Standardized, high-quality output for clinical studies in Diagnostics: the TLGcat

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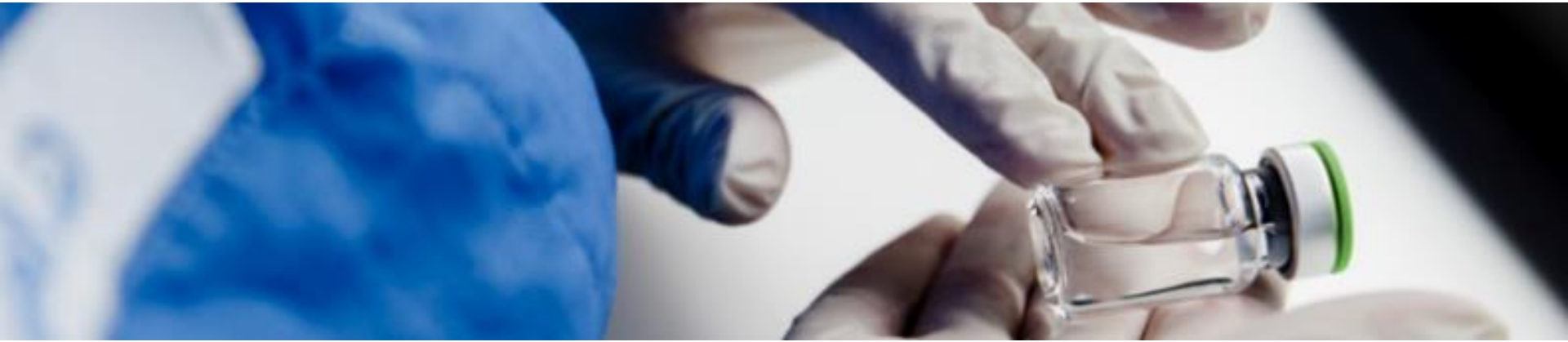
Diagnostics

The World Needs Better Ways To Prevent, Diagnose And Treat Diseases



2/3 of diseases

are either still not treated adequately or not treated at all

71%

of all deaths globally are caused by non-communicable diseases (NCDs), and therefore the medical need is urgent

1/2

of the world lacks access to essential health services

only 4%

of patients are in clinical trials; we are missing valuable insights and data from 96%

The Value Of Diagnostics

Diagnostics can play a leading role in the fight against disease and in meeting increasingly complex healthcare challenges.

Diagnostics account for

~ 70%

of clinical decision making.

Causing only about

~ 2%

of total healthcare spending.

Registrational studies in Diagnostics

- Device + assay + patient sample = result
- Need to demonstrate safety and efficacy like for a drug
- Perform analytical and clinical performance studies
  > Vast heterogeneity: hundreds of analytes, different technologies, different specimen, …
- Analytical performance: e.g. demonstrate
  - Linearity
  - Precision
  - Limit of Blank / Detection / Quantitation
- Clinical performance:
  - Define intended use of assay
  - Demonstrate it in target population, usually vs. a predicate device
  - Example for an intended use of Elecsys® HCV (Hepatitis C) Duo assay:

"Elecsys® HCV Duo is an immunoassay for the in vitro qualitative detection of hepatitis C virus (HCV) core antigen (HCV Ag) and antibodies to HCV (anti-HCV) in human serum and plasma. The test, in conjunction with other laboratory results and clinical information, may be used to aid in the diagnosis of and the screening for HCV …"

HMS analytical software

Roche

The TLGcat

Scope

Unmet need

Despite the similarity of analysis types and their reporting, there is a **lack of standardization for clinical performance studies**, causing time-consuming analyses and validation procedures. For analytical performance studies, a variety of tools is already available at Roche Diagnostics.

Vision

Fast and **high-quality** reporting of clinical study results, embedded in a highly **efficient submission** process, accelerating time-to-market and hence patients' access to our products.

Mission

Develop a standardized Tables, Listings & Graphics catalog: the ***TLGcat***

Reconcile it with Clinical Operations and Regulatory Affairs, and

Automate report generation.

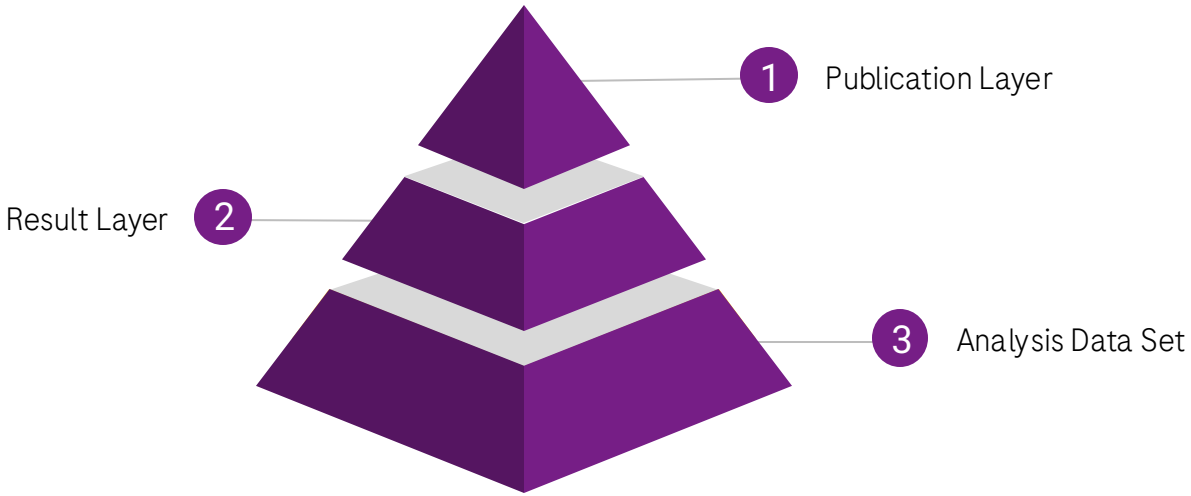
Introduction

3-layer structure

Publication Layer represents the output, i.e. the TLG, as aligned with stakeholders from our disease areas

Result Layer holds every result variable that is needed to fill the Publication Layer's TLG

ADS (analysis datasets) are transformed raw data and follow the specification of a certain TLGcat function



TLG: Tables, Listings & Graphics; TLGcat: TLG catalog

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What does success look like?

What does success look like?

The TLGcat:

- covers the most common analyses for several disease and customer areas, and is
- aligned with Clinical Operations and Regulatory Affairs.

Minimum viable product:

- Reproducibility ✔
- Reference Ranges ✔
- Qualitative Method Comparison (✔)
- Quantitative Method Comparison ⏸
- Demographics ⏸

A style guide, i.e. common requirements for fonts, margins, headers etc., ensures a similar look & feel.

TLG shells

Example: Reproducibility

Table X: Summary table of reproducibility using *REML/ANOVA*, *including/excluding* outliers.

Sample	Mean	N	*N (outliers removed)*	Repeatability SD	Repeatability CV [%]	Between-Run SD	Between-Run CV [%]	Between-Day SD	Between-Day CV [%]	*Within-Site Within-Lot SD*	*Within-Site Within-Lot CV [%]*
Sample 01	5.0	267	3	0.10	1.84	0.05	1.03	...			
Sample 02	59.0	268	2	0.89	2.05	0.64	...				
Sample 03	5.0	265	5	0.08	2.67	...					
...	62.0	270	0	0.84	...						

*negative variance estimates were set to 0.

Table X: Variances table for reproducibility using *REML/ANOVA, including/excluding* outliers.

Sample	Mean	N	*N (outliers removed)*	DF	SD Estimate	SD 95% LCL	SD 95% UCL	CV Estimate	CV 95% LCL	CV 95% UCL	Claim Fullfilled yes/no
Sample 01	5.0	267	3	8.95	0.11	0.11	0.25	...			TRUE
Sample 02	59.0	268	2	7.45	2.58	1.70	...				TRUE
Sample 03	5.0	265	5	11.10	0.20	...					TRUE
...	62.0	270	0	12.93	...						TRUE

*negative variance estimates were set to 0.

TLG shells

Example: reference ranges

Table X: Quantile estimation for *<assay> [<units>]* with *<90/95%>* confidence interval using *<method, e.g. non-parametric, symmetric>*

grpvar1 (disease grp)	*grpvar2 (sex)*	*grpvar3 (agegrp)*	N	Quantile	Estimate	LCL	UCL
A	female	young	150	*Minimum*		n.a.	n.a.
A	female	young	150	*0.5%*			
A	female	young	150	*1%*			
A	female	young	150	*2.5%*			
A	female	young	150	*5%*	52.1	*	*
A	female	young	150	*10%*	56.7	40.2	12.6
A	female	young	150	*25%*			
A	female	young	150	*Median*	70.5	48	14.3
A	female	young	150	*75%*			
A	female	young	150	*90%*	54.8	64.4	17.2
A	female	young	150	*95%*	57.2	*	*
A	female	young	150	*97.5%*			
A	female	young	150	*99%*			
A	female	young	150	*99.5%*			
A	female	young	150	*Maximum*			
A	female	old	905	*Minimum*			
A			905				

HMS analytical software

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So how to get there?

So how to get there?

Within Roche Clinical Biostatistics, we have:

- Expansive knowledge and experience with statistics and submissions
- Programming skills for tailored study analysis
- Numeric cores available, developed in house: e.g. mcr, VCA, VFP, refineR

How to get there?

Within Roche, we have:

- Expansive knowledge and experience with statistics and submissions
- Programming skills for tailored analysis
- Numeric cores available, developed in house: e.g. mcr, VCA, VFP, refineR

BUT: we are lacking professional software development skills, especially

- Coding:
  - Runs on very different data sets, for different indications
  - Easy to maintain
  - Easy to expand with new features
- Validation:
  - Collection of test cases
  - Automatized testing
- Documentation:
  - Fulfilling internal Roche Requirements and bullet proof for external audits

=> Joint venture with HMS

HMS Analytical Software

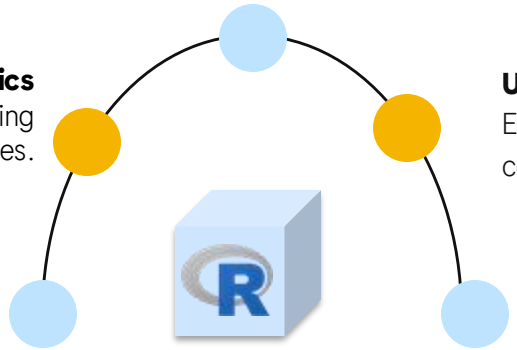
R Packages

What are they and why are they useful?

Comprehensive documentation
Includes detailed guides and manuals.

Advanced statistics
Capable of performing complex statistical analyses.

Unit tests
Ensures code reliability and correctness.



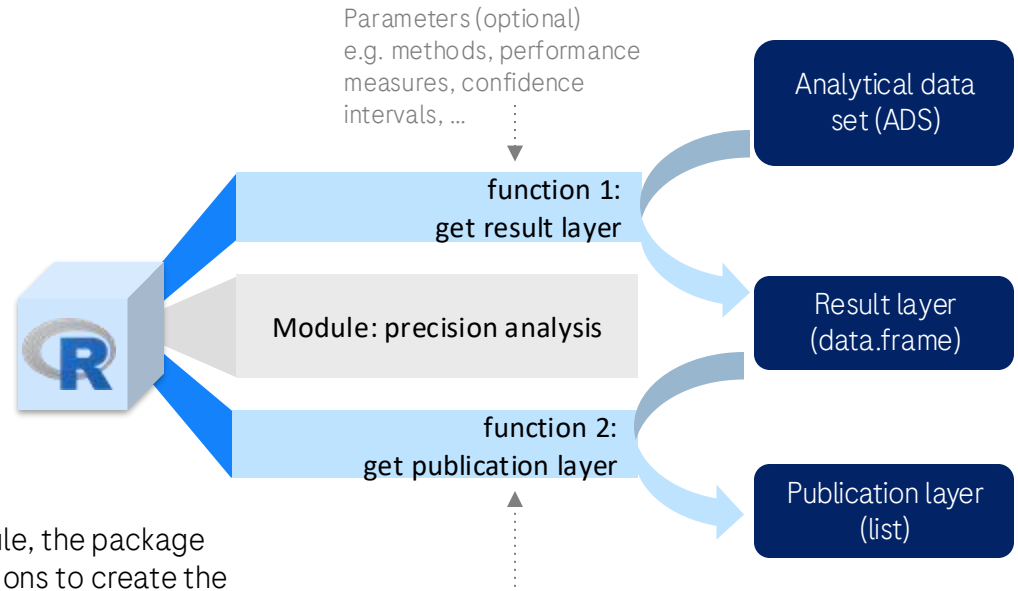
Collection of R functions
A set of reusable functions for various tasks.

Executable analysis templates
Ready-to-use templates for common analyses.

Advantages

- Self-contained format: Packages include all necessary components.
- Easy integration: Seamlessly fits into existing workflows.
- Rich ecosystem: Extensive tools and community packages for documentation and testing.
- Agile-friendly: Well suited for software engineering in agile environments.

The R package from a user's perspective



unit	assay	ci.method	symmetry.type	quantile
ng/ml	test	Non-parametric	symmetric	0.000
ng/ml	test	Non-parametric	symmetric	0.005
ng/ml	test	Non-parametric	symmetric	0.010
ng/ml	test	Non-parametric	symmetric	0.025

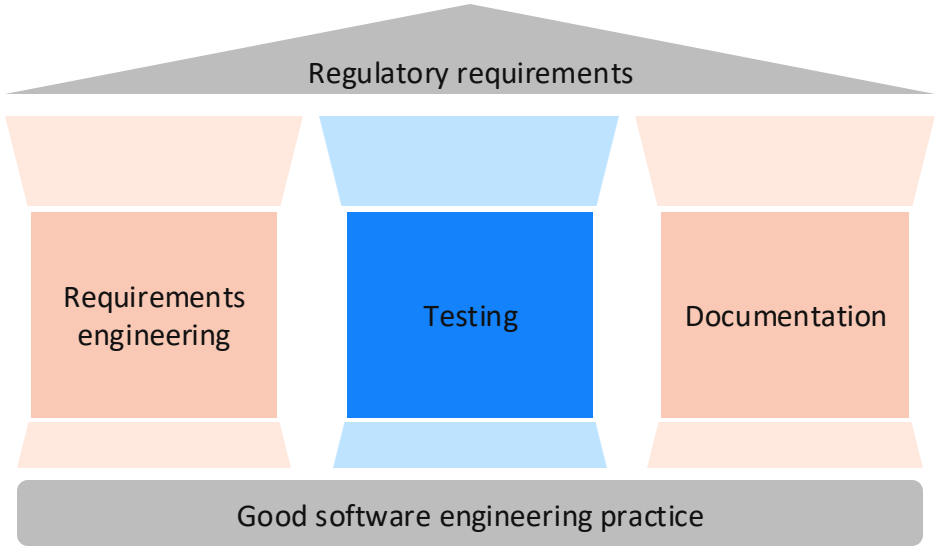
```
pub_layer$caption_string %>%
  print()
#> [1] "Quantile estimation for test [ng/ml] with 90% confidence interval using Non-parametric, sym
pub_layer$footnotes_string %>%
  cat()
#> LCL: Lower Confidence Limit; UCL: Upper Confidence Limit
#> n.a.: not available due to low sample size
pub_layer$table
```

grpvar1 (group)	grpvar2 (gr2)	grpvar3 (gr3)	N	Quantile
grp01	1	1	6	Minimum
grp01	1	1	6	0.5%
grp01	1	1	6	1%
grp01	1	1	6	2.5%
grp01	1	1	6	5%

- For each module, the package provides functions to create the result and publication layer based on the ADS
- Functions can be further parameterized or used with default values for standard use cases

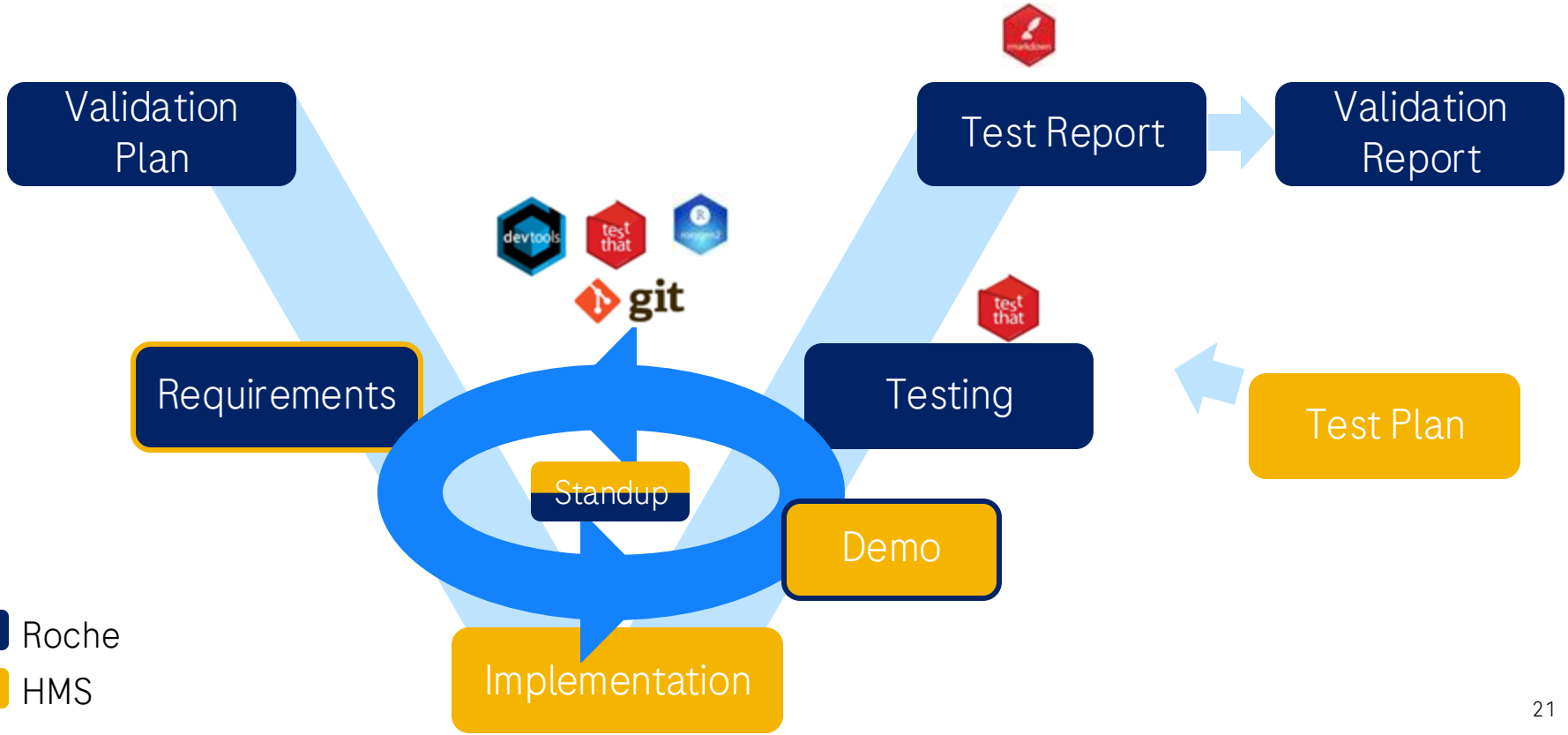
R package development in regulated industries

Many principles overlap with good software engineering practice



Agile V-Model

How we work together



V-Model: Requirements

- Highly collaborative and interactive
- Close alignment between HMS developers and Roche experts

Key success factor: people

Committed contacts who
- ✓ Had time blocked
- ✓ Were in close contact with both developers and internal experts

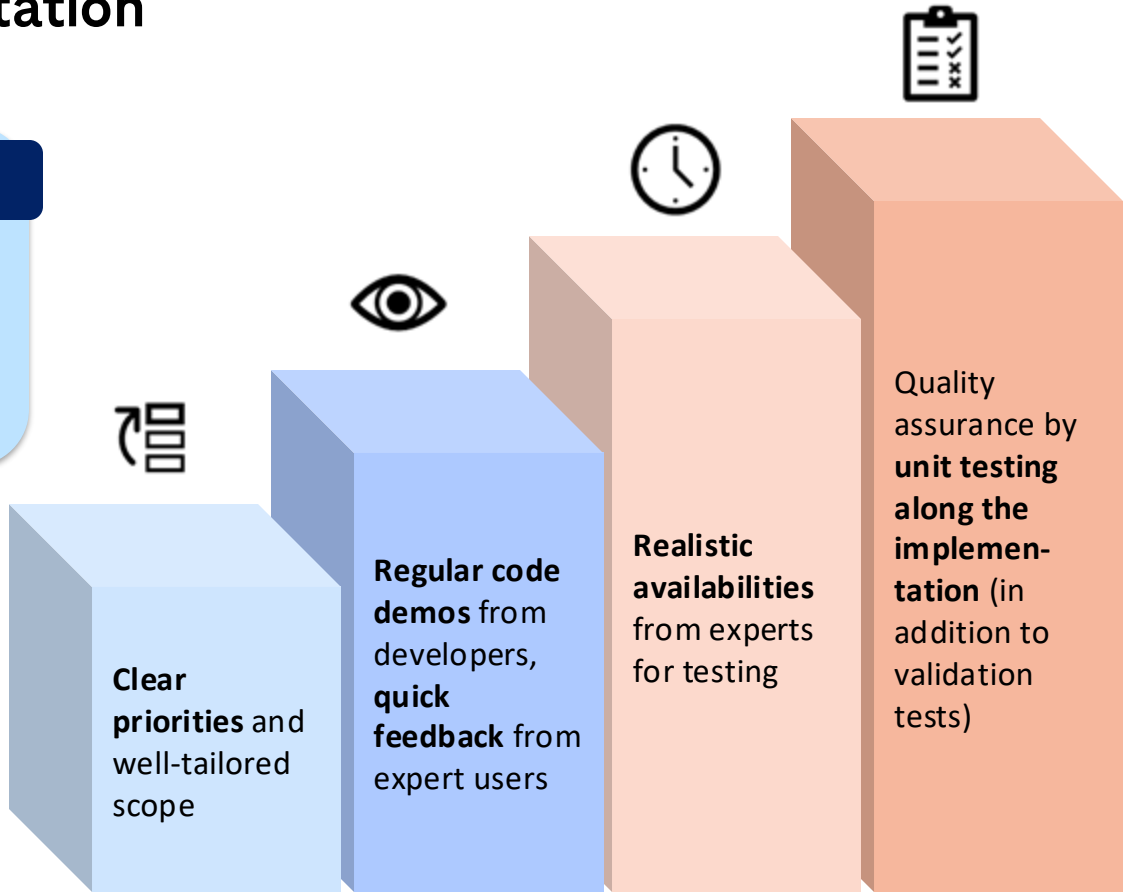
Key success factor: processes

- ✓ **Closely timed feedback** cycles regarding feasibility and implementation of requirements
- ✓ **Continuous alignment** with QM, participation in sprint-planning/ progress meetings

V-Model: Implementation

Success factor: Trust in people

- Developers are trusted to do their best work in the time available
- Expert users are trusted to be realistic in their expectations



V-Model: Testing

Success factor: Ways of working

- Close **collaboration with QM** to align contents and orchestration of documents
- **Clear scope** helps to limit validation efforts
- Availability of support regarding **test environments** and deployment **pipelines**

Success factor: Tools

- **Very good test data** that is representative of the actual study data
- **Automatic document rendering** within R
- Largely **automated tests** increase reproducibility (standard unit test frameworks, testthat)
- Roche-approved internal **package repository**

Conclusions - Roche Diagnostics perspective

Achievements:

- Faster programming, with all advantages following this saving:
  e.g. 1500 lines of code before compared to 50 now for a standard precision analysis
- Higher quality of the analysis results
- Reduced efforts for validation

=> Gain of efficiency

Next steps:

- collect experience from submissions to see if regulators' needs can be covered
- afterwards: we plan to make the TLGcat publicly available

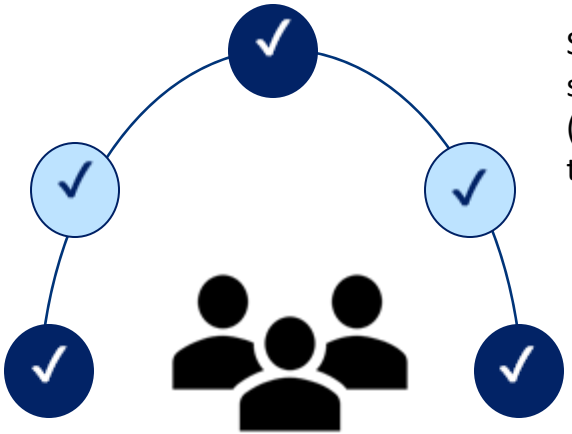
Overall, the collaboration of the clinical biostatistics team at Roche Diagnostics with the HMS team turned out to be very successful.

Conclusion - HMS Analytical Software perspective

Collaborative development like it's supposed to be

Agile framework with well-tailored processes

Working mode, close collaboration on requirements



Shared backlog to collect next steps in all directions (stakeholders, development team)

Clear division of roles, dedicated ownership per deliverable

Expert guidance regarding internal QM requirements

Find us at our booth for more insights!

Doing now what patients need next