R-based submission containing common analyses within the FDA e-submission system and process

Scope

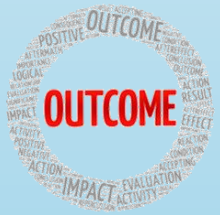
4 TLFs
Simulated data from CDISC pilot

Pilot projects submitted to FDA

Pilot 1

Timeline

Initial submission to FDA in 2021.11



Demonstrated the possibility of R-based submission to FDA, paving the way for future R-based regulatory submissions

Significance

This was the first publicly available submission using an open-source language and a reproducible package structure

Pilot projects submitted to FDA

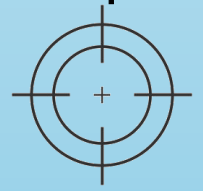
Pilot 2

To test the idea of bundling a Shiny application into a submission package and transferring it successfully to FDA reviewers

Objective

Expanded upon Pilot 1 by including a Shiny app developed using the {golem} framework, also submitted through the FDA e-submission system

Scope



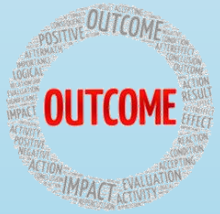
A shiny app that displays the 4 TLFs submitted in pilot 1, with basic data set filtering functionalities
Simulated data from CDISC pilot (same as Pilot 1)

Pilot projects submitted to FDA

Pilot 2

Timeline

Public review of initial submission to FDA in 2022.10



Demonstrating the feasibility of R-based submission and serving as a blueprint for future regulatory submissions. Specifically, showcased the potential of R and Shiny apps in regulatory context

Significance

Submitted interactive, reproducible analyses to the FDA

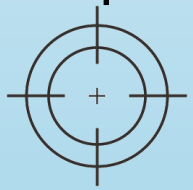
Pilot projects submitted to FDA

Pilot 3

Objective

Focused on delivering tables, figures, and ADaM datasets using R

Scope



SDTM, ADaM datasets and TLFs
Analysis Data Reviewer's Guide (ADRG)

Timeline

Initial submission to FDA through the eCTD gateway in 2023.08
FDA verbal response from Jan-July 2024
Re-submitted on 2024.04, final FDA response on 2024.08

eCTD: electronic Common Technical Document

Pilot projects submitted to FDA

Feature	Pilot 1	Pilot 3
Focus	Common analyses, R scripts for TLFs (Tables, Listings, Figures)	ADaM datasets, analysis scripts for TLFs, Analysis Data Reviewer's Guide (ADRG), and proprietary R packages in compressed file formats
ADaM Datasets	No specific ADaM datasets included	Utilized R to generate and include ADaM datasets in the submission package
ADRG	Not present	Included a detailed ADRG providing step-by-step instructions for FDA reviewers to reproduce the analysis scripts, and the generated ADaMs and TLFs
Proprietary R Packages	{pkglite} was used for submitting the submission package	{pkglite} was not used and validated the submission of proprietary R packages in compressed file formats as an alternative to {pkglite} or installing directly from GitHub

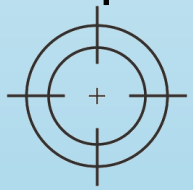
Pilot projects submitted to FDA

Pilot 4

Objective

To deliver the Shiny App from Pilot 2 using webassembly and containers

Scope



Novel technologies such as Linux containers and WebAssembly to bundle a Shiny application
Source datasets and analyses contained in R submission Pilot 1–3

Timeline

Submitted to FDA on September 20, 2024

Pilot projects submitted to FDA

Technologies such as containers and WebAssembly software to package a Shiny application into a self-contained unit, streamlining the transfer and execution process for enhanced efficiency

WebAssembly

WebAssembly allows R to be executed at near-native speed directly within web browsers, providing users with the ability to run R code without having R installed locally

WebR is essentially the R programming language adapted to run in a web browser environment using WebAssembly

Containers

podman

docker

SINGULARITYCE

Podman stands out for its daemonless architecture, enhancing security by eliminating the need for a central daemon process

Podman prioritizes security with its rootless container support, offering a robust solution for security-conscious users

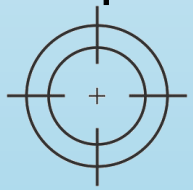
Pilot projects submitted to FDA

Pilot 5

Objective

Aims to deliver an R-based submission to the FDA using Dataset-JSON

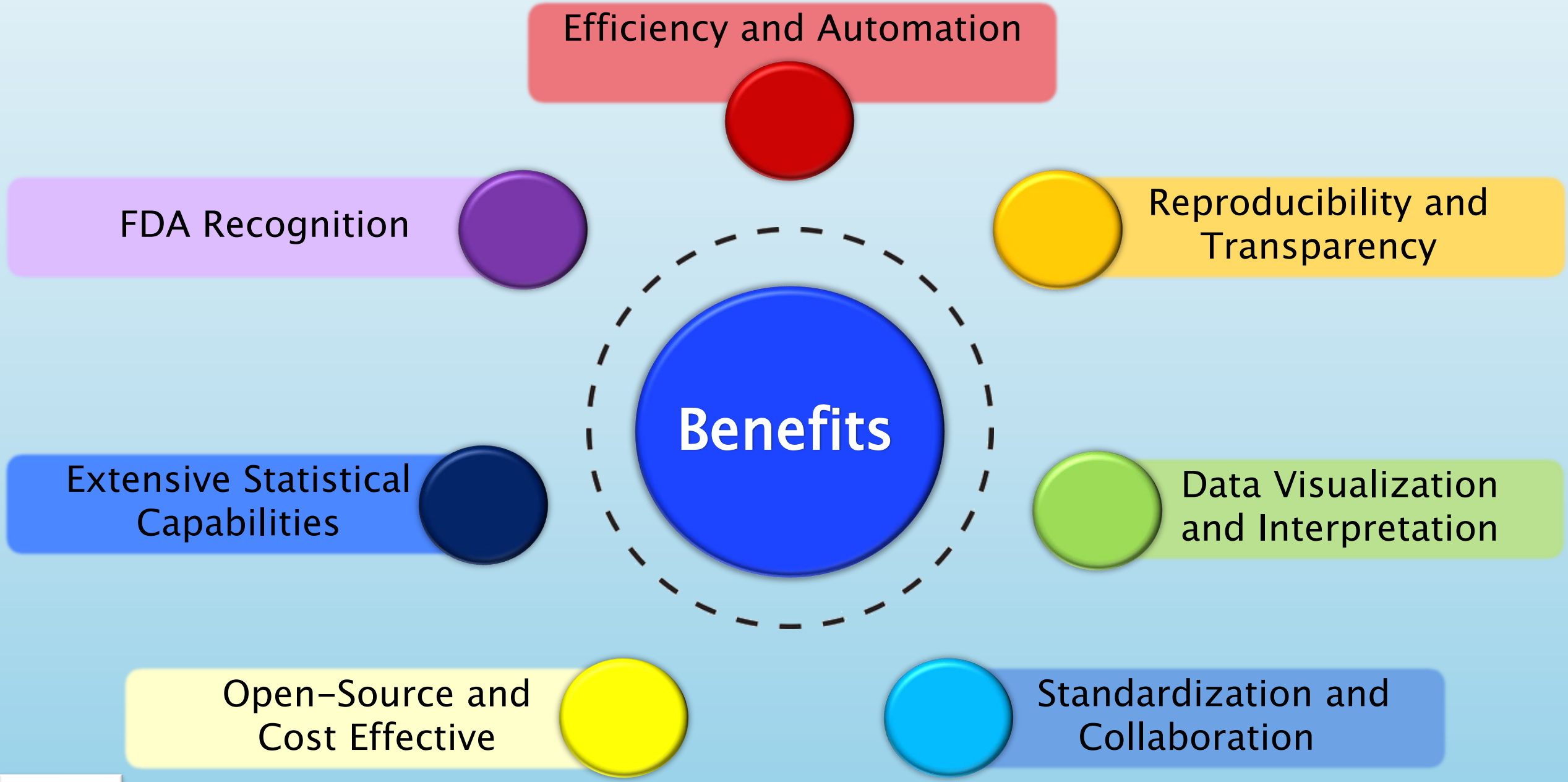
Scope



Part 1: Replicate Pilot-3, ADaM datasets were written as xpt files instead new transport file type datasetjson
Part 2: Several more ADaMs and more Tables and figures using datasetjson

Timeline

Launched in 2025


Efficiency and Automation
FDA Recognition
Reproducibility and Transparency
Benefits
Extensive Statistical Capabilities
Data Visualization and Interpretation
Open-Source and Cost Effective
Standardization and Collaboration

Challenges

Regulatory Compliance and Standardization

- Evolving Regulatory Landscape
- Global Regulatory Differences
- Data Integrity and Security
- Data Standardization and Format

Reproducibility and Documentation

- Reproducibility and Documentation
- Version Control
- Documentation

Data Quality and Security

- Inconsistent Data
- Data Privacy and Confidentiality
- Quality and CMC Considerations
- Data Validation

Future Possibilities for Clinical Industry

- FDA accepting R marks a significant shift in clinical data analysis
- Interactive data methods reduce feedback time, aiding faster decisions
- Efficiently manage data to automate SDTM and ADaM datasets and enable transparent submission
- With R's popularity rising, the need for clinical data professionals skilled in R will increase
- Ideal for budget-constrained organizations as open-source
- It clearly indicates to a broader adoption of R in clinical studies and regulatory submission

References

- https://www.google.com/search?safe=active&sca_esv=a7afae622429358f&rlz=1C1GCHB_enIN1134IN1134&sxsrf=AHTn8zpXd4-qxj7wxCUJBWuNBrkXlH34mA:1741342967813&q=pilot+R+projects+submitted+to+FDA&source=lnms&fbs=ABzOT_A1aq79iS84nP6J0j1icOz8NlHPFOhu00XYLBllteZ-8PY0Y4JfR1Iz2k5LNnc2HmroC6AbnUa8xwlp8PgNdyXtQMZc4pZTTKP1Z5SSESbMm8naW30r1JWFGFJ-Ez6UVQicjqZHHwMrF7_QtKqeUR1R8da3fPsH7_-Uv7WBWywgOVPSpoMAJsc24R-8075IERIZ823TcIW6qDWzH0YLD9zOaeiHXj7IH_XN5oUvNQhOI92fMtQ&sa=X&ved=2ahUKEwiG75yI4PeLAxWfyzgGHX3EHdwQ0pQJegQIEhAB&biw=1280&bih=559&dpr=1.5
- https://rconsortium.github.io/submissions-wg/pilot1.html
- https://rconsortium.github.io/submissions-wg/pilot2.html
- https://rconsortium.shinyapps.io/submissions-pilot2/
- https://r-consortium.org/posts/news-from-r-submissions-working-group-pilot-3/
- https://r-consortium.org/posts/using-r-to-submit-research-to-the-fda-pilot-4-successfully-submitted/
- https://r-consortium.org/posts/submissions-wg-pilot5-pilot6-and-more/
- https://rinpharma.shinyapps.io/riskassessment/_w_ce0edf34/
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- chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.lexjansen.com/pharmasug/2024/SI/PharmaSUG-2024-SI-269.pdf
- chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.lexjansen.com/pharmasug/2024/SS/PharmaSUG-2024-SS-376.pdf
- https://www.researchgate.net/figure/Timeline-of-R-history-with-selected-milestones_fig1_360246719

Thank You!

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