



PRACTICABILITY OF R IN CLINICAL DOMAIN



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Agenda

- ❖ About R environment
- ❖ SDLC(Software Development Life Cycle) of R
- ❖ 21CFR part 11
- ❖ GxP
- ❖ FDA on using R for submissions
- ❖ Use cases
- ❖ Conclusion



About R Environment

R is a language and environment for statistical computing, data manipulation and creating graphs.

R provides a wide variety of statistical (linear and nonlinear modelling, statistical tests, time-series analysis, classification, clustering, etc.) and graphical techniques.

R has many built-in functions and libraries, and is extensible, allowing users to define their own functions and procedures.

The R language is widely used among statisticians and data miners.

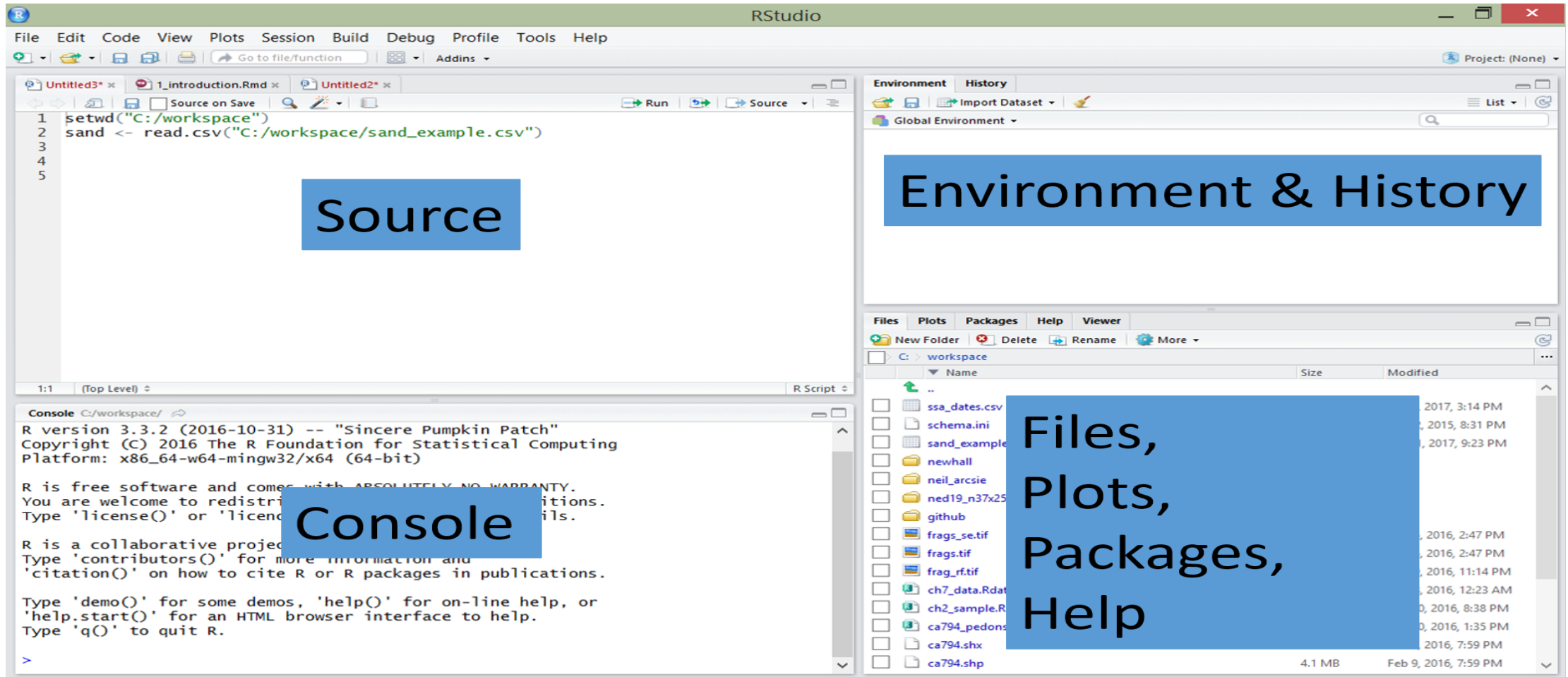
R is available as Free Software.



About R Environment cont.

R Studio

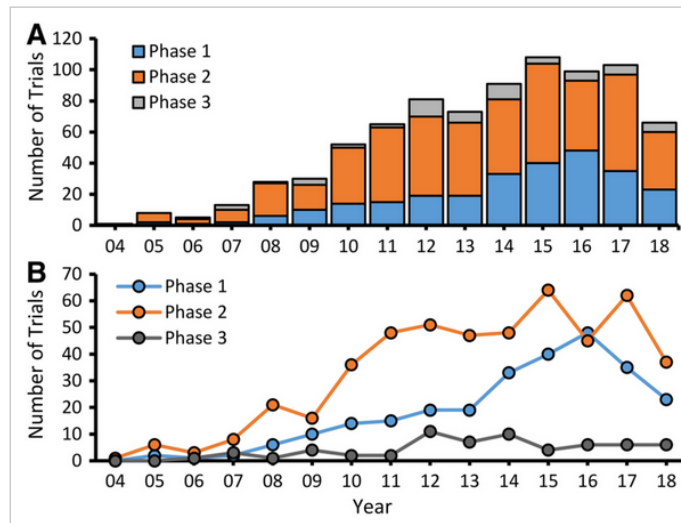
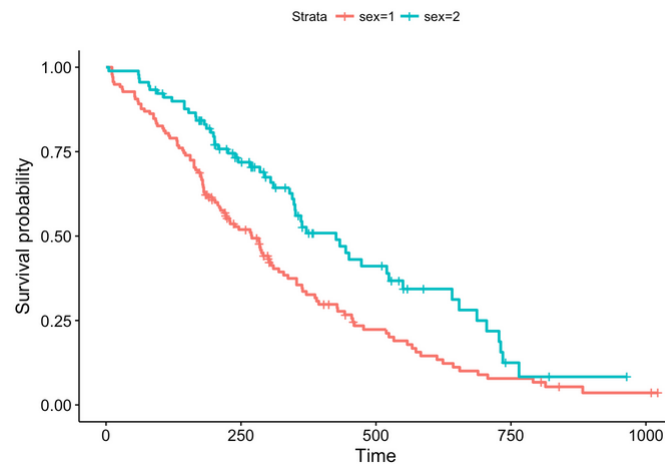
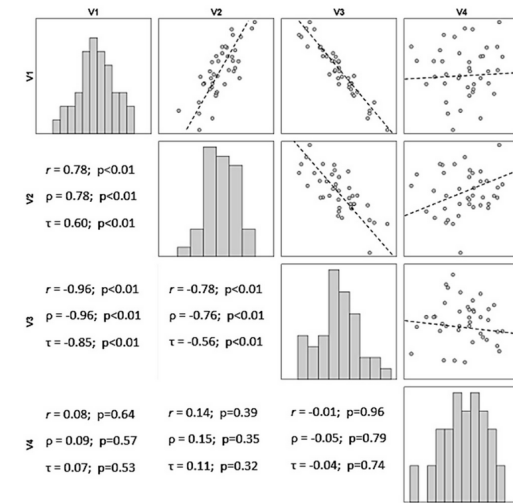
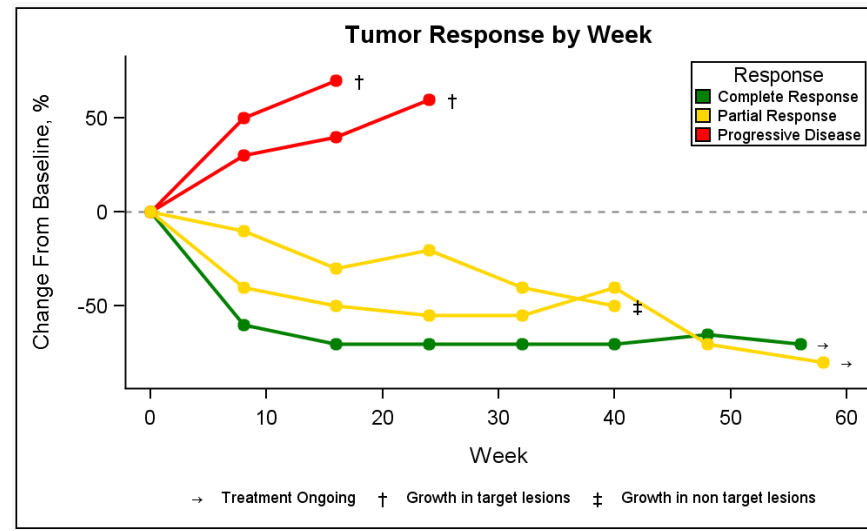
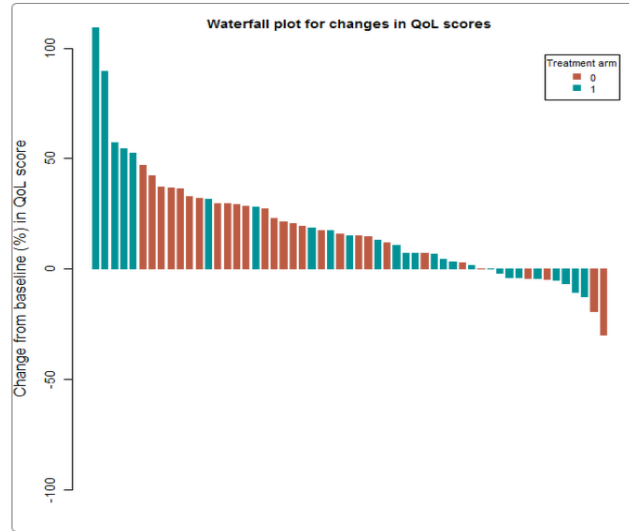
R Studio is an integrated development environment (IDE) that allows you to interact with R more readily. RStudio is similar to the standard R Gui (Graphical User Interface), but is considerably more user friendly.





About R Environment cont.

Data Visualization



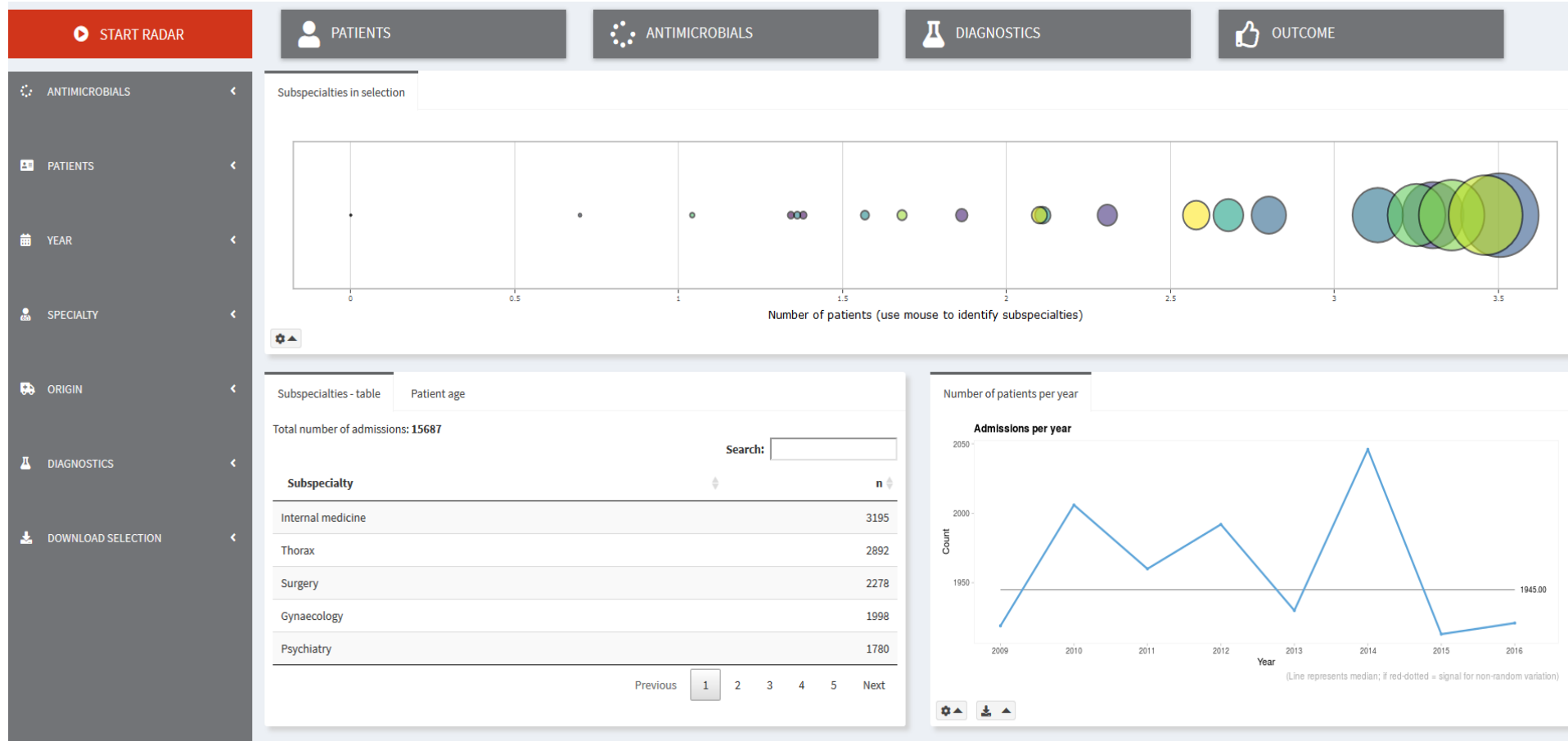
- ❖ Ggplot2, dygraphs, plotly, shiny etc are great package in R for Data Visualization.
- ❖ R helps you to connect to many databases and data types.
- ❖ Interface with other languages and scripting capabilities
- ❖ A large number of algorithms and packages for statistics flexible
- ❖ Offers effective data handling and storage facility
- ❖ Flexible, extensible and comprehensive for productivity



About R Environment cont.

R Shiny

Shiny is a new package from RStudio that makes it incredibly easy to build interactive web applications with R.





About R Environment cont.

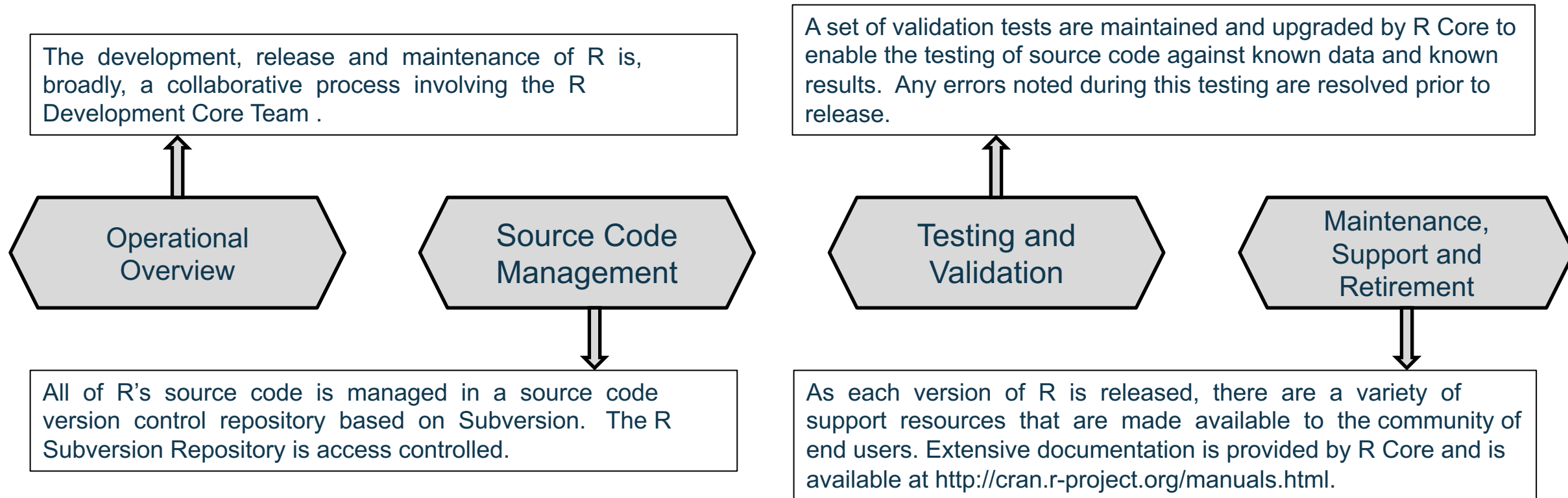
R Shiny

Features:

- ❖ Build useful web applications with only a few lines of code—no JavaScript required.
- ❖ Shiny applications are dynamic. Outputs change instantly as users modify inputs, without requiring a reload of the browser
- ❖ Attractive default UI(User Interface) theme based on Twitter Bootstrap.
- ❖ A highly customizable slider widget with built-in support for animation.
- ❖ Pre-built output widgets for displaying plots, tables, and printed output of R objects



SDLC(Software Development Life Cycle) of R





21 CFR Part 11 Compliance

- ❖ 21 CFR part 11 explains how a company can use electronic quality records and digital signatures in place of paper based documentation and 'wet signatures' in such a way that complies with FDA regulations. "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].
 - // If there are predicate rules that require records to be maintained, and these records are managed electronically, then Part 11 controls apply to those records.
 - // If there are predicate rules that require a signature to be applied, and this signature is applied electronically or digitally, then Part 11 controls apply.
- ❖ It is not mandated that 21 CFR Part 11 is appropriate to data analysis software systems that are not primarily intended for storage and transmission of electronic medical records. It remains the responsibility of an individual organization however to define the applicability of Part 11 and validation to their systems.
- ❖ Validation is defined by the FDA as: "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."
- ❖ The software package(s) used for statistical analyses should be fully documented in the submission, including version and build identification.



21 CFR Part 11 Compliance

Controls for closed systems.

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

The software package(s) used for statistical analyses should be fully documented in the submission, including version and build identification.

(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 provided output will be available in both machine- and human-readable formats.

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

(d) Limiting system access to authorized individuals.

(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. Record changes shall not obscure previously recorded information. Such audit trail documentation shall be retained for a period at least as long as that required for the subject electronic records and shall be available for agency review and copying.

(f) Use of operational system checks to enforce permitted sequencing of steps and events, as appropriate.

These capabilities are similar to those of any statistical software application and are consistent with the implementation of good analytical practice like appropriate coding techniques that implement good and defensive programming style.

(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.

(h) Use of device (e.g., terminal) checks to determine, as appropriate, the validity of the source of data input or operational instruction.



21 CFR Part 11 Compliance

(i) Determination that persons who develop, maintain, or use electronic record/electronic signature systems have the education, training, and experience to perform their assigned tasks.

(j) The establishment of, and adherence to, written policies that hold individuals accountable and responsible for actions initiated under their electronic signatures, in order to deter record and signature falsification.

In the event that an electronic signature must be applied to the record, this must be achieved using a third-party system. R does not provide functionality for the application of electronic signatures.

(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.

All releases of R include documentation covering installation, administration, programming and related user guides. R documentation is created once per Release Version; thus these documents are uniquely identifiable and associated with a specific release of the software.



GxP Compliance

- ❖ Backup and Recovery
- ❖ Contingency Plan
- ❖ Disaster Recovery
- ❖ Change Control Management
- ❖ Configuration Management
- ❖ Error Handling
- ❖ Maintenance and Support
- ❖ Corrective Measures
- ❖ System Access

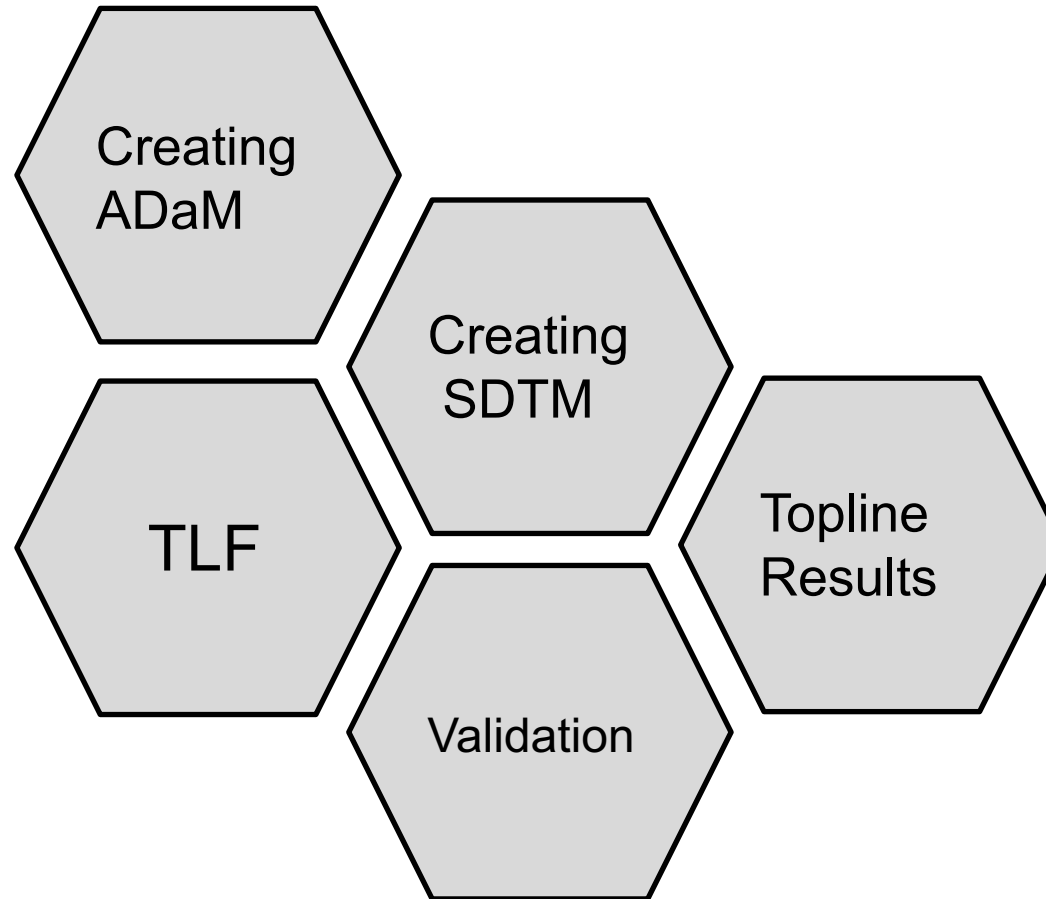


FDA – on using R for submission

- ❖ 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
- ❖ All results from data should be reproducible independent of software used.
- ❖ In submissions, FDA reviewers would like to know: which R functions were accessed; how they were accessed; and that the results are accurate, reliable and consistent.
- ❖ 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.



Use cases





Conclusion

- ❖ We can make R FDA compliant.
- ❖ Cost effective.
- ❖ Vast number of packages.
- ❖ Data visualization.
- ❖ Skill availability.



References

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

<http://www.phusewiki.org/docs/Conference%202016%20AD%20Papers/AD12.pdf>

<http://washstat.org/presentations/20181024/Schuette.pdf>

<https://www.fda.gov/media/109552/download>



Thank you!

