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# Implementing JumpStart at Novo Nordisk A/S

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## ABSTRACT

The Clinical trial analysis package from FDA: JumpStart now mentioned as Scripts contributed by FDA are available through PhUSE GitHub repository. These scripts are developed by FDA for clinical trial data analyses early in the review process. This paper describes how Novo Nordisk A/S (NN) has implemented the use of these scripts.

Novo Nordisk A/S has decided to use the scripts contributed by FDA for:

High level validation
Summary of a study data for statisticians and medical experts
Supplement for risk based monitoring, data surveillance and medical writer
For regulatory affairs

The biggest advantage of having outputs from scripts contributed by FDA available is:

You see data as FDA see them.
You see issues/signals that you may have overlooked.

You must be familiar with your study data to maximize the benefit of the output hence end-users are project statisticians, medical experts and medical writers and others deeply involved in interpretation of study data and safety signals.

## INTRODUCTION

Scripts contributed by FDA are developed by FDA and consists of series of clinical trial analyses. The purpose in developing the scripts was to have an early data summary in the review process to assess data composition, quality, analyses options and tools for the analyses. The aim is to improve the reviewers understanding of data and provide an effective evaluation of submission data.

The scripts are developed in SAS® Software and results are outputted in MS-Excel. The scripts are documented in a white paper (see reference link).

The scripts are made available for all PhUSE-members on the PhUSE GitHub repository.
GitHub is a web-based version control repository and Internet hosting service (see reference link).

Novo Nordisk A/S joined the SDA - **SCRIPT DISCOVERY & ACQUISITION PROJECT TEAM** this year. The SDA project cooperates between FDA and PhUSE and is part of CSS (Computational Science Symposium) Working Group.

## LEARN SCRIPTS CONTRIBUTED BY FDA.

You simply learn what the scripts can provide by looking at the output. When running the scripts on a clinical study you get nine or more outputs in Excel:

- Graphic view of Adverse Events (Adverse Events Panel Relative Risk and Adverse Events Panel Odds Ratio)
- AE Severity
- Excluded AEs
- Demographics
- Disposition
- Exposure
- Liver analysis (HY's low)
- MedDRA at a Glance.

Using the outputs from the scripts you can:

**VIEW YOUR STUDY IN A SECOND! (OR 10 MIN)**

It is an advantage that the outputs are in Excel because of the build-in facilities. You get a quick overview of your data and more interesting: you will see the data as FDA will see them.

## IMPLEMENTATION PROCESS

The implementation of the scripts at Novo Nordisk A/S was done as a separate project during CDISC standards implementation. It was driven by the Programming Anchor and Biostatistics and the scope was:

- Implementation of publically known FDA scripts.
- Evaluate the FDA reporting tool based on SDTM, via a pilot
- Based on the pilot outcome: how can it be integrated in Novo Nordisk A/S tools/processes

This should identify how the application could be included and used organizationally correctly. The pilot was performed by the Programming Anchor where new software and applications often are tested and implemented from. Furthermore a project team voluntarily tested the scripts on their study data.

## CHALLENGES AND CORRECTION

As SDA members the project team easily downloaded the scripts from the GitHub repository, (see reference link).

All the scripts are excellent documented by FDA, (see reference link).The first task was to adapt the scripts for running in our environment and provide feedback to the SDA group.

The scripts were easily adapted except for the script outputting *MedDRA at a glance*.

There was an immediate interest from the Biostatistics organization and the team was often contacted like: Can we use it on our study?☺

## TECHNICAL UPDATES

Before commencing the adaption the team was notified by SDA that the script outputting *MedDRA at a glance* was not working correctly. Hence in order to get a total output package the script was changed, by adding an input parameter to the source (macro). The macro holds the MedDRA version. Designated Medical Event (DME) data from EMEA were not available but a draft version was downloaded from EMEA's (European Medicines Agency) homepage which fixed the script *MedDRA at a glance*.

Adaption of the script:

- corrected libname to Excel
- changed location of the log
- insert clearing of SAS work

Efforts was spend to check and run the exposure scripts, but through the SDA project information was received that FDA did not prioritize this output as for now; so this part of the script package was not prioritized in NN, just as the oncology part, because NN is not in oncology at present.

The updated NN script package was uploaded to the GitHub.

## STAKEHOLDERS

The output generated from the script package is really elegant in layout and very informative. Hence it was discussed whom would benefit from receiving these comprehensive summaries.

Meetings were arranged with leading programmers, data surveillance experts, Risk Based Monitoring experts, medical writers and medicals experts, project statisticians and managers.

The feedback from lead programmers was disappointing; they did not immediately find the outputs useful.
The data surveillance and Risk Based Monitoring experts found the output excellent. These groups are using SAS JMP® Clinical and it was tested whether the script outputs already was generated in the existing surveillance. It was elucidated that the outputs to a wide extent were overlapping.

The project statisticians found that the script output was an excellent tool for a fast overview of study data and actually the outputs were circulated to all the project functions (medical experts, medical writers and statisticians)

and were well received for their user-friendliness.

The project statisticians often know their clinical trials by heart. They know each and every detail in their study, all adverse events, safety signals, withdrawals, completers etc. Hence the output from the scripts is a confirmation that nothing is overlooked in a given study.

Feedback from the study group was positive; especially the usefulness and friendly layout of the summary tables was well received. It opens the opportunity that medical writers can use the output during writing the clinical trial report because it is easy to use the Excel output for checking and reviewing a trial.

The output *MedDRA at a Glance* was judged highly valuable; it contains information on adverse events that occurred during the specific trial according to the location in the MedDRA hierarchy, using the system organ class (SOC), high-level group term (HLGT), high-level term (HLT), and preferred term (PT). The user can choose which two arms to compare and set thresholds which determine whether the risk difference, relative risk, or negative log p-value for difference in proportion between the two arms is a signal of interest.

This output can be used to check that no safety signals have been overlooked.

Based on these project meetings the key stakeholders for the script output package were decided to be project statisticians, medical writers and medical experts. It was also decided to check that the standard setup of reports from SAS JMP Clinical covered the output from the scripts.

## WHOM TO RUN AND WHEN

After the pilot project the implementation of scripts contributed by FDA was handed over to Biostatistics Department. As it makes no sense to run The Scripts on un-blinded data, so it was decided to run the package after data base lock. Since the time between data base lock and results meeting is very busy the scheduled run time was decided to be just after result meeting. The package will be run by the SAS JMP Clinical super users and the output will be distributed to study group and other relevant colleague.

## STATUS

We have run the scripts contributed by FDA on 4 Trials. There have been no reports about discrepancies between the output package and the trial report. The feedback has been very positive and has been concentrated around: YES we have seen that signal; YES we have those withdrawals, etc. So, by looking at the outputs end users can get confirmation on their evaluations and conclusions of a study.

The use of SAS JMP Clinical turned out to cover the outputs from the scripts or at least nothing new was discovered.

## WISHES

A server version would be preferred but the amount of templates would clearly provide a challenge.

## REQUIREMENTS

The scripts use has these requirements:

Scripts contributed by FDA

- ✓ must run on PC SAS / local on Enterprise Guide
- ✓ runs on SDTM data.
- ✓ must be run AFTER Pinnacle 21 has checked data, or else it will throw errors.
- ✓ runs best on trial design with 2 parallel arms.
- ✓ have a max on trial design with 6 arms, due to templates in Excel
- ✓ cannot run on 64 Bits machines due to the Excel libname statement.
- ✓ is not good for crossover Trials.
- ✓ is not possible to run from affiliates due to data transfer issues to affiliates.

## CONCLUSION

The presentation and implementation of scripts contributed by FDA was well received at Novo Nordisk A/S. This is due to the outputs user-friendliness and the use of Excel.

Novo Nordisk will run the scripts just after key result meeting and the output will be used for high level review and validation for clinical personnel deeply involved interpretation study data and safety e.g. project statisticians, medical writers and experts.

Due to the limitations with the trial design we cannot run on all trials but the scripts will be run on all possible trials

with focus on Phase 3.

For small companies that do not have the package SAS JMP Clinical it is highly recommended to download the programs from the PhUSE GitHub and use them in the review process of a study.

The feedback from the SDA project is that FDA is interested in a more widely use of the programs by the industry. AND we still can use **volunteers** to test scripts.

## REFERENCES

Link to FDA homepage: https://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm397921.htm
Link to white Paper: http://www.phuse.eu/documents/cswhitepaperfdacontributedscripts-7164.pdf
Link to The Scripts: https://github.com/phuse-org/phuse-scripts/blob/master/contributed/Scripts_Top_Dir.zip
Link to SDA project:http://www.phusewiki.org/wiki/index.php?title=Standard_Scripts
Link to documentation: https://github.com/phuse-org/phuse-scripts/tree/master/tested/SAS/SpecDocs

If you're interested in joining the SDA group:

Please contact Rojas, Alfredo alfredo.rojas@accenture.com or Rebeka Revis, Rebeka_Revis@Lilly.com or Mary E Nilsson nilsson_mary_e@lilly.com

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