R "Validation" Hub Meeting

18 June 2019

Attendees:

Andy Nicholls (GSK) – Meeting Chair
Lyn Taylor (Phastar) – Meeting Secretary

Anna Krystalli (University of Sheffield)
Bella Feng (Amgen)
Bob Engle (Biogen)
Chris Toffis (Syne qua non) – PSI AIMS SIG
Eli Miller (Covance)
Eric Milliman (Biogen)
Eric Nantz (Eli Lilly)
John Sims (Pfizer)
Joseph Rickert (R-Studio)
Juliane Manitz (Merck Serono)
Matt Fidler
Min Lee (Amgen) - TransCelerate
Nate Mockler (Biogen)
Parker Simms (No affiliation) - Website design
Patric Stracke (Sanofi)
Prabhakar Burma (Acerta Pharma)
Raj Malathker (J&J)
Rebecca Krouse (RHO Inc.)
Rinki Jajoo (Merck)
Rose Hart (Bresmed)
Satish Murthy (J&J)
Tomas Drgon (FDA)
Xiao Ni (Novartis)
Yilong Zhang (Merck)

Agenda

- Review of actions – (15 minutes)
- Validation Workshop at the R in Pharma Conference – proposed plan and topics (Andy, 15 minutes)
- Defining Validation – feedback / discussion from the Executive Committee KO meeting (Andy, 25 minutes)
- AOB – Someone to take notes next month? (5 mins)

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Previous Action Items

Action Item	Assigned team member(s)	Deadline	Status
Communication, dissemination of information about the project to the wider group Possible Funding discussion if we need to write a package to pull metrics Will re-assess for the next Autumn application	Andy Nicholls/ Lyn Taylor/ Joe Rickert	Sept 2019	Ongoing
Review of the website content: Direct review back to Andy, via GitHub or message via slack as you prefer. - Update from Parker: Validation overview page, a page for "what R is" and how it relates to validation, and a new page for federal regulation (FDA.gov) were created/updated. - Andy -requested that Parker push it to be live and invited the team to use Trello to give any feedback back to Parker. - Possible future action to get the R consortium website to point to our minutes on our website.	Kieran Martin, Min Lee, Juliane Manitz, John Simms, Keaven Andersen, Alex lock-Achileos	R in Pharma Conference Aug 21st.	Ongoing
Risk assessment workstream – Continue work on objectives – set date for package structure to be agreed. - Team are still Working on package structure and once laid out can use dplyr as an example to push through the risk assessment. Min Lee asked what's the status of it and could it be reviewed by the team? Andy asked if they can aim to have something in place for R in pharma conference so they can use the package as an example and get feed back on it. The team don't have a long term plan set yet for when package to be complete but this can be discussed at the next meeting.	**Yilong Zhang,** Rebecca Krouse, Doug Kelkhoff, Matthias Trampisch, Eric Nantz	R in Pharma Conference Aug 21st.	Ongoing
Requirements/tests workstream set objectives + milestones - **ACTION:** Tilo to Plan to present on package qualification at the next session. - Most discussion to date was on how to structure Unit tests. They looked at ValidR (mango) and what does a unit test has to cover. Questions such as do we count tidyverse as already validated came up as well as how do we use unit tests for new packages? Tilo has done a lot of package qualification work, but it comes down to checking the functions that the package does and to what	**Keaven Anderson**, Nate Mockler, **Tilo Blenk.**	July 2019	Ongoing

level we test and how do we validate that and deal with new versions. The group are still in a fact finding phase and still need to set long term objectives and milestones.			
Validation white paper workstream – appoint spokesperson and set objectives + milestones - Target to produce white paper by R in pharma conference. - Andy will prioritize it to be ready for R in pharma conference.	Andy Nicholls, Paulo Bargo	May 2019	Ongoing
Write text for the overview website page and request review by website review team - Parker has updated the overview page and it's ready to go live so this can be closed	Min Lee (and then Kieran Martin, Juliane Manitz, John Simms, Kieven Andersen, Alex lock-Achileos to review)	May 2019	Closed
Write blog post on gathering metrics and using these in a risk assessment - Doug – to confirm if he's OK to do this still.	Doug Kelkhoff	TBC	Open
Investigate how to educate people in the structure of R packages. Yilong suggested including on the website an overview of the structure – so if someone has high level questions we can direct them to the information. Andy added this could be in the form of a FAQ page. - Add to website To DO's on Trello and remove from actions here.	TBC	May 2019	closed

Discussion

Tilo will present on package qualification in July.

Joe Rickert will be presenting at the UseR pharma conference, and will put together a couple of slides to advertise/ make awareness of our group. Joe to send Andy the slides. If anyone else wants to review, then they should email Joe & Andy.

Validation Workshop at the R in Pharma Conference

Andy has been invited to run a validation workshop at the R in pharma conference in July and it will be a 4 hour workshop.

Last year it was just an hour, this time with 4 hours Andy is putting together something more interactive. Current plan is shown below.

Workshop Lead: Andy Nicholls
Workshop Support: Sean Lopp
Advisor: Phil Bowsher

4 Hour Workshop

Abstract:

TODO

Course Outline:

Introductions (5 minutes)

Packages 101: (30 minutes)
- What is a package?
  - Source
  - Installation
  - Packages are inter-dependent
- What is a repository?
- What is a library?
- Exercise: Something based on devtools

This sheet shows how to work with the 7 most common parts of an R package:

```
⊖ Package
  ▪ DESCRIPTION        Setup
  ▫ R/                 Write code
  ▫ tests/             Test
  ▫ man/               Document
  ▫ vignettes/         Teach
  ▫ data/              Add data
  ▪ NAMESPACE          Organize
```

The contents of a package can be stored on disk as a:
- **source** - a directory with sub-directories (as above)
- **bundle** - a single compressed file (.tar.gz)
- **binary** - a single compressed file optimized for a specific OS

Or installed into an R library (loaded into memory during an R session) or archived online in a repository. Use the functions below to move between these states.
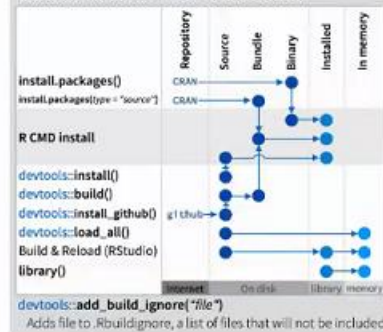
Step 1: Reproducing Your Environment (90 minutes + break)
- Fast Overview of Strategies
  Example / Demos of these exercises:
  https://resources.rstudio.com/webinars/time-travel-r
  https://github.com/rstudio/webinars/blob/master/70-time-travel-with-r/Time%20Travel%20with%20R.pdf

- Exercise: Identify your organization on the strategy map
- Exercise: Shared Baseline with Frozen Repository
- Exercise: Using renv + Git on a project
- Exercise / Demo: Using validated repo + Docker

Now that we know how to recreate an environment, how can we "trust" what is in the environment?

Step 2: Trusting Your Environment (~100 minutes)
- What will the environment be used for?
  - Regulatory submissions?
  - Package development?
  - Exploratory work?
- What packages do we need?
- Overview of Validation Hub and Philosophy
- Exercise: walk through a checklist of package metrics for your favorite package
- Walk through a checklist for a package as a group. Debate & Discussion
- Handling checklist 'failures'

Step 3: Qualifying an Environment
- Unit testing
- Test frameworks
- Executing tests

Environment Requests:

Hi Team, Please outline here the packages and infrastructure needed for this workshop. Please then send an email to Cole and Jason (both at Rstudio.com) with those requirements.

For the Step 3: Andy will go to Nate's testing stream to include the work of that stream.

The following feedback was obtained during the meeting.

Joe suggested that the order be changed so that it goes packages 101, then step 2 (trusting the environment) and then step 1. This would talk about the problem first before discussing potential solutions. Min agreed.

Feedback from Phil Bowsher and Shaun is that people don't realize the basics of packages and knows the full ins and outs of how they fit together. So they agree that it is worth starting with the basics of the "Packages 101".

Tom Drgon suggested to also include a terminology section including GXP, GLP, 21CRFpart11, qualification, validation etc. Also, it would be nice to package a suite of documentation which demonstrates an example framework of what you need to do to use R in regulatory environment and have evidence of the qualification / validation.

Andy informed the group that he has been contacted by Mango Solutions as they would like to get involved with the R in Pharma workshop. Potentially they could be involved with "Step 3: Qualifying an environment". However, the charter for R in pharma conference is to maintain a non-commercial field. Hence having Mango come in to help with the workshop may present a conflict of interest, if it was a vendor promoting their product. However, Mango do have a wealth of knowledge in the area which we could utilize.

Joe Rickert informed the group that they don't restrict vendors coming, but they should talk about the problem, solution and share information and not use the forum to tell their product. Raj Malathker agreed that it would be useful to have their expertise.

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Min Lee asked if they'd been invited or are they want to come because of the workshop to promote their product? Given there is no conference fee, then the R in pharma committee invites the attendees to correspond with their charter, so it's not open for vendors to attend as they may wish to.

Lyn Taylor informed the group that at the start of the AIMS R Validation project, the AIMS SIG did invite Mango to present to them about ValidR to help the team learn more about validation of R. Following this presentation the group decided to avoid any potential conflict of interests by proceeding with the project independently from any commercial interest.

The group agreed that Andy should find out what Mango wanted to do, and what they thought they would contribute and then we can make a decision as to whether their knowledge is of value to us and can we utilize this resource without having any conflict of interest.

A potential solution is to consider Mango doing a separate workshop at Harvard but that this may be better outside of the R in Pharma conference since it's only got 150 seats for the conference and the demand for attendees far exceeds availability.

Defining Validation

Andy gave feedback from the executive committees discussions and work on the proposed framework for validation: (https://docs.google.com/presentation/d/16vTnEVmoCOkkD-jsz5sFDN9H9Tz3G_Jx3Hw6d_sshS8/edit?ts=5d091a1d)

Request for all to review and continue discussion on Slack. The plan is to have an agreed understanding of the key definitions, since the language can have different meanings for different people in stats vs software backgrounds.

Regarding a "Trusted source" – this refers to the way the authors create their software and if we feel it to be a thorough development and validation framework then we can consider them a trusted source. It was questioned why we trust SAS and it was widely considered acceptable that we can also trust R Studio / tidyverse and the R Foundation (recommended & base packages) due to the same logic. Users should assess the confidence in the package and based on that, decide if we need to write requirements or tests to validate the package. These tests may fall into a final qualification test.

Doug has previously asked why don't we create a risk assessment anyway even for the trusted packages. However, Andy would argue that for most of the R packages Andy uses, he trusts them because he's used them substantially in the past and they've worked giving him the expected output. However, this is probably less easy to trust the stats packages as without replication in another software package it's hard to be confident the results are accurate.

Joe Rickert asked if the team imagined that over time, more sources would reach the requirement of a trusted source or would the need to define a trusted source be removed because the risk assessment would also be applied to the trusted sources like SAS?

Andy responded with; if you apply the risk assessment to an R package and establish that you are happy with what the author has done, even if the author updates that package, then it's likely that the high degree of trust carries through to the next version. Therefore, there may be no need to re-assess the

new version.   Maybe we do a risk assessment on the 1st few versions but eventually, it would be in the position that we've looked at this author so many times and never found a problem that we'd trust them going forward.   Other people may have different opinions about the risk though.

Min Lee responded, that to an auditor, it doesn't matter how much risk you associate with a package, it's what you document regarding the assessment and test/validation. If R is used, then the auditor will ask you for evidence and documentation to support/ justify your use. Raj Malathker agreed that reproducibility is key.

Joe Rickert commented that with R, you actually produce the source code, so it's fully transparent and open. There may be a formality about how to submit it for interrogation, but it's the ultimate proof of giving the right results because you can verify what's its doing.

Min Lee agreed, but added that we still need to show evidence of what the software is doing for the regulators to review. Therefore it's down to the author to document their testing well however there is wide variability of what is done for a package and that is perhaps where the idea of a "trusted" source comes in. If we trust the author and they provide evidence of testing, then this can be supplied to the auditors.

The team raised another discussion point about how does R work in an environment where parts of the framework change over time. Historically, in R it was hard to reproduce and R is not static and is constantly evolving. The accuracy of a package could change over time, as different packages are installed which can break something that previously worked. Hence it is critical for the team to ensure reproducibility.   We need to be able to conduct a submission in R using a particular version and if the work is reviewed at a later date, we need to be able to reproduce it.

Joe Rickert provided a solution for this, first set a standard for project by making R static in time for a project through the use of Docker which puts R into a container that can be retrieved at a later date. Then when you come back to the project, we can compare latest R versions to the version used at the time and ensure consistent or continue to use the previous versions which are documented. Team agreed that it should be part of the risk process to Dockerise what you are working on and it would be good to automate this.   Min commented that this would ensure traceability, such that when you have an output, you can trace it back to the source/ docker version used to create it. By us documenting the risk of the accuracy and ensure traceability and reproducibility then the evidence from a regulatory perspective is complete.

Andy added that this roadmap of how to use R in the regulatory environment is what the validation Hub wants to achieve.   The Risk assessment, testing and white paper all feed into this framework. We need to simplify the plans ahead and define milestones/goals.

Andy will give everyone read only access to the diagram and invite people to review and give feedback on SLACK. The exec committee will also meet and discuss the flow prior to the next meeting.

AOB: Lyn is not available for the next meeting so Min agreed to take notes.
[Post meeting note: Keaven will take notes given Min also has a potential conflict]

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Write blog post on gathering metrics and using these in a risk assessment Doug – to confirm if he's OK to do this still.	Doug Kelkhoff	TBC	Open
Review the framework through the following link and provide feedback in SLACK https://docs.google.com/presentation/d/16vTnEVmoCOkkD-jsz5sFDN9H9Tz3G_Jx3Hw6d_sshS8/edit?ts=5d091a1d)	All	15th July	Open