

Case Study in Support of German Payer Evidence

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ABSTRACT

The Law on the Reorganization of the Pharmaceutical Market (German abbreviation: AMNOG) became effective on January 1st, 2011. Module 4 requires a systematic overview regarding the (additional) medical benefit (description of the methodology and results) and indication of patient groups with an additional benefit.

The statistics and programming is quite different from traditional clinical study reporting of safety and efficacy in support of regulatory approvals. Proof of additional benefit requires different types of tables, statistical modeling, studies, etc.

This case study provides an overview of the decisions and choices that statistics and programming made over the course of years in support of a de-identified study drug. Depending on how many studies are reported, how many sub-populations, how many endpoints, etc. the number of tables can be quite large. You will learn how we developed a programming approach including standardized code and tracking systems to manage the challenge.

INTRODUCTION

According to Wikipedia:

The **Arzneimittelmarkt-Neuordnungsgesetz (AMNOG)**, English translation: "Pharmaceuticals Market Reorganisation Act") is a German law relating to the marketing of [pharmaceutical](#) products in [Germany](#). It requires drug manufacturers to submit evidence to the [Federal Joint Committee \(Germany\)](#) to show that their new products are more effective than previous products. It is credited with reducing the cost of healthcare in Germany.

Knowing why something is done is less than half the effort of completing the task. An overall review of the team structure, programming challenges, timeline restraints, etc. should help others when they are asked to support German Payer in their company. This presentation is meant to provide that summary, not the technical details, just a review of one case and one process.

SCOPE OF WORK

As the team was formed, information was collected to estimate resources and timelines. There is generally a long time period before the final report is due as expert review must be accounted for after the final results are delivered. Relevant information collected for resource estimation were:

- Studies: n = 4
- Populations: n = 1
- Sub-populations: n = 11
- Endpoints: n = 33
- Time points: n = 4
- Potential tables: n = 5000

REQUIREMENT

Addressing both the programming and communication challenges was key to a successful delivery. Programmers set out to minimize new coding by reusing prior SAS code. The German team agreed to create and version control TFL specifications using word. Various tracking excel spreadsheets were created to maximize communication with the German Team. Additionally, TFLs created in SAS were package into PDF's having bookmarks and a hyperlinked table of contents. Transfer of files

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between the groups was managed via a private FTP website affording a good audit trail.

STATISTICAL CONSIDERATION

The team agreed, at the onset, to review all statistical questions as a team. Any modified SAS code, that was modified as numbers became small, was reviewed and approved by our statistician before implementation by programming.

Small numbers were identified as sub-populations became more granular. This led to formatting changes to accommodate missing data as well as informational footnotes to help explain the results. All changes were tracked using an issue tracker and approved before production output was sent to the team.

PROGRAMMING CHALLENGE

Each study was reported out separately, there was no pooling. One study have 8 sub-population to define. Each sub-population was challenging to define as baseline and windowing rules were applied. The sub-populations and TFLs were completed on a rolling basis. That resulted in later sub-populations requiring changes to TFLs issued earlier. A change to any one sub-population required changes to all sub-population programs.

PROGRAMMING SOLUTION

Realizing that programs had to be kept in sync, one set of programs for sub-population #1 were maintained and automatically copied and changed for each sub-population. This loop process created a quick delivery to the team for their review. A novel script program using regular expressions controlled the copy process, changes and versioning.

```
**-----;
** Step 1 – Copy and rename files;
**-----;
data _null_ ;
  x "ls &dirx/* .sas";
  x "cd &dirx";

  x "for file in t*ob1*.sas ; do mv $file `echo $file | sed 's/ob1/itt/'` ; done";
  x "for file in t*itt*.sas ; do mv $file `echo $file | sed 's/10_/99_/'` ; done";

  x "chmod g+w *.sas";
  x "ls &dirx/* .sas";
run;
```

```
**-----;
** Step 2 – Change file content search string “10_” to “99_”;
**-----;
data _null_ ;
  x "cd &dirx";

  x perl -e "s/ob1/itt/g;" -pi $(find t*.sas -type f);
  x perl -e "s/OB1/ITT/g;" -pi $(find t*.sas -type f);

  x find . -name 't*_itt.sas' |xargs perl -pi -e "s/10_/99_/s";
run;
```

```
**-----;
** Step 3 – Change file content search string “1.0.1-” to “1.0.99”;
**-----;
data _null_ ;
  x "cd &dirx";

  x perl -e "s/1.0.10/1.0.99/s;" -pi $(find t010099_tdm_itt.sas -type f);
```

```
x perl -e "s/1.1.10/1.1.99/s;" -pi $(find t010199_tlb_itt.sas -type f);
```

TIMELINE AND RESOURCE

The team originally requested all tables be delivered in two weeks, however after review of the scope, programming set-up a 3 month delivery window that extended to 6 months due to scope changes. All tables were delivered in batches. There were two types of batch deliveries, overall tables and sub-group tables. Given the extra effort to QC sub-group tables, they were delivered after overall tables. There were 4 programmers assigned to this effort, albeit from time-to-time, we lost resources to other priorities.

SUB-POPULATION

Deriving the 8 sub-populations became the most difficult project tasks. The team often went back to prior reports to decide on baseline medication rules, on-treatment medication windows, treatment-dependent logic, etc. Additionally, they kept consistent with prior numbers by comparing any results back to prior reports.

SCOPE CHANGE

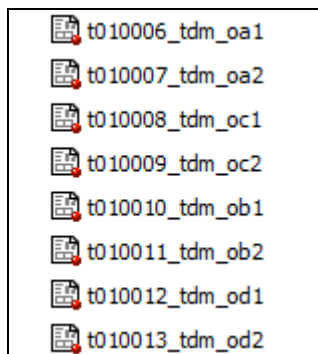
Analyses were not pre-specified in payer evidence as in clinical study reports. Scope changed due to the use of different model to calculate p-values, representation of missing values, title changes, addition of explanatory footnotes, and efforts to match numbers used in prior work.

TRACKING

Tracking advanced good communication and notification. Using Excel spreadsheets, the team tracked programs, outputs, QC, issues, deliveries and timelines. These trackers made it easier to evaluate the critical path and re-prioritize as needed. The actual results were written up by an external firm that had their own set of timelines. Without daily knowledge of the overall delivery, there would have been a greater risk of miscommunication and delay.

NAMING CONVENTION

The great number of TFLs required a program and output a naming convention that avoided overwriting content while finding files easy to find. The convention also had to allow the use of regular expressions to create copies of the programs for other sub-populations. Sort order was also a consideration for ease of reference.



QUALITY CONTROL

Quality was maintained via double programming of all programs. Where possible, numbers were compared to previous submission output. Statisticians performed independent programming of statistical calculations, especially p-values. The entire dossier was finally reviewed by the German Payer team.

DELIVERY

There were approximately 1000 TFLs programmed. Given change requests, 3000 TFLs were ultimately reviewed. All output was provided in PDF format that facilitated easy review. Transfer of files

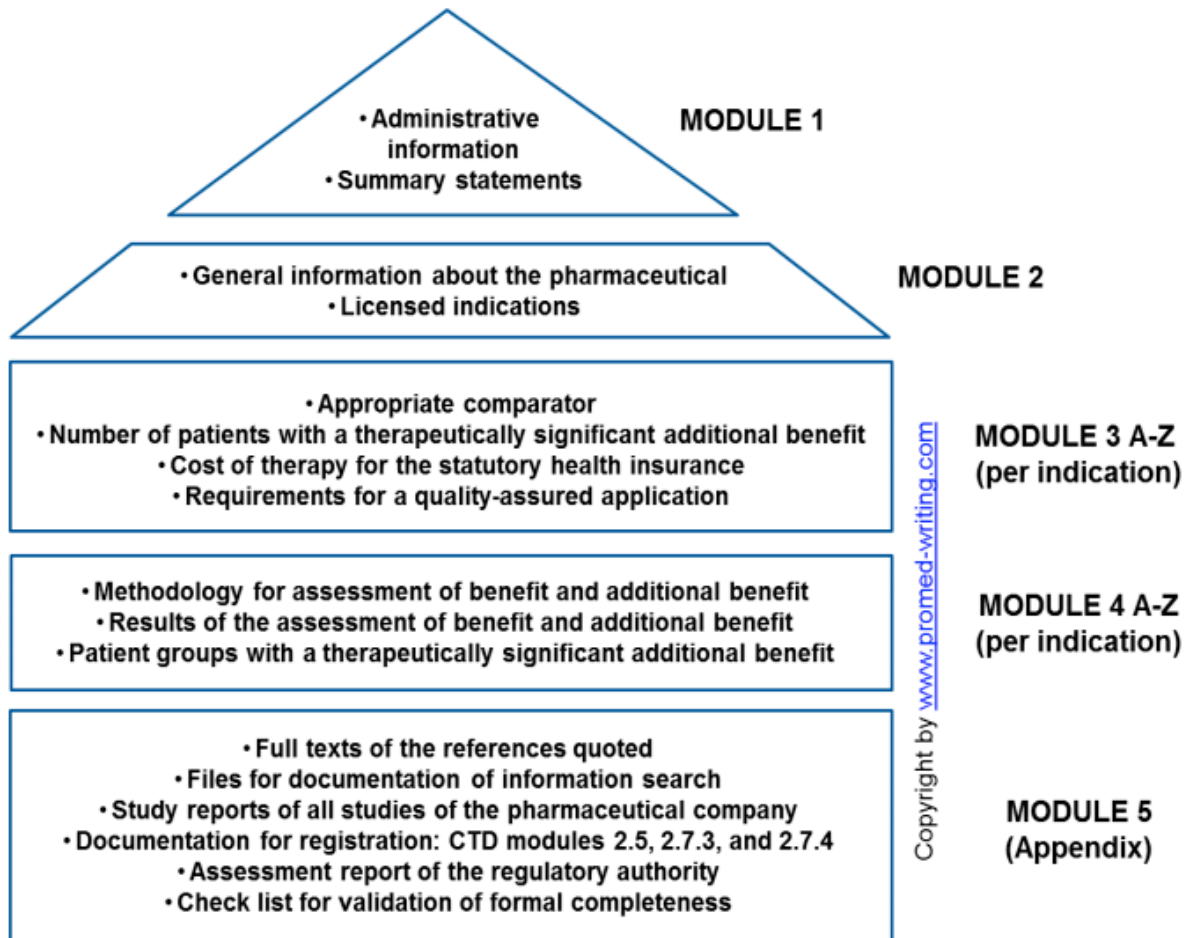
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occurred through a FTP service that provided traceability, audit logs, and versioning.

CONCLUSION

Use of randomized clinical trial data provided the best data to evaluate sub-populations for our indication seeking added benefit classification. At times, the exercise was rather like data mining, however the comparison against our comparator in support of a value added effect was well thought out by a range of experts.

The effort was essential to remain competitive in the German market. Thus the resources assigned were justifiable. But as in all programming efforts, the programming department will continue to explore streamlining as a method to provide the same support in a more efficient way. Perhaps there are common tables, like safety, which can be delivered quickly and easily.



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	Classification
1	Major
2	Significant
3	Minor
4	Not quantifiable
5	No additional benefit documented
6	Benefit lower than the use of the ACT

REFERENCE

1. Macheleidt, Oliver, LEO Pharma Germany Senior Manager Health Outcomes Research, "It's difficult to meet HTA criteria according AMNOG – reason why?", Retrieved on October 5, 2016 from http://www.dsbs.dk/moder/AMNOG_HTA_Germany.pdf
2. Wikipedia, Search term "AMNOG", Retrieved on October 5, 2016 from <https://en.wikipedia.org/wiki/AMNOG>

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RECOMMENDED READING

This section is not required.

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