



Pan-pharma Industry collaboration - new horizon, success stories

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Working groups, R consortia - current state
What can be done differently?

Working groups; Consortia and GitHub spaces

Different spaces of collaboration

Working groups:

- PhUSE,
- Transcelerate,
- CDISC,
- R Consortium

CDISC open source alliance - [CORE](#)

CRAN packages

Github spaces:

- [Openpharma](#)
- [Insightsengineering](#)
- [Phuse-org](#)
- [Phamraverse](#)
- [Bioconductor](#)
- [RConsortium](#)
- [rOpenSci](#)
- [RStudio](#)
- [Atorus-research](#)
- [Merck](#)
- [Roche](#) / [Genentech](#)

Working groups; Consortia and GitHub spaces

What is there in open space for Pharma Industry?

- CRAN
- GitHub packages
- CRAN Task View: Clinical Trial Design, Monitoring, and Analysis
- A Guidance Document for the Use of R in Regulated Clinical Trial Environments- [base and recommended packages](#)
- [Pharmaverse.org](#)

19018 (April 2022)

?????

62

29

22

What can be done differently?

Window of opportunity

What is so special about this point of time?

- **Lesson learned:** Companies spent years on the SAS macro based system, specific to the computing environment, up and downstream dependencies
- **Availability:** R is open source, and also offers almost 20 k packages; statistical algorithms and new packages everyday
- **Challenges:** Growing clinical studies complexity, data modalities, secondary use of the clinical data and time pressure requires more flexibility
- **Infrastructure:** Using R in GxP environment has been seen for year as additional effort
- **Opportunity to industry:** Influencing the industry and setting the similar ways of working and using tools

What can be done differently?

Benefits of codebase collaboration

Direct

- **“Collaboration builds stronger relationships and trust”** – leading to cost-saving and sharing of resources
- **“Collaboration can produce powerful research”** – sharing ideas, collecting broader feedback

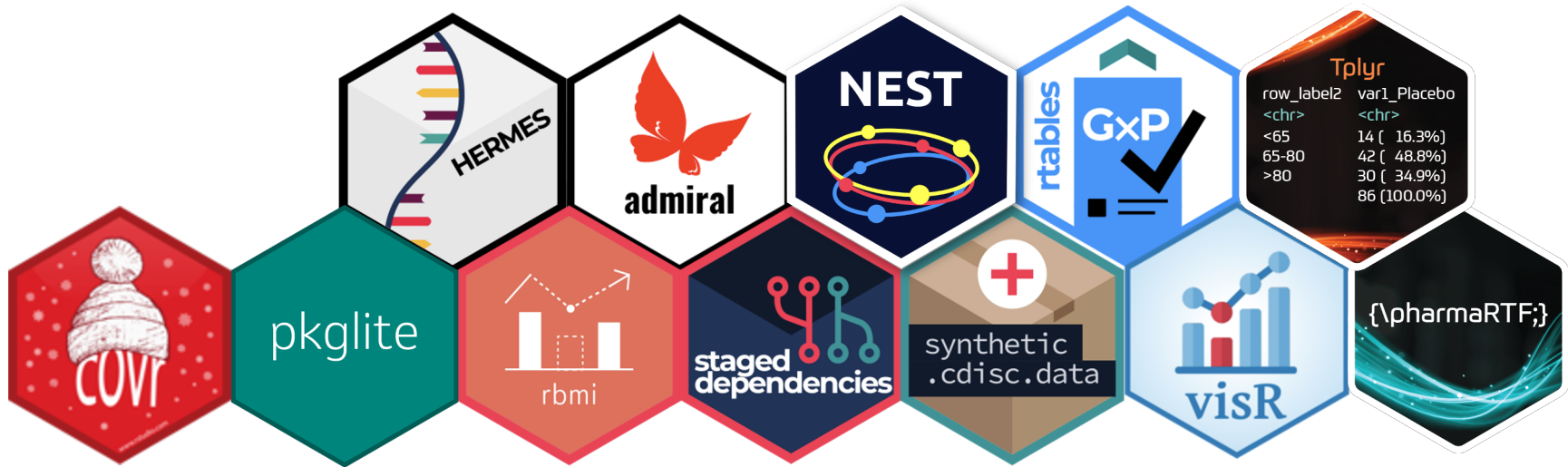
Indirect

- **“Become the go-to source for information and industry expertise”** – recognition from industry organizations
- **“The ability to influence and make a change”** – leading to acceptance of solutions making a difference to patients' lives

Current examples of working and consolidating efforts

Current examples of working and consolidating efforts

Specific examples for Pharmaceutical Industry



Current examples of working and consolidating efforts

admiral



Status: open sourced

Collaboration: Roche - GSK

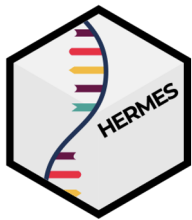
Impact: Modularized toolbox that enables the pharmaceutical programming community to develop ADaM datasets in R. First significant collaboration between two Pharma companies, bringing together another xxx to help testing and feedback.

Details:

- Build a toolbox of re-usable functions and utilities to create ADaM datasets in R in a modular manner
- Pharmaceutical communities and companies are encouraged to contribute to admiral following the provided programming strategy and modular approach
- All functions are documented, tested, include examples and are listed in the [Reference section](#)
- Vignettes how to create ADSL, BDS and OCCUR datasets, including example scripts
- Vignettes for ADaM dataset specific functionality (i.e. dictionary coding, date imputation, SMQs ...)

Current examples of working and consolidating efforts

Hermes



Status: open sourced

Collaboration: Roche

Impact: Provides classes and functions for quality control, filtering, normalization and differential expression analysis of pre-processed RNA-seq data. Quickly add RNA-seq analysis teal modules to your teal app.

Details:

- Import RNAseq count data into the hermes ready format.
- Annotate gene information automatically from a central database (e.g. BioMart).
- Add quality control (QC) flags to genes and samples.
- Filter the data set.
- Normalize the counts.
- Quickly produce descriptive plots.
- Perform principal components analysis.
- Produce a templated QC report.
- Perform differential expression analysis.

Current examples of working and consolidating efforts

rtables



Status: open sourced

Collaboration: Roche

Impact: Designed to create and display complex tables with R. The cells may contain any high-dimensional data structure which can then be displayed with cell-specific formatting instructions. Development is driven by the need to create regulatory ready tables for HA review - and it was validated and deployed to Roche GxP

Details:

- cell values and their visualization separate (i.e. no string based tables)
- values need to be programmatically accessible in their non-rounded state for cross-checking
- multiple values displayed within a cell
- flexible tabulation framework
- flexible formatting (cell spans, rounding, alignment, etc.)
- multiple output formats (html, ascii, latex, pdf, xml)
- flexible pagination
- distinguish between name and label in the data structure to work with CDISC standards
- title, footnotes, cell cell/row/column references

Current examples of working and consolidating efforts

rbmi



Status: open sourced

Collaboration: Roche

Impact: New statistical methodology.

rbmi is a R package for analysis of clinical trials with continuous longitudinal outcomes. It is directly triggered by the [ICH E9 \(R1\) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials](#)

Details:

- rbmi implements estimators based on multiple imputation that might be used to align the estimation of the treatment effect with the defined estimand
- It supports imputation under a missing at random (MAR) assumption, reference-based imputation methods, and delta adjustments (as required for sensitivity analysis such as tipping point analyses).
- The package implements both Bayesian and approximate Bayesian multiple imputation combined with Rubin's rules for inference, and frequentist conditional mean imputation combined with (jackknife or bootstrap) resampling.

Current examples of working and consolidating efforts

NEST



Status: partially open sourced

Collaboration: Roche plus collaboration

Impact: Enabling data scientists to understand the ever increasing growth of data generated from clinical trials. Set of tools enabling faster, more efficient exploratory analysis and regulatory delivery of clinical trials insights in R.

Details:

- The **rtables** package is the foundation layer of NEST's tabling capabilities
- The **tern** package is the reporting layer that sits on top of our **rtables** foundation.
- The **teal** package is a framework developed at Roche that leverages the R Shiny package to scale development of our shiny apps.
- TLG- Catalog
- Biomarker Analysis Catalog (BAC)
- Sample Apps

Current examples of working and consolidating efforts

staged dependencies



Status: open sourced

Collaboration: Roche

Impact: Simplifies the development process for developing a set of inter-dependent R packages: *upstream* (packages your repo depends on) and *downstream* (packages which depend on your repo's package) dependency packages within your development set of packages.

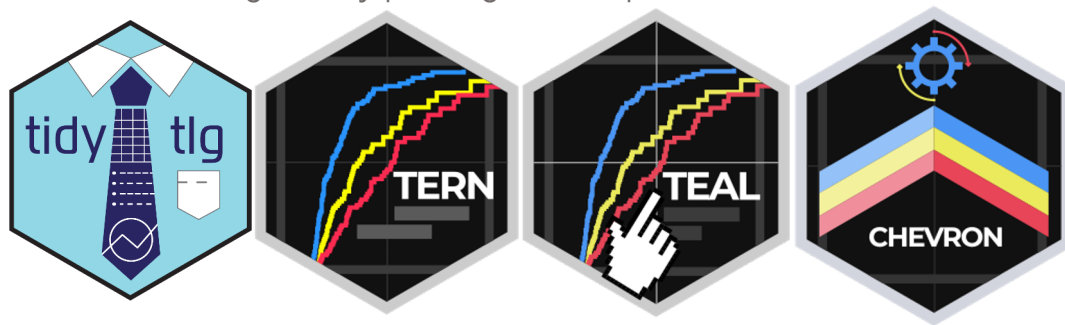
Details:

- By using a git branching naming convention in development work, it makes straightforward to:
- Install upstream dependencies (and the current package): install remote upstream dependencies and the local version of the current package using the requested branches for each repository.
- Check and install downstream dependencies: install downstream and their required upstream dependencies using the requested branches for each repository.
- Test and install downstream dependencies: see above. It tests instead of checks.
- Install all dependencies app: A Shiny application to unselect those dependencies that should not be installed.

What is on the horizon in open space

What is on the horizon in the open space

Different regulatory packages examples



Pharma specific packages scaling-up¹:

- regulatory,
- exploratory analysis,
- innovating submission process

Boehringer Ingelheim was able to easily reproduce CSR tables originally done with SAS²

¹ pharmaverse.org

² [APF – Statistikleiter Treffen Special edition: "Usage of R..." part2/2](#)

What is on the horizon in the open space

Gaining efficiency in the study results delivery internally and externally

What are the capabilities

Challenging the way analyses are delivered

- Efficacy: https://genentech.shinyapps.io/teal_efficacy/
- Exploratory: https://genentech.shinyapps.io/teal_exploratory/
- Safety: https://genentech.shinyapps.io/teal_safety/

Innovative submission

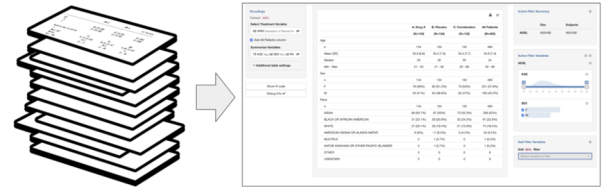
- R Consortium minutes from April [here](#)

Flexible usage of teal framework

Conclusions

Conclusions

- There are **many of the R-packages** available and not all of them are applicable to the pharmaceutical industry
- There are advantages of code base collaboration, changing the current **paradigm of silo'd solutions** and moving to various initiatives
- Existing high quality R-packages for pharmaceutical companies are the starting point in this journey, supporting the shift into **“new ways of working”**
- The industry effort in building, collaborating and design new R-packages, brings **new capabilities** and possibly triggering further downstream changes
- Challenge study results delivery: **from paper to interactive**



Doing now what patients need next