



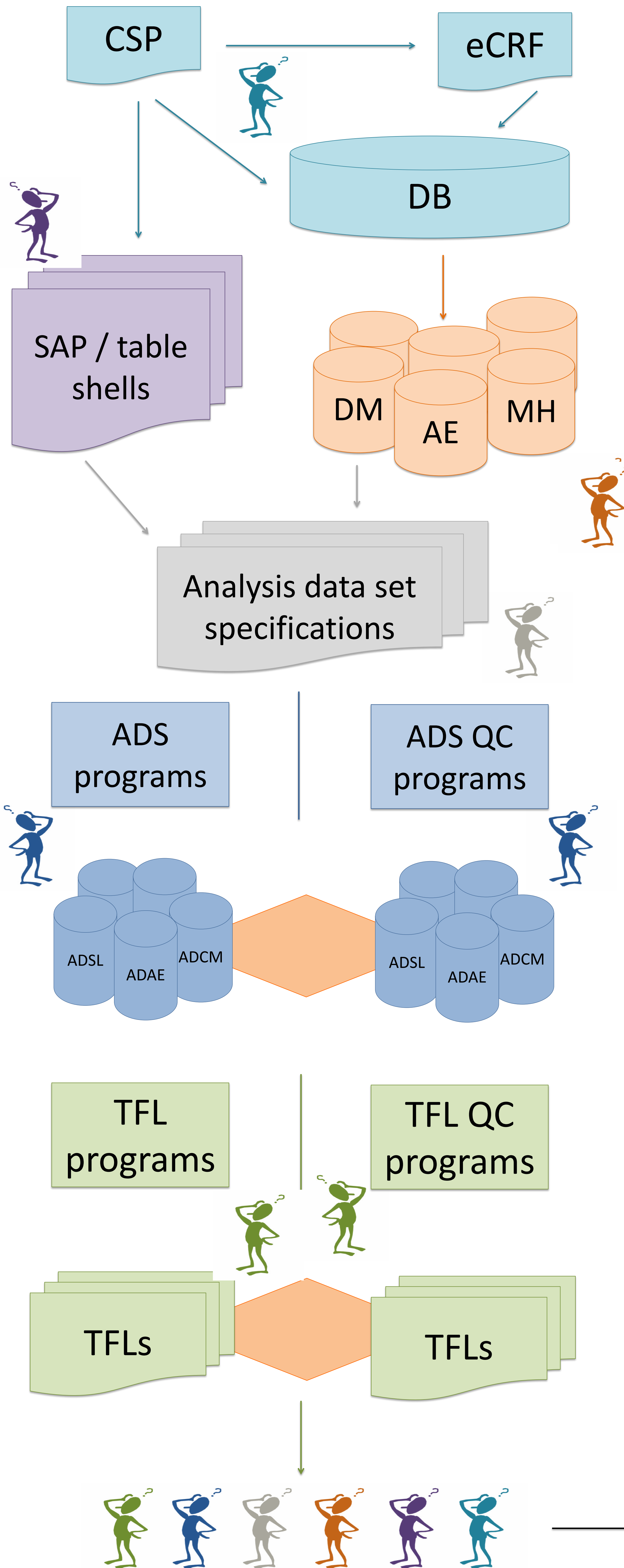
Background

In order to ensure reliability of clinical trial analysis results, validation effort has grown in the pharmaceutical industry over the past 20 years, specifically since 21CFR Part 11 was published by the FDA. Since then, validation methods evolved and became an integral piece of statistical programmers' and statisticians' daily job with the ultimate goal of reducing the risk for errors and increase quality.



Independent double programming has developed to be the gold standard for the validation of programs and outputs created around the analysis of clinical data. It is applied not only for the validation of analysis datasets but also for tables/listings/graphs by re-creating the respective reporting datasets. Alternative validation methods, like independent Source-Code/Log-File and Output Review are more and more pushed back even for low-risk objects.

The long way of data from collection to results



Challenges around data collection

- Translation of CSP to eCRF / protocol amendments
- Time pressure until DB-Live
- Align data validation rules with statistical analysis
- Training of site personnel / monitoring effort
- Patient-reported outcome data
- Unclean data / Missing data
- Time pressure between LPO and DB-Lock
- Number of people / different parties involved
- Cross-functional communication

→ Data integrity is key

Challenges around data conversion to CDISC SDTM

- Data manipulation to ensure SDTM compliance
- Changing source data structures due to eCRF changes
- Changing SDTM standards
- Timepoint of mapping / continuously changing data
- Handling of external data
- Level and status of validation

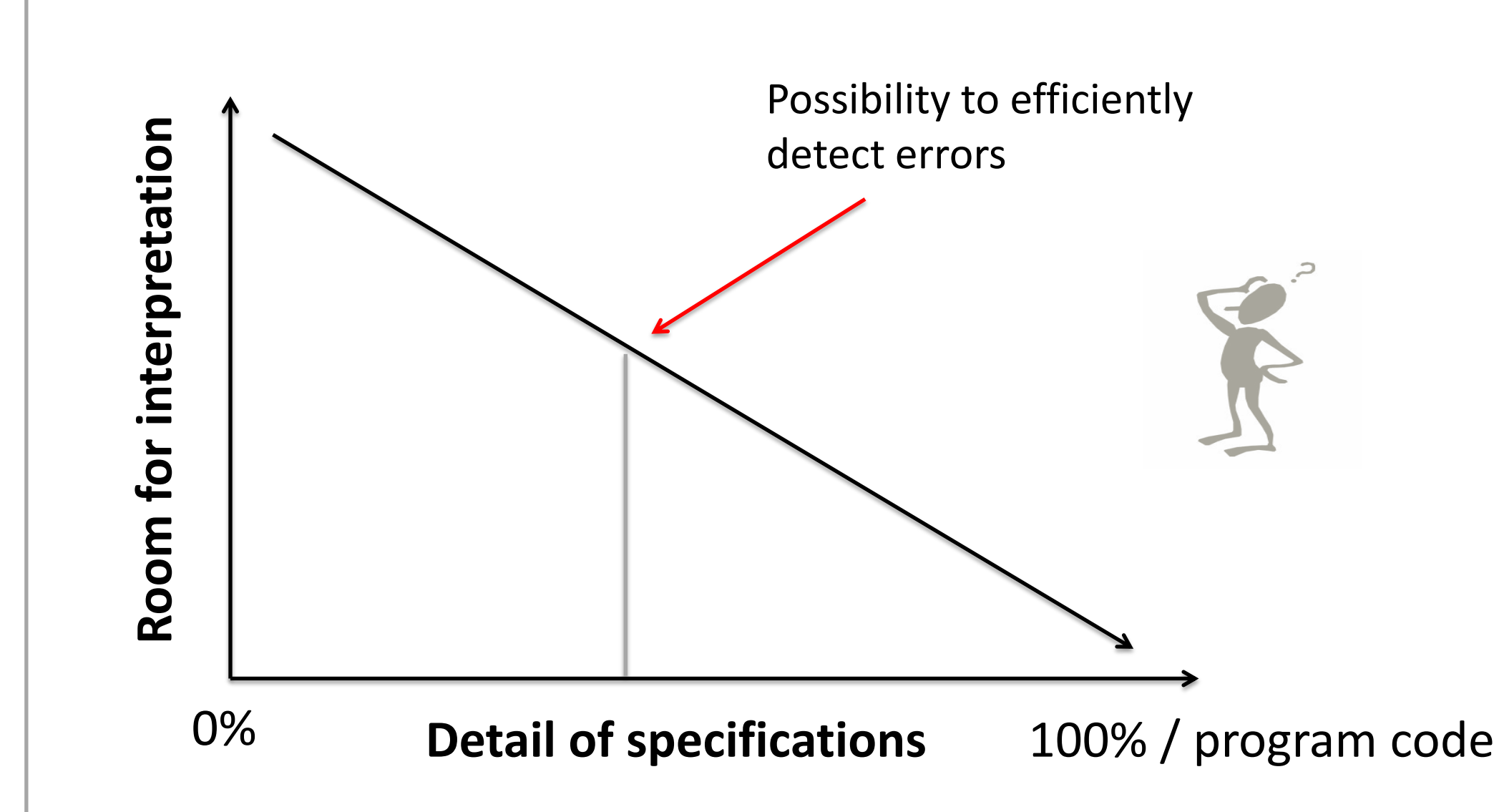
Challenges around analysis planning

- Contribution of stakeholders
- Changing requirements



Are we applying the same level of QC throughout the whole process?

The key role of analysis data set specifications



Doppeltes Nachdenken
geht vor
doppeltem Programmieren



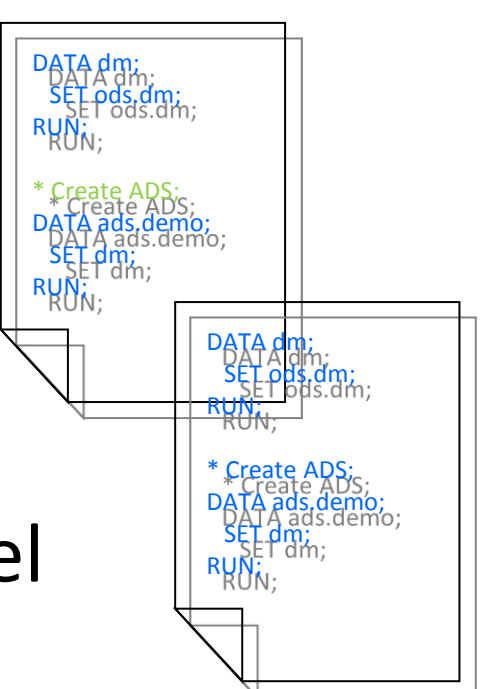
Limitations of independent double programming

- Specifications need to be challenged continuously
- Independency usually not physically implemented
- Data driven adaptations necessary in two sources
- Programming bias triggered by proc compare results
- Huge data volumes with variety of data
- Lack of knowledge exchange
- Experience of staff
- Additional effort / costs



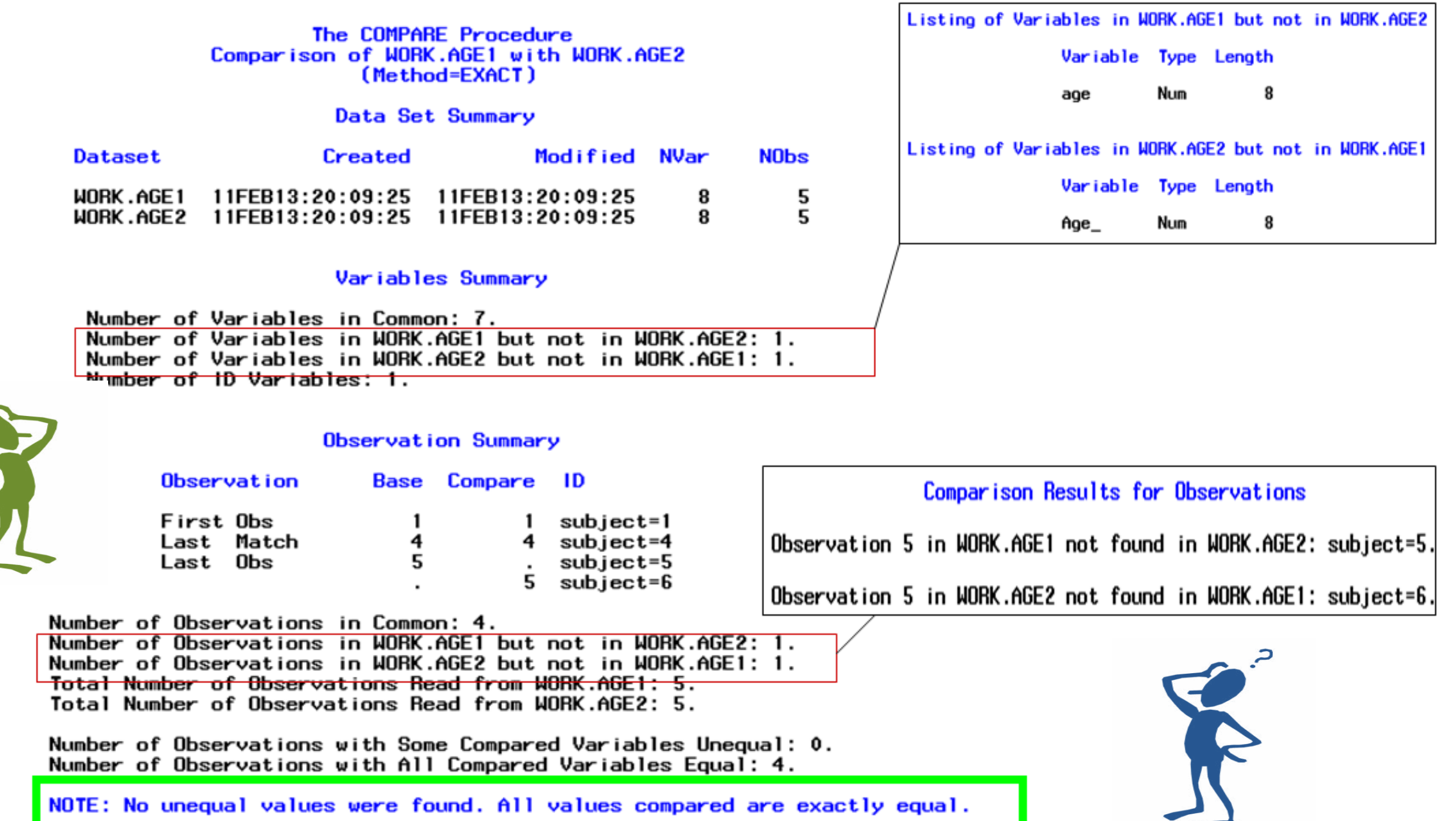
Why independent double programming?

- Unbiased QC
- Proven evidence „all values are exactly equal“
- Validation can easily be repeated
- 1st and 2nd line programming can be done in parallel
- At least one programmer can be less experienced



Quality is more than Equality

PROC COMPARE is a powerful procedure, but



“We recommend that you base your approach on a justified and documented risk assessment and a determination of the potential of the system to affect product quality and safety, and record integrity. For instance, validation would not be important for a word processor used only to generate SOPs.”
FDA Guidance for Industry Part 11, Electronic Records; Electronic Signatures — Scope and Application, August, 2003



Cross-functional teamwork and communication from clinical study protocol to final statistical results and clinical study report are key to overall quality

„All values are exactly equal“ suggests correctness but
double programming neither eliminates human errors nor issues in the data

Conclusion

Independent double programming can be a powerful validation method. The overall quality achieved very much depends on how it is implemented as well as on the quality measures applied throughout the whole data flow. Despite the effort involved it does not necessarily prove 100% correctness. Experience of staff cannot be replaced by any other means. In order to make best use of limited resources, alternative or hybrid validation models should be considered depending on the risk involved.



References

FDA Guidance Documents:
<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm125125.pdf>

Recommended Reading

Risk Based Approach Applied to the Validation of Report Objects, Christoph Ziegler, Roche, PhUSE SDE Frankfurt 2009, <http://www.phuse.eu/download.aspx?type=cms&docID=797>