The R Validation Hub

www.pharmar.org

Mission statement

- *R Validation Hub is a cross-industry initiative whose mission is to enable the use of R by the Bio-Pharmaceutical Industry in a regulatory setting, where the output may be used in submissions to regulatory agencies.*

- Our platform will always be free to use!

Who are we?

- Executive Committee
  - Andy Nicholls (AIMS)
  - Lyn Taylor (AIMS)
  - Joe Rickert (R Consortium)
  - Min Lee (Transcelerate)
  - Yilong Zhang (Metrics stream)
  - Keaven Anderson (Testing stream)

- Over 30 pharmaceutical organisations represented

https://www.r-consortium.org/announcement/2018/05/29/announcing-the-r-consortium-isc-funded-project-grant-recipients-for-spring-2018

Roadmap

1. Process and Communication
   - ✔ Publish website
   - ✔ Agree high level process
   - Develop white paper [Target 22nd August]
   - Ensure content reflected accurately in website [Target 22nd August]
   - Tools at pilot implementation stage [Target 22nd August]
2. Validation / Qualification Suite
   - Release metrics package
   - Release Shiny app and reporting tools for risk assessment
   - Share test suite
   - *Build test execution tool*
   - *Provide an example deployment*
   - Agree criteria used to determine whether a package is fit for the Pharma Repository
3. Repository
   - Build Pharma R Repository

Questions

Today's Workshop

1. R Packages 101 (Sean Lopp) - 30 minutes
2. Trusting your environment (Andy Nicholls) – 90 minutes
3. Reproducing your environment (Sean Lopp) – 60 minutes
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Trusting Your Environment

Andy Nicholls

Agenda

- Setting the scene
- Package Risk
  - Exercise – Why do I trust this package? [20 mins]
  - Exercise – Risk Assessment in Practice [20 mins]

Setting the Scene

Setting the Scene

U.S. FOOD & DRUG ADMINISTRATION

Statistical Software Clarifying Statement

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 http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm), "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.

May 6, 2015

https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587506.pdf

Background Reading

- Regulatory documentation
  - FDA 21 CFR Part 11
    - Guidance for Industry: Part 11, Electronic Records; Electronic Signatures – Scope and Application
  - Statistical Software Clarifying Statement

- Further reading:
  - R: Regulatory Compliance and Validation Issues. A Guidance Document for the Use of R in Regulated Clinical Trial Environments.

Why applies to us?

- Broadly, there are two types of software application:
  - Those that collect + store data, and often require electronic signature
  - Those that don't
- R itself is not used to collect / store data
- It is not a mechanism for collecting electronic signatures
- 21 CFR Part 11 is therefore not directly applicable

We are not actually trying to *validate* R!

But R may be *part of a system* that we wish to validate

To trust the system we need to trust R (and any packages that we use)

Regulation

- FDA's Glossary of Computer System Software Development Terminology:

*"**Validation**: 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."*

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System Validation

- The system validation must incorporate all of the following elements:

- Accuracy
- Reproducibility
- Traceability

A Note on Reproducibility / Traceability

- This is a big topic in itself
- The continuous evolution of R presents several challenges w.r.t both reproducibility and traceability

- Later we'll look a lot more closely at reproducibility

- For now let's consider accuracy…

Consider the following questions:

- Is SAS accurate?
- What makes us so sure?

Accuracy

- SAS is widely considered a ‘trusted’ resource
  - Everyone uses it
  - It’s accuracy has been proven over a long period of time
  - SAS internally validate the software
- Surely the above also applies to R?
- Doesn’t it also apply to some R packages?

R Package Accuracy

- Packages:
  - May come from anywhere
  - Be written by anyone
  - May or may not follow a typical Software Development Lifecycle

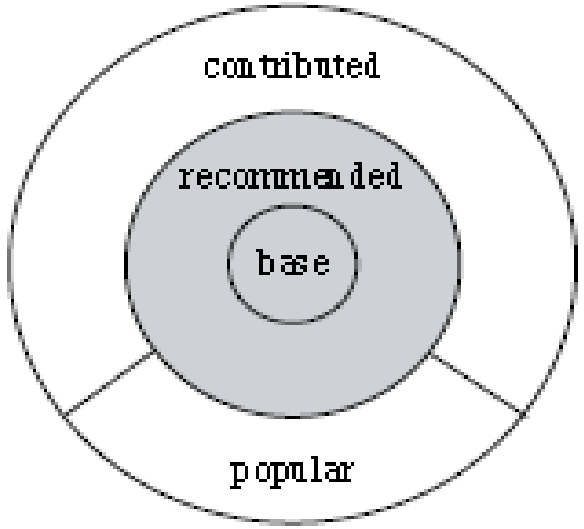

Figure Source: German et al (2013): The Evolution of the R Software Ecosystem (German, 2013)

Exercise – Why do I trust this R package?

- Split into groups
- Brainstorm the reasons why we trust (or not) an R package
- How would you demonstrate this trust in an audit?

A Risk-based Approach

- We cannot test every possible use of a package
- We don’t do this with SAS or Base R

- Using what we know about R packages, we *can* implement a risk based approach to package assessments

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The riskmetric package

- The R Validation Hub have been working on a package to help qualify/quantify package risk

- The basic process:
  - Collect metrics
  - Assess the metrics against some criteria
  - Generate a risk score

A riskmetric Demonstration

- We pick 6 packages:
  - dplyr
  - broom
  - haven
  - lme4
  - RBesT
  - foreach

- Let’s generate some metrics…

More on riskmetric

- The package now had a website - https://pharmar.github.io/riskmetric/
- We* have built a framework
- We want your feedback!
- We want **you** to help build the rest!

*We = Yilong Zhang, Douglas Kelkhoff, …

Risk in Practice

- Automating a risk assessment will simplify life!
- But the metrics don’t always tell the whole story
- Human intervention is therefore unavoidable
- We must consume the information and action accordingly
- A suitable SOP should govern this process

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Risk Assessment App

- You are about to use a prototype app to conduct a risk assessment
- The final app will:
  - Collect metrics
  - Optionally allocate a risk score
  - Allow human intervention to respond to the metrics and score
  - Generate package assessment reports in order to document the exercise

Exercise – Risk Assessment in Practice

- Split into groups
- Pick a package and assess the level of risk it poses
  - dplyr, broom, haven, lme4, RBesT, foreach
- Are you comfortable using the package as part of a qualified environment?
  - If not, what would give you the confidence you need?

Feedback

- This is your opportunity for feedback
- What else would you need from the app?

Testing

- Tests
  1. can help give us confidence that a package does what it is supposed to
  2. help qualify an environment (see later)
- Tests written for (1) can also be used for (2)
- The appropriate level of testing is up to you!

Summary

- Collecting and documenting risk is key in establishing a level trust
- We won't always trust an R package
- If we're not fully confident we may wish to take additional steps to establish an appropriate level of trust
- We can do so by writing tests

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