The Challenges of Validating R

R in Pharma Workshop

Who are you?

- Statistician?
- Programmer?
- DevOpps?
- Data Scientist?
- Pharmacometrician?
- Bionformatrician?
- Lost?

Who am I?

Andy Nicholls (@andyofsmeg)

- Statistician and Data Scientist
  - **Josh Wills** on Twitter: *"**Data Scientist** (n.): Person who is better at statistics than any software engineer and better at software engineering than any statistician."*
- Currently work in GSK's **new** Statistical Data Sciences team
  - BSO for R HPC Environment for Stats and Programming
- Member of PSI Application and Implementation of Methodologies in Statistics SIG
  - Focus on R Validation
- Previously PM, Tech Lead and Product Owner for Mango Solutions' ValidR
- **DISCLAIMER: I speak for none of the above organisations!**

Workshop Outline

- Setting the scene – 20 mins
  - Overview key regulatory information on validation
- Breakout discussions on key topics – 20 mins
- Summary of discussions – 15 mins

Setting the Scene

Overview

- Background and definitions
- Validation
  - Base R
  - R Packages
- The R Consortium Project

FDA 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

- We *don't have to use SAS* for statistical analysis
- Use of R remains limited
- Why?
  - SAS is the best thing ever invented?
  - R is rubbish?
  - Lack of knowledge/training?
  - Lack of understanding of regulatory requirements?

Goal of the PSI AIMS SIG is to improve knowledge and understanding in these areas

AIMS SIG

- Application and Implementation of Methodologies in Statistics (AIMS)
- Formed in May 2016
- Representatives from PPD, PRA, Syne Qua Non, Servier, Bordeaux University Hospital, Clinical Epidemiology Unit, Roche, GSK
  - Looking to expand membership
- Current focus on the use of R software in the industry and validation of R specifically

- Recently initiated an R Consortium project to build a Validation Hub
  - More later

https://www.psiweb.org/sigs-special-interest-groups/aims

Some Definitions

Definitions

- **Validation (FDA) -** Establishing **documented evidence** which provides a **high degree of assurance** that a specific process will **consistently produce** a product meeting its **predetermined specifications and quality attributes**.
- **Verification, software (NBS)** - In general the demonstration of consistency, completeness, and correctness of the software at each stage and between each stage of the development life cycle.
- **Quality assurance, software (IEEE)** (1) A planned and systematic pattern of all actions necessary to provide **adequate confidence** that an item or product **conforms to established technical requirements**. (2) A set of activities designed to **evaluate the process by which products are developed** or manufactured.

https://www.fda.gov/iceci/inspections/inspectionguides/ucm074875.htm

NIST - National Institute for Standards and Technology

NBS - National Bureau of Standards

Definitions

Qualification

- **Qualification, installation** (FDA) - Establishing confidence that process equipment and ancillary systems are compliant with appropriate codes and approved design intentions, and that manufacturer's recommendations are suitably considered.
- **Qualification, operational** (FDA) - Establishing confidence that process equipment and sub-systems are capable of consistently operating within established limits and tolerances.
- **Qualification, process performance** (FDA) - Establishing confidence that the process is effective and reproducible.
- **Qualification, product performance** (FDA) - Establishing confidence through appropriate testing that the finished product produced by a specified process meets all release requirements for functionality and safety.

https://www.fda.gov/iceci/inspections/inspectionguides/ucm074875.htm

What does this mean for Base R?

R Foundation Documentation

Further Reading

- R: Regulatory Compliance and Validation Issues
  - Guidance document for the use of R in regulated clinical trial environments (March 2018)
  - Focus on FDA / ICH guidelines
  - Applicable to Base R plus Recommended Packages
- R: Software Development Life Cycle
  - Description of R's development, testing, release and maintenance processes

R Foundation's Interpretation

"The FDA explains that validation encompasses the overall program and is designed to assure quality and consistency for a process/product throughout its lifecycle. In contrast, verification is an activity performed during and/or between phases of the overall lifecycle. Software testing is one form of verification.

Qualification can be seen as a phase of verification and/or testing within an overall validation program."

https://www.r-project.org/doc/R-FDA.pdf

The R Foundation's Documentation

Key Points

- "The members of R Core constitute a widely recognized, international team of experts on statistical computing and software development."
- Source Code Management (SVN) used such that development is traceable
  - And publicly available
- Accompanied by 'NEWS' file
- Mailing lists and bug tracking system facilitate user feedback
- "A set of validation tests are maintained and upgraded by R Core to enable the testing of source code against known data and known results"
- Regular release cycles
- Availability of patched releases

https://www.r-project.org/doc/R-FDA.pdf

Summary

In layperson's terms

- We can use (base) R so long as we are comfortable that it has been developed in a way that ensures quality and consistency

- Provided this matches up with our own internal Quality Assurance SOPs, Base R is fine to use for regulatory work once we've qualified the environment internally (essentially, verifying that our installation has been successful)

Your Thoughts?

DISCUSS

What about R packages?

Other R Packages

- R packages may:
  - Come from anywhere
  - Be written by anyone
  - Or may not follow a typical SDLC
- Ultimately, **may or may not do what they are supposed to do**
- Hopefully, they have been extensively tested in the community!

The Challenges of Validating R Packages

Validation platform

- PSI AIMS SIG have initiated an R Consortium endorsed project to create an online validation platform for R
- The platform will
  - Standardise the packages we use
  - Provide links to useful QA information
  - Be a platform for sharing tests
  - Enable statistical discussion
  - Lead to a more consistent approach to R validation (and open source in general)
  - Be free to use

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

The Challenges of Validating R Packages

Validation Questions

- What are the predetermined specifications? How do we define them?
- Does it meet these specifications?
- How sure are we?
- How do we document all this?

The Challenges of Validating R Packages

Other Key Questions

- Does a package import require the same level of scrutiny?
- What, if any, additional work is required to validate extensions such as shiny / rmarkdown?
  - How do you QC a shiny app?
- How can we validate packages that use 3rd party dependencies, eg R2jags, rstan?
- How often should we upgrade our R environments?
- How do we ensure reproducibility?

Challenges of Validating R Packages

The Evidence

- Collating this information is only the first step
- The next challenge is the interpretation
  - Package is written by Hadley Wickham but has only been available for 6 months
  - Package hasn’t been updated in over a year but has 100,000 downloads in the last month
- Every QA team will have different opinions on what is required
- Can we steer our QA teams towards a common approach?

Workshop

Workshop Structure

- Let’s split into groups and try to answer some questions

- Assessing Risk / Verification
- R Environments
- R Community

Assessing Risk / Verification

For Consideration

- How do we define requirements?
  - Do we need to?
- What metrics do we need to collect for a risk assessment?
- What level of testing is required to mitigate risk?
- How should package imports be handled?
- How should 3rd party dependencies be handled?
- How do you validate a shiny app?

R Environments

For consideration

- How often should we update an R environment?
- How do we balance progression with stability?
- Mechanisms for deployment
- How should 3rd party software be handled?
- Should the industry try to standardise on a set of R packages?
- Reproducibility - do we need backwards compatibility? Can we use containers for this?

R Community

For consideration

- How do we answer colleagues comparing R with SAS?
  - Do we need to?
- Should we try to define a standard that package developers can aspire to (eg badges)?

More Information

- To join the SIG (Europe only) contact Lyn Taylor at taylorlyn@prahs.com
- For more information on the Consortium Project contact andy.p.nicholls@gsk.com

Thank you!