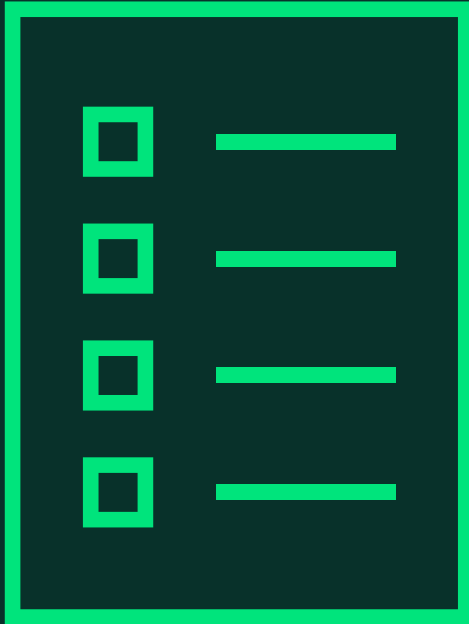


AD05: Development of a Customised Statistical Computing Environment for Clinical Trial Data Analysis

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PHUSE EU Connect
11-Nov-2024

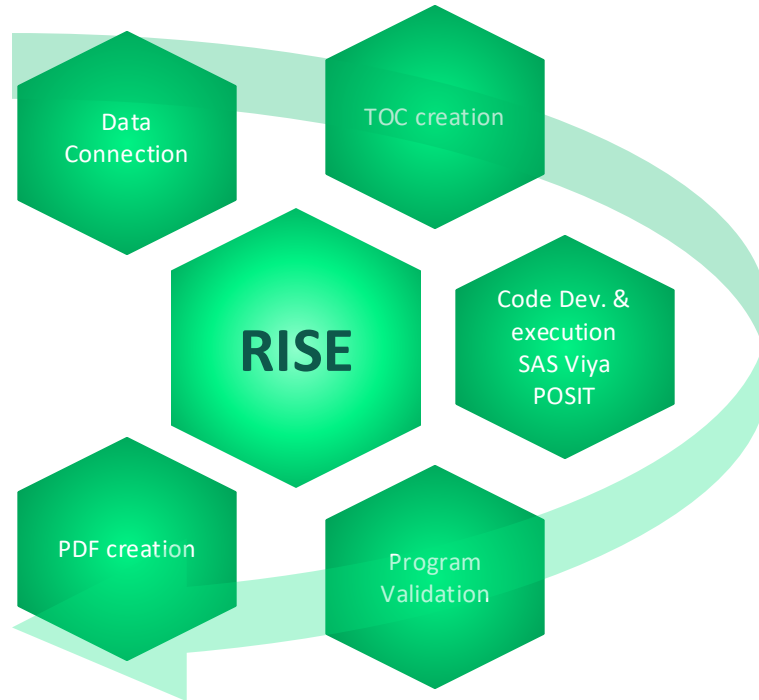
Agenda



- **RISE Introduction**
- **RISE Features**
- **System Architecture & Technical Insights**
- **Outlook**

RISE

Reporting Integrated Statistical Environment



Web application focusing on regulatory relevant reports (CTR, ISS, ISE, per. Reports etc.)

- Planning (*what needs to be done*)
- Organizing (*who is doing what*)
- Developing (*utilizing SAS/R for interactive code development*)
- Executing (*batch run of programs*)
- Output QC (*facilitates & documents validation status*)
- PDF creation (*in line with framework conditions*)

RISE

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- PDF creation (in line with framework conditions)

- RISE UI reflects a TOC (Table of contents) of a required report
- The TOC is a “to-do” list and defines the structure and content of the resulting report

Workbench 1313_0021

TOC WORKBENCH SETTINGS

custom: test

Programmer view Validator view

EDIT TOC TREE

☐	TOC ID	LABEL	SUBLABEL	CLASS	PROGRAM	OUTPUT NO.	LOG	OUTPUT	PROGRAMMER	ACTION
☐	15.1	Disposition of Patients		Chapter						
☐	15.2	Efficacy evaluation		Chapter						
☐	15.2.1	Primary efficacy endpoint (section)		Section						
☐	15.2.1.1	Primary efficacy endpoint (subsection)		Subsection						
☐	15.2.1.1.1	Analysis of time to first relapse of B1XXXXXX (pooled) vs. placebo (FAS, ITT FU period) - TEST2		Figure	xprog.sas	10002	ee ✓		LR	⚙
☐	15.2.1.1.2	Analysis of time to first relapse of B1XXXXXX (pooled) vs. placebo (FAS, ITT FU period) - TEST3		Figure	program.r	4	ee ✓		LR	⚙
☐	15.2.1.1.1	Analysis of time to first relapse of B1XXXXXX (pooled) vs. placebo (FAS, ITT FU period) - TEST		Table	program.sas	24000	ee ✓		LR	⚙
☐	15.2.1.1.3	This is a test		Figure	fkmv01sun.sas	202	ee ✓		LR	⚙
☐	15.2.1.1.4	Cumulative risk over time for B1409306 (pooled) vs. placebo (FAS, ITT FU period)		Figure	fkmv01sun.sas	1	ee ✓		LR	⚙
☐	15.2.1.1.5	Cumulative risk over time for B1409306 (pooled) vs. placebo (FAS, ITT FU period)		Figure	fkmv01sun.sas	111	ee ✓		LR	⚙

RISE

Web application focusing on regulatory relevant reports (CTR, ISS, ISE, per. Reports etc.)

- Planning (what needs to be done)
- **Organizing (who is doing what)**
- Developing (utilizing SAS/R for interactive code development)
- Executing (batch run of programs)
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- Trial team defines responsibilities in the UI (developer, validator, validation method)
- Users can search/filter the TOC for their tasks

The screenshot displays the RISE web application interface. The main section is titled 'TOC' and 'WORKBENCH SETTINGS'. It features a search bar with 'custom: test' and an 'EDIT TOC TREE' button. Below is a table with columns: TOC ID, LABEL, SUBLABEL, CLASS, PROGRAM, OUTPUT NO., and ACTION. The table lists various items, including 'Tools', '15.1 Disposition of Patients', '15.2 Efficacy evaluation', and several sub-items under '15.2.1 Primary efficacy endpoint (section)'. The selected item is '15.2.1.1 Analysis of time to first relapse of BIXXXXXX (pooled) vs. placebo (FAS, ITT FU period) - TEST2', which is a Figure generated by 'xprog.sas' with an output number of 10002. To the right, the 'TOC Item Settings' panel is visible, showing 'Selected Items' with the same item name, a 'Status' dropdown set to 'IN DEV', a 'Programmer' dropdown, and 'TOC Item Properties' with checkboxes for 'Mark this as CT.gov', 'Mark this as TLR', 'Disable Print', and 'Disable Run'.

TOC ID	LABEL	SUBLABEL	CLASS	PROGRAM	OUTPUT NO.	ACTION
Tools	TTT		Chapter			
15.1	Disposition of Patients		Chapter			
15.2	Efficacy evaluation		Chapter			
15.2.1	Primary efficacy endpoint (section)		Section			
15.2.1.1	Primary efficacy endpoint (subsection)		Subsection			
15.2.1.1: 1	Analysis of time to first relapse of BIXXXXXX (pooled) vs. placebo (FAS, ITT FU period) - TEST2		Figure	xprog.sas	10002	⚙️
15.2.1.1: 2	Analysis of time to first relapse of BIXXXXXX(pooled) vs. placebo (FAS, ITT FU period) - TEST3		Figure	program.r	4	⚙️
15.2.1.1: 1	Analysis of time to first relapse of BIXXXXXX (pooled) vs. placebo (FAS, ITT FU period) - TEST		Table	program.sas	24000	⚙️
15.2.1.1: 3	This is a test		Figure	flmv01sun.sas	202	⚙️
15.2.1.1: 4	Cumulative risk over time for BIXXXXXX		Figure	flmv01sun.sas	1	⚙️

RISE

Web application focusing on regulatory relevant reports (CTR, ISS, ISE, per. Reports etc.)

- Planning (what needs to be done)
- Organizing (who is doing what)
- **Developing** (utilizing SAS/R for interactive code development)
- Executing (batch run of programs)
- Output QC (facilitates & documents validation status)
- PDF creation (in line with framework conditions)

- Each TOC item is associated with a program
- Clicking the program link opens the program in its IDE (SAS Studio or R Studio)
- Libraries/global variables can be defined in the RISE workbench settings and are available in the opened IDE

The screenshot displays the RISE web application interface, which is divided into three main sections:

- TOC (Table of Contents):** A table listing various items and their associated programs. The table has columns for TOC ID, LABEL, CLASS, and PROGRAM. The 'PROGRAM' column contains links to specific programs, such as 'xprog.sas', 'program.r', 'program.sas', 'fkmv01sun.sa', and 'fkmv01sun.sa'. The 'xprog.sas' link is highlighted with a red box.
- Libraries:** A list of connected libraries, including ADAM, CH_JP, DICT, DICTB3, GENDATA, MAPS, MAPSGFK, MAPSSAS, OCFORMAT, RISEMETA, ALLDATA, DATA_STORAGE, FOLDERS, INCLUDE_PROGRAMS, PROGRAMS, SESSION_INFO, STUDYAUTO, TOC_ITEM_PARAMETERS, SASDQREF, SASHELP, SASUSER, SDTM, STDMAC, STNDRDS, and WORK. The 'RISEMETA' and 'SDTM' libraries are highlighted with red boxes.
- Code editor:** A window showing the SAS code for the selected program. The code is written in SAS and includes several PROC SQL statements for data manipulation and reporting. The code is as follows:

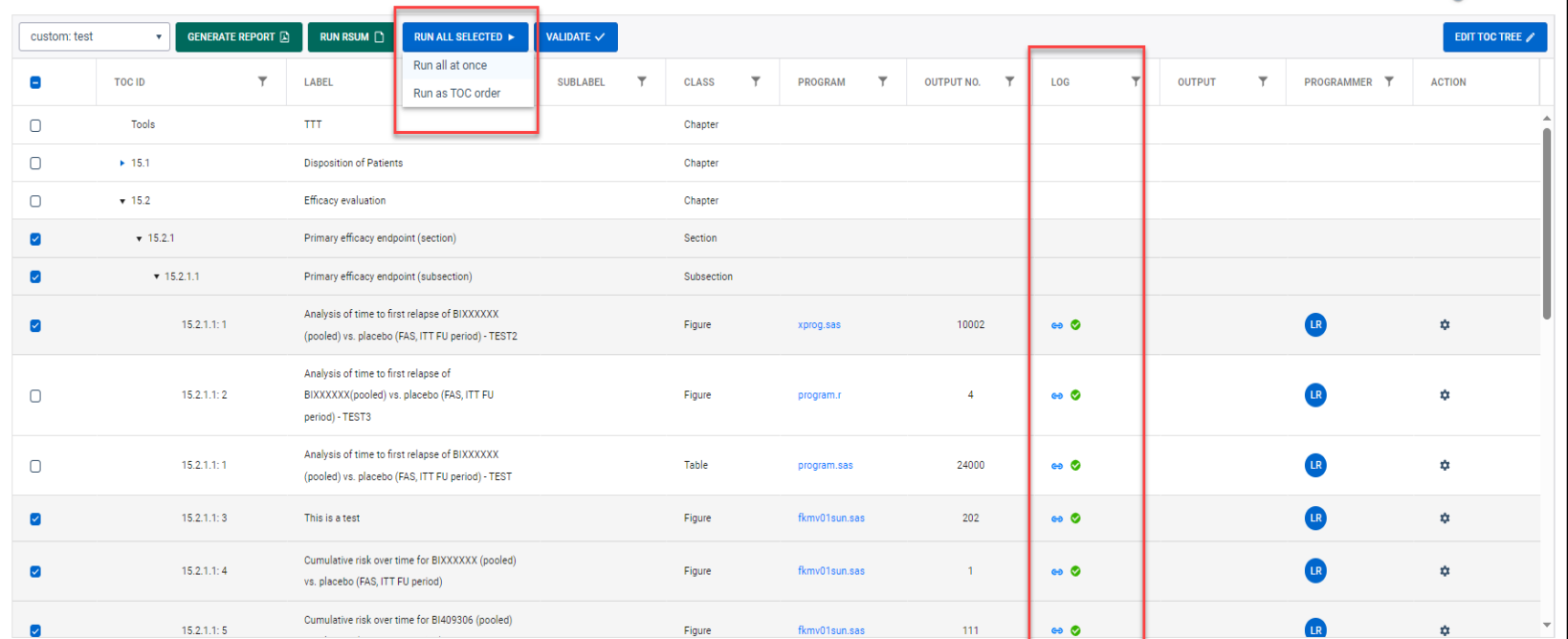
```
1 proc sql noprint;
2 create table cnt as
3 select distinct "Total" as division
4 count(distinct team) as cnt
5 from sashelp.baseball;
6 quit;
7
8
9
10
11 proc sql noprint;
12 create table cnt_div as
13 select distinct division,
14 count(distinct team) as cnt
15 from sashelp.baseball
16 group by division
17 order by 1;
18 quit;
19
20
21 data cnt_all;
22 set cnt cnt_div;
23 run;
24
25 proc sort data = cnt_all; by division;
26 proc transpose data = cnt_all out = cnt_tr;
27 id division;
28 label;
29 quit;
30
31 data cnt_perc;
32 set cnt_tr;
33 array perc east west total;
```

RISE

Web application focusing on regulatory relevant reports (CTR, ISS, ISE, per. Reports etc.)

- Planning (what needs to be done)
- Organizing (who is doing what)
- Developing (utilizing SAS/R for interactive code development)
- **Executing (batch run of programs)**
- Output QC (facilitates & documents validation status)
- PDF creation (in line with framework conditions)

- Programs can be executed in batch
 - Sequential run
 - Parallel run
 - Scheduled runs
- Execution status visible to all team members
- UI indicates execution results (Errors, Warnings, missing logfiles)



The screenshot displays the RISE web application interface. At the top, there are buttons for 'GENERATE REPORT', 'RUN RSUM', 'RUN ALL SELECTED', and 'VALIDATE'. A dropdown menu for 'RUN ALL SELECTED' is open, showing options: 'Run all at once' and 'Run as TOC order'. The main table lists programs with columns: TOC ID, LABEL, SUBLABEL, CLASS, PROGRAM, OUTPUT NO., LOG, OUTPUT, PROGRAMMER, and ACTION. The 'LOG' column is highlighted with a red box, showing status icons (e.g., green checkmark, blue circle with 'LR').

TOC ID	LABEL	SUBLABEL	CLASS	PROGRAM	OUTPUT NO.	LOG	OUTPUT	PROGRAMMER	ACTION
Tools	TTT		Chapter						
15.1	Disposition of Patients		Chapter						
15.2	Efficacy evaluation		Chapter						
15.2.1	Primary efficacy endpoint (section)		Section						
15.2.1.1	Primary efficacy endpoint (subsection)		Subsection						
15.2.1.1:1	Analysis of time to first relapse of BXXXXXXX (pooled) vs. placebo (FAS, ITT FU period) - TEST2		Figure	xprog.sas	10002	✓		LR	⚙️
15.2.1.1:2	Analysis of time to first relapse of BXXXXXXX(pooled) vs. placebo (FAS, ITT FU period) - TEST3		Figure	program.r	4	✓		LR	⚙️
15.2.1.1:1	Analysis of time to first relapse of BXXXXXXX (pooled) vs. placebo (FAS, ITT FU period) - TEST		Table	program.sas	24000	✓		LR	⚙️
15.2.1.1:3	This is a test		Figure	fkmv01sun.sas	202	✓		LR	⚙️
15.2.1.1:4	Cumulative risk over time for BXXXXXXX (pooled) vs. placebo (FAS, ITT FU period)		Figure	fkmv01sun.sas	1	✓		LR	⚙️
15.2.1.1:5	Cumulative risk over time for BI409306 (pooled)		Figure	fkmv01sun.sas	111	✓		LR	⚙️

RISE

Web application focusing on regulatory relevant reports (CTR, ISS, ISE, per. Reports etc.)

- Planning (what needs to be done)
- Organizing (who is doing what)
- Developing (utilizing SAS/R for interactive code development)
- Executing (batch run of programs)
- **Output QC (facilitates & documents validation status)**
- PDF creation (in line with framework conditions)

- UI can be switched to validator view
 - Batch execution of validation programs
 - No need to maintain separate validation TOC
- Users can define which version of programs to run for each TOC item

TOC ID	LABEL	SUBLABEL	CLASS	VAL PROGRAM	VAL OUTPUT NO.	VAL LOG	VAL OUTPUT	VALIDATOR	ACTION
Tools	TTT		Chapter						
15.1	Disposition of Patients		Chapter						
15.2	Efficacy evaluation		Chapter						
15.2.1	Primary efficacy endpoint (section)		Section						
15.2.1.1	Primary efficacy endpoint (subsection)		Subsection						
15.2.1.1:1	Analysis of time to first relapse of BIXXXXXX (pooled) vs. placebo (FAS, ITT FU period) - TEST2		Figure	val/val-xprog.sas	1			LR	⚙
15.2.1.1:2	Analysis of time to first relapse of BIXXXXXX(pooled) vs. placebo (FAS, ITT FU period) - TEST3		Figure	val/program-val.sas	1			ML	⚙
15.2.1.1:1	Analysis of time to first relapse of BIXXXXXX (pooled) vs. placebo (FAS, ITT FU period) - TEST		Table	val/xyz.sas	1			MH	⚙
15.2.1.1:3	This is a test		Figure	val/dir/other/pgm...		🔗	✅	LR	⚙

RISE

Web application focusing on regulatory relevant reports (CTR, ISS, ISE, per. Reports etc.)

- Planning (what needs to be done)
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- Executing (batch run of programs)
- **Output QC (facilitates & documents validation status)**
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Versioning a file:

- Creating a backup of a file from the development area (Windows FS) in a write protected area (S3)
- Validation workflow can be easily followed (one-click)

Validation: Displaying 17 items relative to rise

☐	FILE NAME	VERSION	PROGRAMMER	VALIDATOR	STATUS	STATUS UPDATED ON	VAL METHOD
☐	abc.sas	1.0	MK	LR	VALIDATED	2024-08-09 14:37	ST
☐	demo.sas	0.1	LR		READY FOR VAL	2024-09-12 15:24	ST
☐	EOT-TTE2V01.sas	0.1	CS		DEV PROTECTED	2024-08-29 10:56	SCR
☐	fkmv01sun.sas	1.1	LR	LR	READY FOR VAL	2024-09-11 14:14	BT
☐	forestplotv05-2.sas	0.1	LR	LR	FAILED	2024-08-09 15:02	BT
☐	forestplotv05-3.sas	0.1	LR		READY FOR VAL	2024-09-04 14:30	BT
☐	forestplotv05.sas	LATEST DEV	CS		IN DEV	2024-06-26 13:07	SCR
☐	lang.sas	LATEST DEV	ML	MH	IN DEV	2024-07-03 12:25	BT / SCR
☐	lr-test-hyphens-4-tosca.sas	LATEST DEV	LR		IN DEV	2024-09-27 12:24	
☐	multiple-pngs.sas	0.1	LR		DEV PROTECTED	2024-09-11 14:13	

Version History

[pgm/abc.sas](#) VALIDATED

✓ Version selected for running in TOC items settings

LR [R...](#)

v. 1.0 at 2024-08-09 14:39 VALIDATED

✓ Version selected for running in TOC items settings

Program Located at: 1313_0021/pgm/abc.sas/1.0/dev_file

Val Methods: ST

Source of Specifications: testing history overview

Additional Validation Information And Stat QC Method(s) Used:

MK [K...](#)

v. 1.0 at 2024-08-09 14:37 READY FOR VAL

LR [R...](#)

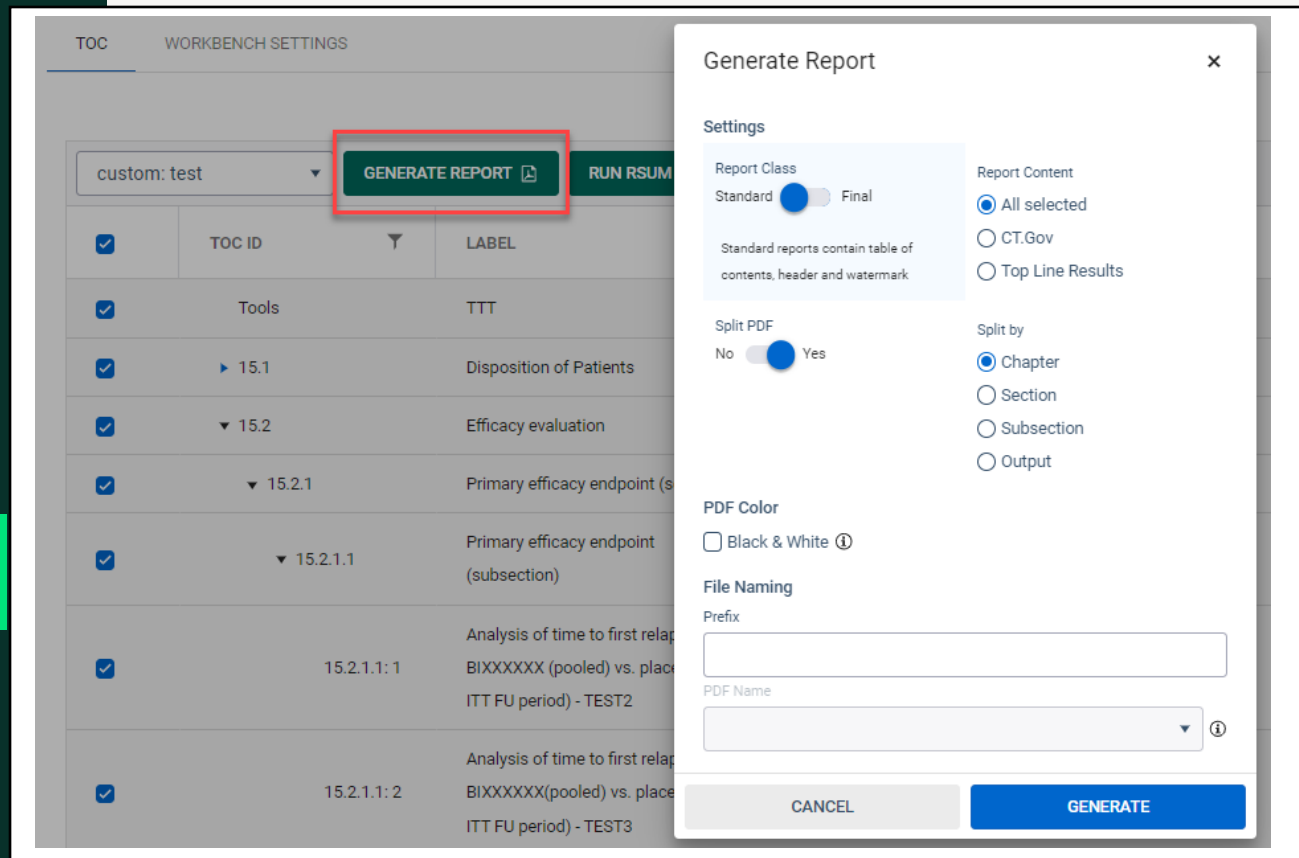
v. 1.0 at 2024-08-09 14:36 DEV PROTECTED

RISE

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- Output QC (facilitates & documents validation status)
- **PDF creation (in line with framework conditions)**

- Individual outputs, sets of multiple outputs or complete clinical study report chapters can be converted from .lst or .png files to compliant PDF documents while respecting the conditions for publishing.
- Users have several options to further decide on content or layout.



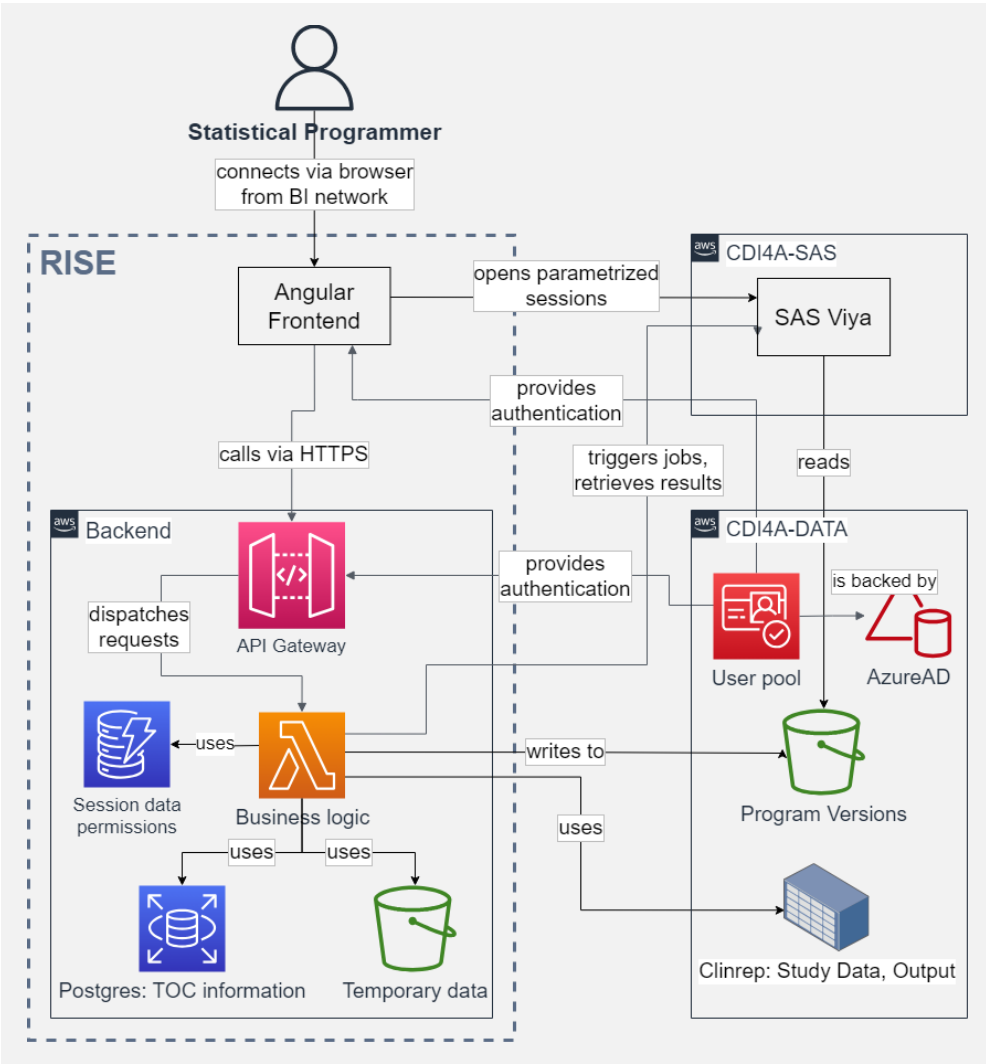
Application Development



HMS
analytical software



System Architecture

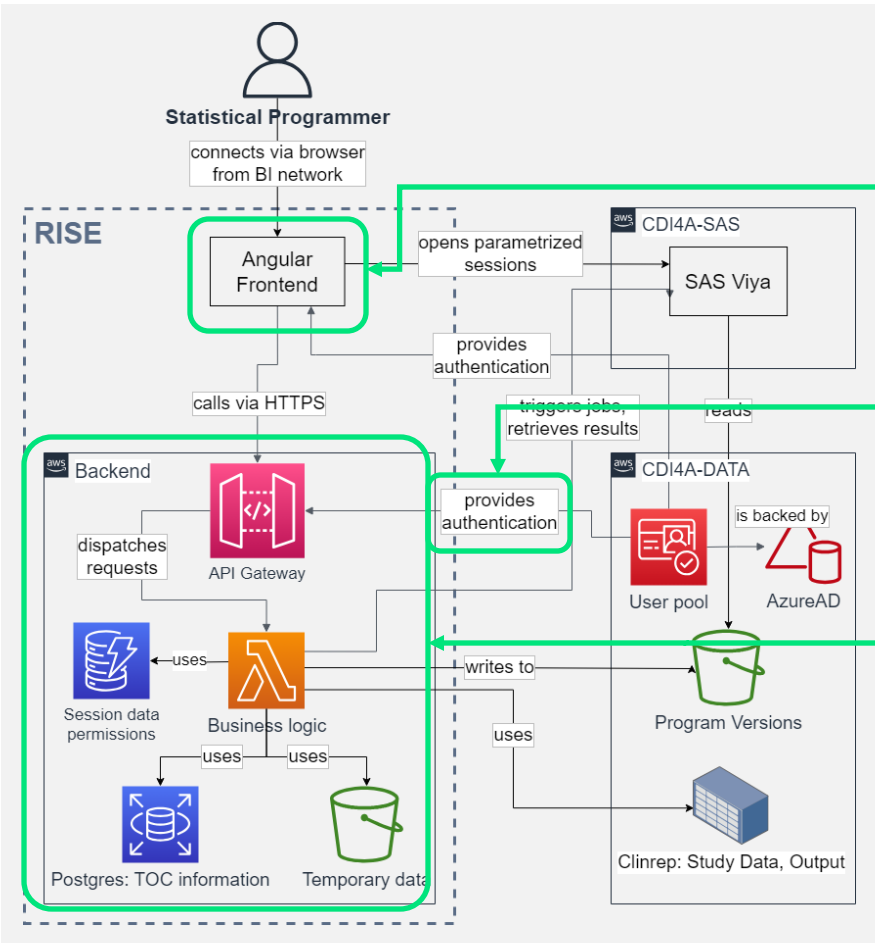


Application Development



HMS
analytical software

RISE IT Requirements



Webapp
single page application

Single sign on

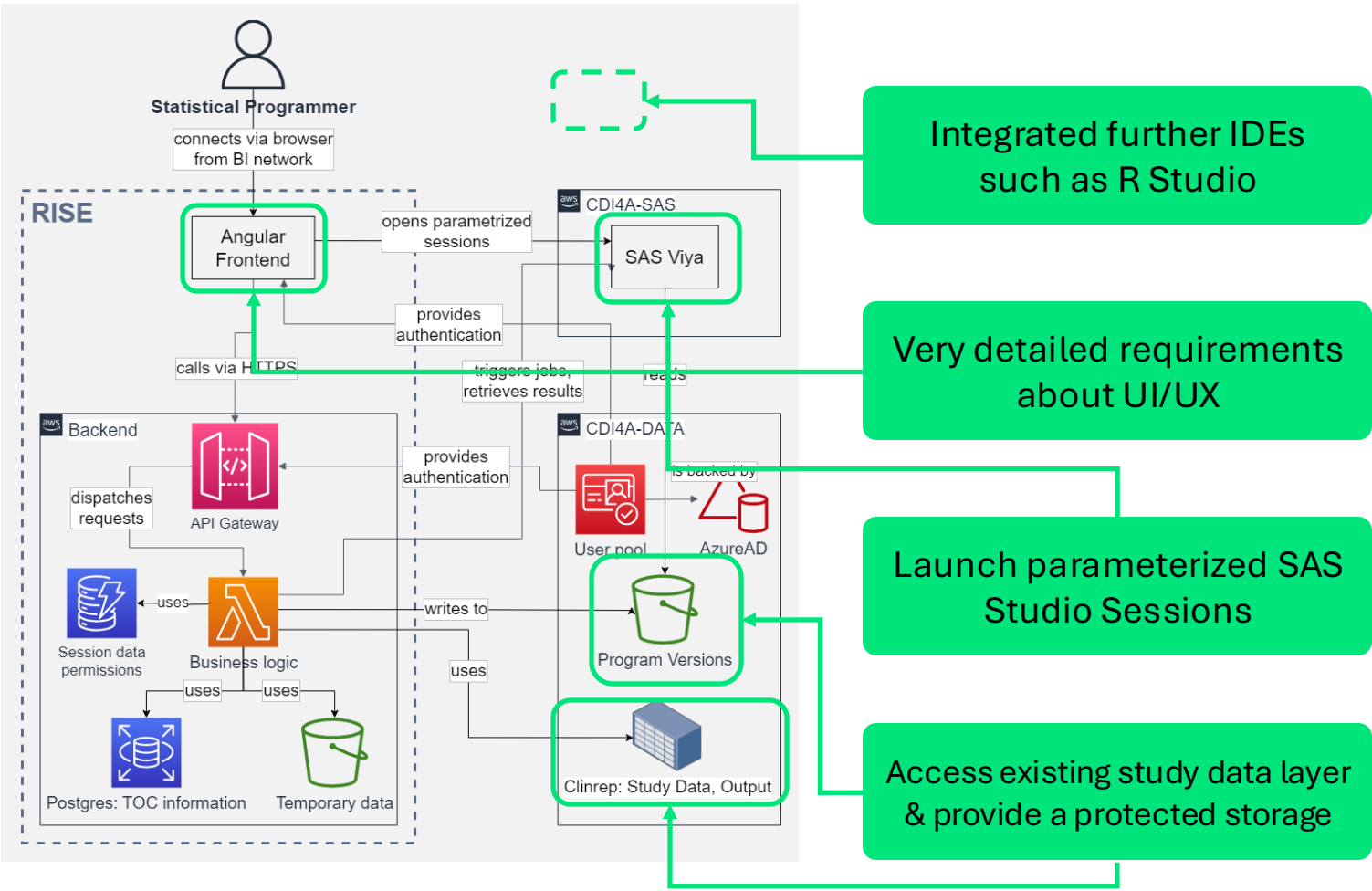
Backend running on AWS,
business logic in Lambdas

Application Development



HMS
analytical software

RISE User Requirements

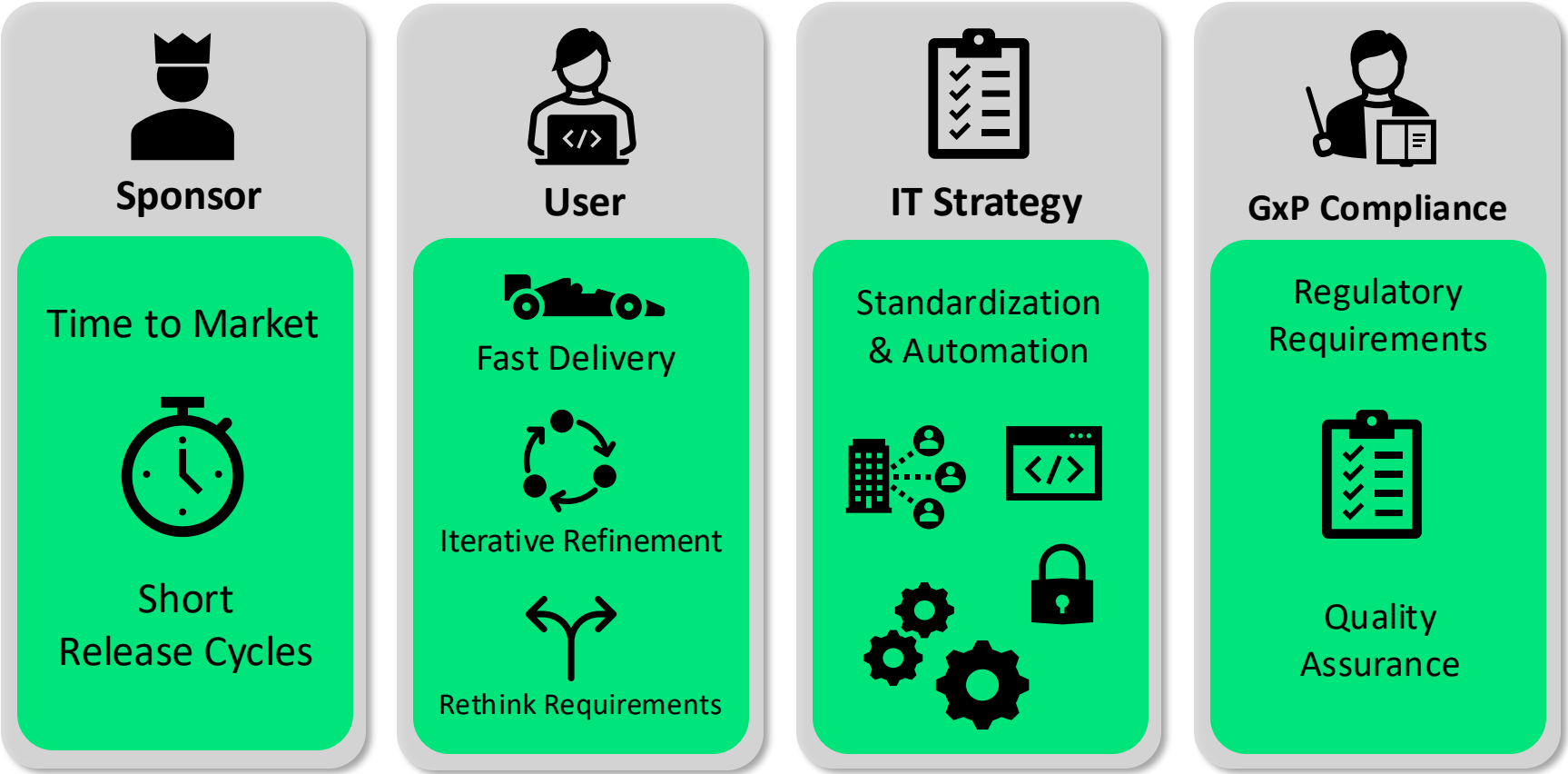


Application Development



HMS
analytical software

A **global standard** for building, deploying, testing, documenting, releasing and running applications.

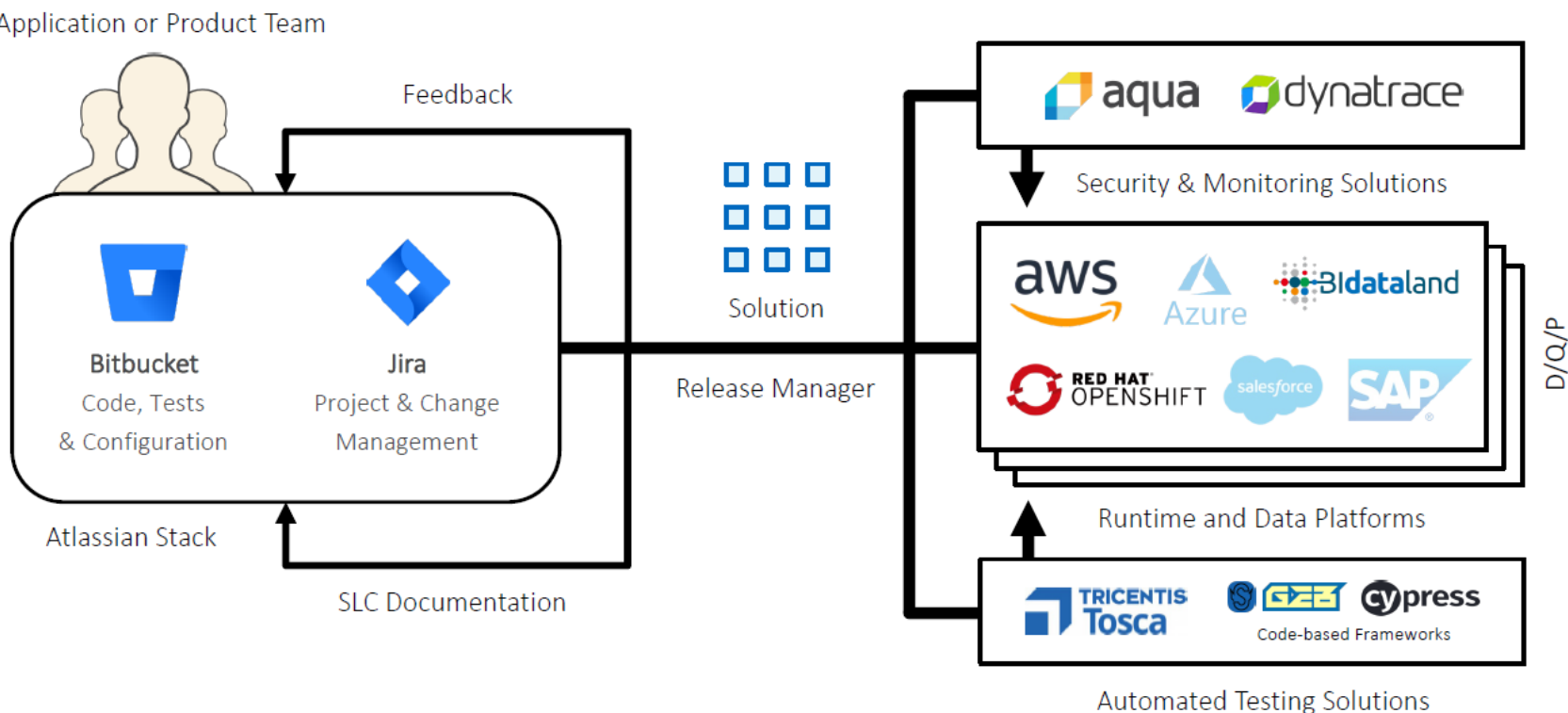


Application Development



HMS
analytical software

Aiming for Continuous Validation OpenDevStack Framework

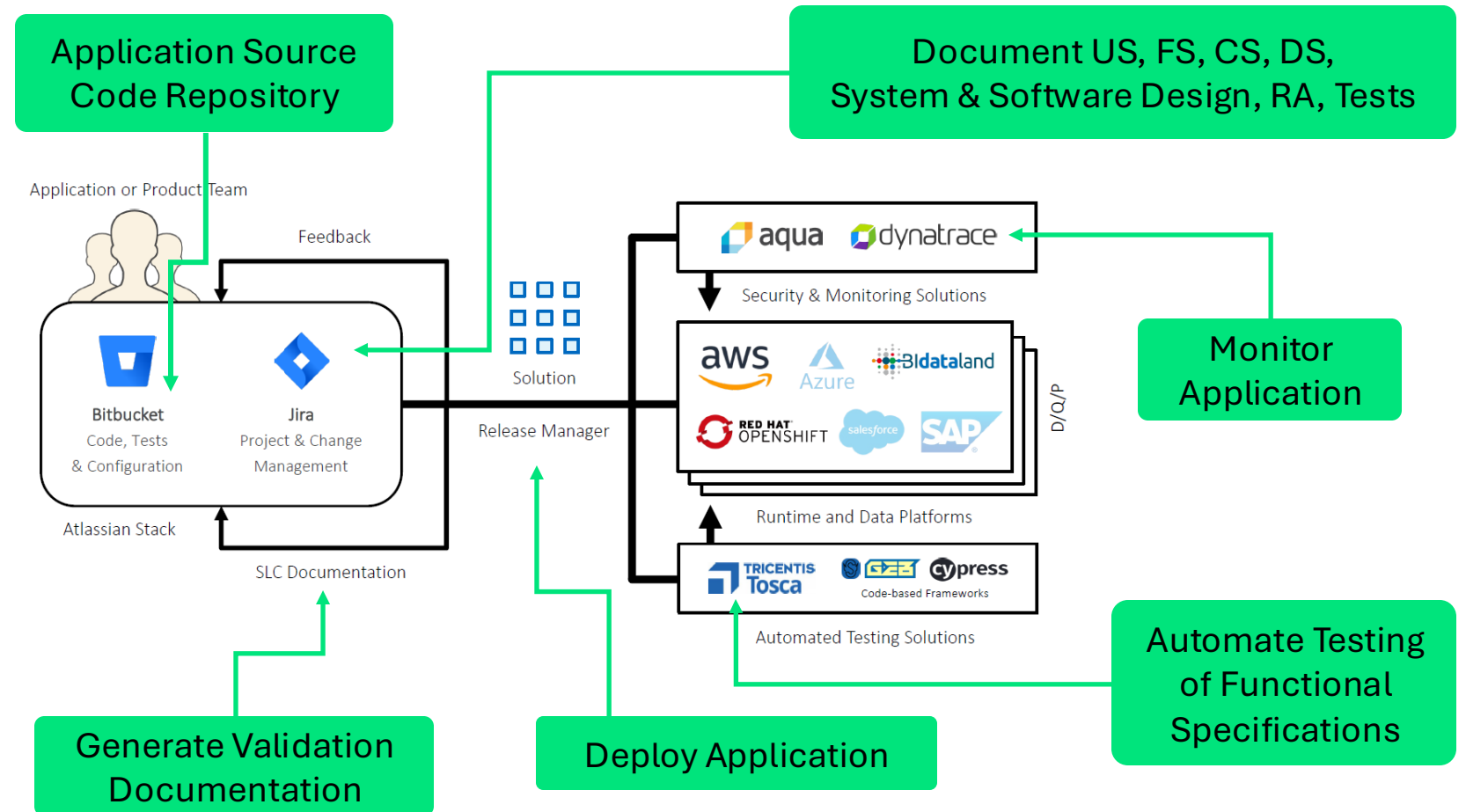


Application Development



HMS
analytical software

Aiming for Continuous Validation OpenDevStack Framework



Current development status and planned releases

RISE version 1



- Create TOC (manually & XLSX)
- Develop & execute programs interactive & batch (SAS)
- File validation
- PDF creation

RISE version 2



- R integration batch
- R integration interactive

RISE version ≥ 2



- Batch job scheduling
- Interactive dashboard
- Notification centre
- Upgrades based on user feedback

Conclusion



Modern challenges require state-of-the-art, adaptable, scalable solutions. However, developing a custom Statistical Computing Environment was a **challenge** not only for technological reasons...

Many stakeholders, expectations and requirements...

- Complete new TechStack and quite new enterprise framework for development of Cloud applications
 - Time-consuming SAS Viya installation and set-up
- Very detailed user requirements that are hard to satisfy with version 1.0
 - Considering: High level of user satisfaction with predecessor application (running since 1997)
- New approach regarding Computerized System Validation
 - Author Validation documentation right from the beginning
 - Automated testing of functional specifications
- Project management: Find the right balance between waterfall and agile approach
 - Many iterations and updates needed for system specifications, implementation and testing

Thank you for your attention!

Please don't hesitate to get in touch with us at PhuseConnect or send mail to:

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