

Software validation in clinical trials: strategy, implementation and experiences in the MAKs project

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ABSTRACT

MAKS ("Makros zur Auswertung Klinischer Studien") is a CDISC SDTM based library of validated SAS® macros for reporting data from clinical studies. User requirements were agreed upon by a task force constituted specifically for the project. Finally, 44 main macros and 93 subroutines (utility macros) were programmed and validated. The project was funded by the TMF e.V. (Telematikplattform für Medizinische Forschungsnetze).

The macros were developed and validated according to the V model. Recurrent programming tasks were stored in subroutines leading to a hierarchical structure.

High level design specifications were set up for the main macros. Detailed program action plans laying out the sequence of substeps were set up.

The validation strategy and its details were documented in a validation plan.

Validation tasks were defined for each macro according to a risk assessment. Actual results of the validation were documented in a validation report.

INTRODUCTION

SAS® macros developed in the scope of MAKs are based on data structured according to the CDISC SDTM model. With MAKs, standard reporting of clinical studies can be performed by simple macro calls.

The focus of this paper is the validation of the MAKs library comprising the validation strategy and its operational implementation.

METHODS

Validation was performed according to the V model of software validation. At the very beginning of the project, user requirements were defined by a project group "SAS macros" of the TMF e.V. For each main macro a high level design specification was set up which comprised at least one table shell and the program action plans (PAPs), which defines the sequence of tasks to be processed within a macro. Requirements for less complex subroutines were restricted to defining their purpose.

A validation plan was developed in which validation tasks were defined for every single macro. These were selected from the following list of actions:

- A Accordance check of input file and paper output for a random sample
- B Biostatistician's review or reproduction of results by a biostatistician
- C Code review (19 standard checks) with respect to the programming guideline
- L Log-file review (ten standard checks)
- O Output review (eight standard checks): Comparison of output with corresponding table shell and consistency check across different outputs
- P PAP check. Macro code must follow sequence specified in the PAP.
- R Reproduction by a 2nd programmer for at least one example
- T Testing of macros according to a pre-specified formal test plan

All subroutines went through activities C and L. For more complex programs R and/or T were applied. Macros that generate p-values or confidence intervals were reviewed by a statistician. Main macros were also validated by means of activities O and P and for listings additionally activity A was performed. A bottom up approach was used: First, all

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subroutines which do not call other subroutines ("level 0" programs) were validated. "Level 1" programs, which only call level 0 programs were validated next, etc. So far, level 7 is the highest level that has been achieved for subroutines.

A standard operating procedure "Validation of SAS programs" served as a further guidance during validation. All results of the validation activities were documented in the validation report. The validation report itself is an EXCEL® sheet which comprises columns for the different validation checks. Each validation run is documented in a single row with a corresponding sequence number. If the validation involved test runs then the specifications and results of the test runs were documented on a separate sheet. If a program or test run failed the validation process then it had to be corrected and the next validation or test run was performed and the corresponding result was documented in a new row in the EXCEL® sheet. This process was repeated for each program until it passed the validation process.

CONCLUSION

Validation of the MAKs library was performed by use of a validation plan developed before the validation started. For every main macro and every subroutine adequate validation tasks were chosen out of a list of possible validation tasks. Some actions were supported by checklists. Further guidance was given to the validation staff by a standard operating procedure "Validation of SAS programs" and a programming guideline. The poster will provide information about experiences gained during the validation.

REFERENCES

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