OPERATION: VALIDATE

Mat D. Davis, Theorem Clinical Research

THEOREM
CLINICAL RESEARCH™

Our Mission: Validate R

- To complete this mission, we need to achieve 3 goals:
  - Fight the perception that it can't be done
  - Figure out how to do it
  - Plan how to control it

FIGHTING PERCEPTION

THEOREM
CLINICAL RESEARCH™

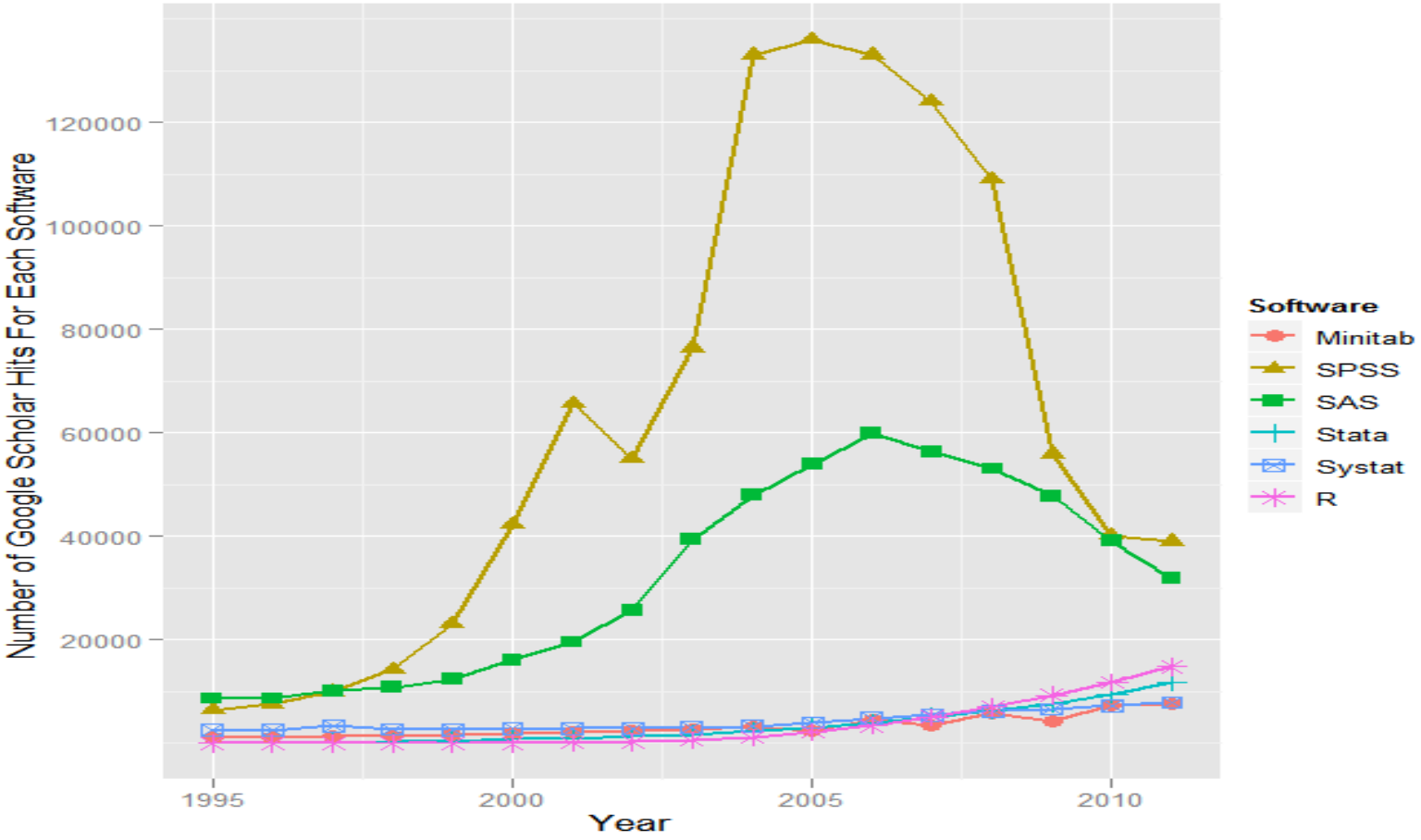
THEOREM CLINICAL RESEARCH™

Fighting Pe  ception

- There is a perception that open source software (R, for example) is not usable in the pharmaceutical industry
  - Or, if it is usable, it certainly can't be used for a submission
- The facts tell a different story…

THEOREM
CLINICAL RESEARCH™

Why Bothe R



-Muenchen, www.r4stats.com

THEOREM CLINICAL RESEARCH™

What about  egulatory?

-  is an approved software package at the FDA and is available for statistical analysis
- As SAS datasets are still the standard to transport data, SAS is a natural choice of software for analysis
- With academia being a main source of recruitment for the FDA, many are trained in  and will continue using it for analysis

THEOREM CLINICAL RESEARCH™

FDA PeRspective: Jae Brodsky

- Use  conference, 2012
  -  is approved software at the FDA
  - FDA has installed base  as well as the following packages:
    - *Datasets, graphics, grDevices, grid, methods, splines, stats, stats4, tcltk, tools, utils*
  - All results should be reproducible regardless of what software is used

THEOREM CLINICAL RESEARCH™

FDA PeRspective: Jae Brodsky

- "Sponsors may use R in their submissions
- Data must be submitted in *xpt* format
- Reviewers would like to know:
  - Which *R* functions were used
  - How they were accessed
  - That the results are accurate, reliable and consistent"

THEOREM CLINICAL RESEARCH™

PhRma Perspective: Andy Nicholls (GSK)

- "Pharmaceutical Industry traditionally uses SAS
  - SAS (generally) thought to be the only software that regulators will accept (not true)
  - Statistical Analysis Plans written with SAS in mind, sometimes even containing example SAS code
  - Industry is not very progressive statistically
    - Same methods and therefore the same SAS code
  - The expertise is generally in SAS
- Told by anyone I spoke to in the industry that R is generally NOT used and that I should focus on SAS!!!"

THEOREM CLINICAL RESEARCH™

PhRma Perspective: Andy Nicholls (GSK)

1. "Look for advantages over alternative software (i.e. SAS)
   - R graphics (arguably) look better than SAS
   - Lattice graphics in R
2. Seek to use R for any non-standard work
   - Study teams are easily impressed by new and different analyses and/or graphics so I used R for any non-standard work
     - Simulation
     - Highly customised graphics"

PLAN OF ACTION

THEOREM
CLINICAL RESEARCH™

THEOREM CLINICAL RESEARCH™

Validation: DescRiption

- **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. Contrast with data validation.
- **validation, process.** (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 characteristics.

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

THEOREM CLINICAL RESEARCH™

Regulatory Compliance

- The R core has put out a great document on validating in the clinical trial environment

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

*www.**r**-project.org/doc/**R**-FDA.pdf*

Meet R

- Programming language for statistical computing and graphics
- F  ee!
- Used largely in the academic setting, has moved into many industrial spheres

- R is open-source software (source code is freely available and distributed)
- Modifications to the "downloadable" base R package are limited to a small subset of individuals, the "R Developmental Core Team"
  - BASE R has a number of validation scripts written by the core team, some of which can be found using the following links:
    - https://svn.r-project.org/R/trunk/tests/
    - https://svn.r-project.org/R/trunk/src/library/stats/tests/

- BASE R can be improved upon by installing additional packages containing functions with various purposes
- Packages are a great strength of R
- Packages also present a validation challenge
  - Some packages have well documented validation, others do not

- From the R: Regulatory Compliance document:

R is not intended to create, maintain, modify or delete Part 11 relevant records put to perform calculations and draw graphics

It is important to maintain the appropriate expectations for R in its use and scope

THEOREM CLINICAL RESEARCH™

21 CF  Part 11 Compliance

- FDA regulations regarding electronic records and electronic signatures
  - § 11.10: Controls for closed systems
  - § 11.30: Controls for open systems
  - § 11.50: Signature manifestations
  - § 11.70: Signature/record linking
- We are interested in § 11.10 for validated software systems
- Does  meet these strict compliance guidelines?

THEOREM CLINICAL RESEARCH™

21 CF R Part 11 Compliance

- (a) Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records.

- The core development team has provided a number of validation checks and shared the results

THEOREM CLINICAL RESEARCH™

21 CF R Part 11 Compliance

- (b) The ability to generate accurate and complete copies of records in both human readable and electronic form suitable for inspection, review, and copying by the agency. Persons should contact the agency if there are any questions regarding the ability of the agency to perform such review and copying of the electronic records.
- R is not intended to create or modify records
- Regardless, R does have the ability to read and output records in readable format

THEOREM CLINICAL RESEARCH™

21 CF R Part 11 Compliance

- (c) Protection of records to enable their accurate and ready retrieval throughout the records retention period.

- According to the R: Regulatory Compliance Document:

  - R is not intended to create, maintain, modify or delete Part 11 relevant records but to perform calculations and draw graphics.
  - Records created by R will, therefore, reside within and be managed by a separate host system.
  - The host system is required to provide for compliance with this part using local policies regarding the retention and archival of such records and the mechanisms and access controls in place.

21 CF R Part 11 Compliance

- (d) Limiting system access to authorized individuals.
  - Modifications to source code are limited to the core development team
  - It is the responsibility of the end company/user to ensure that system access is limited on the other end

21 CF R Part 11 Compliance

- (e) Use of secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records.
  - Modifications to source code are limited to the core development team. Such audit trails are carefully document and restricted
  - It is the responsibility of the end company/user to ensure that this regulation is followed on the other end

THEOREM CLINICAL RESEARCH™

21 CF R Part 11 Compliance

- (f) Use of operational system checks to enforce permitted sequencing of steps and events, as appropriate
  - From the R: Regulatory Compliance Document:

R was designed with an architecture, technology, process and interface that provide for operational system checks for software function or features. Components in R provide for error checking mechanisms to preclude certain actions, which when combined with computer system level functionality, can limit certain user operations.

THEOREM CLINICAL RESEARCH™

21 CF R Part 11 Compliance

- (g) Use of authority checks to ensure that only authorized individuals can use the system, electronically sign a record, access the operation or computer system input or output device, alter a record, or perform the operation at hand.
  - Achieved through the restricted core development team as well as end user specifications
- (h) Use of device (e.g., terminal) checks to determine, as appropriate, the validity of the source of data input or operational instruction.
  - Achieved through previously mentioned validation and end user checks in accordance with good programming technique

THEOREM CLINICAL RESEARCH™

21 CF R Part 11 Compliance

- (k) Use of appropriate controls over systems documentation including:
  - (1) Adequate controls over the distribution of, access to, and use of documentation for system operation and maintenance.
  - (2) Revision and change control procedures to maintain an audit trail that documents time-sequenced development and modification of systems documentation.

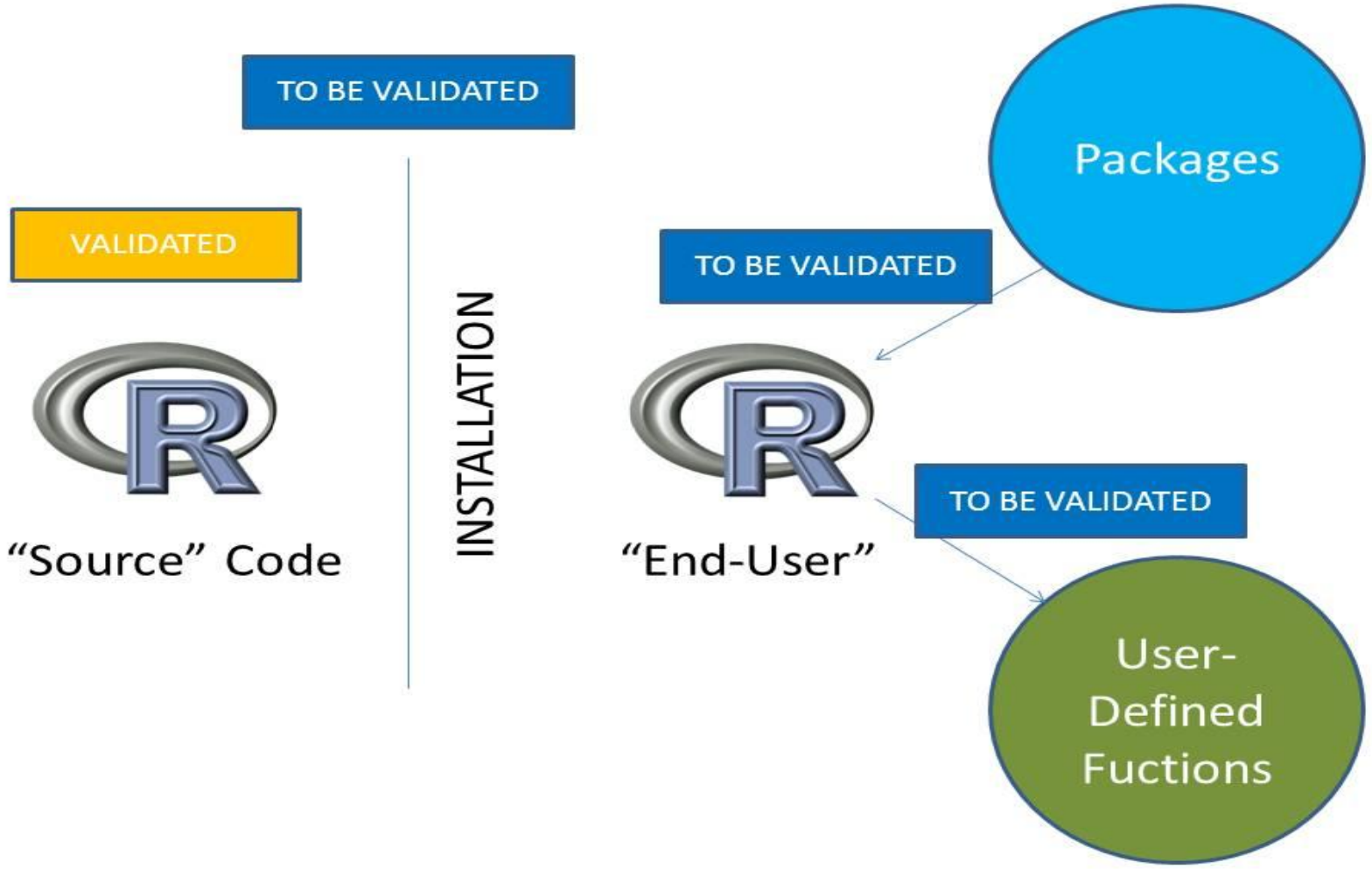
- Achieved by the restricted R development core and the system established by the end user.

OPERATION IN PRACTICE

THEOREM
CLINICAL RESEARCH™

THEOREM
CLINICAL RESEARCH™

Installation P Rocedure



THEOREM CLINICAL RESEARCH™

Installation Conside  ations

- Open-Source does NOT mean that all users can edit the source code
- Users would do well to mimic the process laid out by the core development team
- Packages should be installed on a case by case basis, evaluated based on the available validation documentation

THEOREM CLINICAL RESEARCH™

Reccomended Packages

- The R: Regulatory Compliance document suggests installing the following additional packages:
  - Boot
  - Class
  - Cluster
  - Codetools
  - Foreign
  - KernSmooth
  - Lattice
  - MASS
  - Matrix
  - Mgev
  - Nlme
  - Nnet
  - Rpart
  - Spatial
  - Survival

THEOREM CLINICAL RESEARCH™

Pu R pose

- R is not intended to replace any existing software
- Rather, it should supplement existing software and provide additional tools to perform appropriate analysis
- A validated R system is a useful complement to other software packages

sas™

R

THEOREM CLINICAL RESEARCH™

Questions/Responses

- Feel free to get in touch to talk validation

Mat D. Davis
Project Statistician
Theorem Clinical Research
Matthew.Davis@TheoremClinical.com

THEOREM CLINICAL RESEARCH™

References

Brodsky, Jae (2012). *Some Challenges of Using R in a Regulatory Environment.* Poster presented at the UseR! Conference, Nashville, TN.

"CFR - Code of Federal Regulations Title 21." *CFR - Code of Federal Regulations Title 21*. N.p., n.d. Web. 20 Sept. 2013

“Inspections, Compliance, Enforcement, and Criminal Investigations: Glossary of Computer Systems Software Development Terminology ”. http://www.fda.gov/iceci/inspections/inspectionguides/ucm074875.htm. Web 20 Sept. 2013

München, Bob. “Will 2015 be the Beginning of the End for SAS and SPSS?” http://r4stats.com/2012/05/09/beginning-of-the-end/. Web 20 Sept. 2013

Nicholls, Andy. “How I’m Selling R at GSK”. *www.londonr.org/How**ImSellingRAtGSK**.pptx*. Web. 20 Sept. 2013

“R: Regulatory Compliance and Validation Issues: A Guidance Document for the Use of R in Regulated Clinical Trial Environments”. The R Foundation for Statistical Computing. *www.r-project.org/doc/**R**-FDA.pdf*. Web. 20 Sept. 2013