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Framework for German Dossier Submissions

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ABSTRACT

When submitting your drug benefit assessments to the German Authority or other (foreign) regulatory agencies, you need to provide your reports in a specific format. These reports are usually in a non-English language, so the characters are different from the English characters that you are used to. The characters contain accents and other special characters, and the numerical results contain commas where you expect decimal points to be, and vice versa. To provide this report, a medical writer typically uses Microsoft Word to copy the results from a Clinical Study Report (CSR) into the document, and includes the appropriate formatting and translations. The copying must be done very carefully, and this process is error prone and very exhaustive. Also, the German authorities might have additional follow-up questions. Therefore, following this process is inefficient. There is a way to make the process more automated, and this paper demonstrated those methods. Firstly, this paper shows you a framework you can use for submitting a German Dossier, such as the time-to-event macros, subgroup analyses, and the processes that you can use to get your data in the right format. Secondly, this paper shows you how you can generate the results in the exact format needed for the German Dossiers. You are shown how to use encoding to read and write special characters, and how to use the REPORT procedure along with the style attributes to get your outputs in the required, correct format.

INTRODUCTION

According to (Gemeinsame Bundesausschuss, 2019) the Federal Joint Committee (G-BA) is the highest decision-making body of the joint self-government of physicians, dentists, hospitals and health insurance funds in Germany. The G-BA must put every new active pharmaceutical ingredient through an early benefit assessment within six months after it is launched on the German market. During the early benefit assessment, the G-BA examines whether the drug is really something new, and if it offers patients greater benefit than comparable treatments that are already available.

For the G-BA to carry out the assessment, pharmaceutical companies are obliged to submit a dossier on the product benefit of the product that they want to launch in Germany. This paper will guide you through creating some of the tables needed for the dossier.

The benefit assessment is not always performed by the G-BA, because the G-BA can delegate the benefit assessment to the Quality and Efficiency Institute for Health Care (IQWiG) or third parties, and therefore you may be more familiar with IQWiG because they have carried out the dossier assessments at the company, which I consult at.

The dossiers themselves are in a quite rigid format: the content to go into the document is largely prespecified, and the tables and figures used to display the data is quite fixed. Therefore, it is possible to create standard programs to produce the outputs. However, to produce the standard outputs. first the data needs to be in the right format, and it is preferred that this format is ADaM data standards.

TIME-TO-EVENT

The majority of the work for the dossier assessments are time-to-event analysis, in particularly on subgroups. Output 1 below was extracted from a German Dossier submission. The submitted document is located here: https://www.g-ba.de/downloads/39-261-2732/2016-10-20_AM-RL-XII_Ramucirumab_Magenkarzinom_D-224_BAnz.pdf

Output 1, shows the Overall Survival and Progression Free Survival times for the two treatment combinations. The Kaplan Meier method estimated the survival times, and Cox Regression calculated the Hazard Ratios.

a) Ramucirumab in Kombination mit Paclitaxel

Studie Rainbow: Ramucirumab + Paclitaxel vs. Paclitaxel + Placebo

Endpunkt	**Ramucirumab + Paclitaxel**		**Paclitaxel** + Placebo		Intervention vs. Kontrolle
	N	Mediane Überlebenszeit in Monaten [95 %-KI] *Patienten mit Ereignis n (%)*	N	Mediane Überlebenszeit in Monaten [95 %-KI] *Patienten mit Ereignis n (%)*	Effektschätzer [95 %-KI] p-Wert Absolute Differenz[a]
Mortalität					
Gesamtüberleben (1)					
Primäre Analyse (stratifiziert)[b]	330	9,6 (2) [8,5;10,8] (3) *256 (77,6)* (4)	335	7,4 [6,3;8,4] *260 (77,6)*	HR: 0,807 (5) [0,678; 0,962] (6) p = 0,0169 (7) + 2,2 Monate
Morbidität					
Progressionsfreies Überleben (PFS) (8)					
Primäre Analyse (stratifiziert)[b]	330	4,4 [4,2;5,3] *279 (84,5)*	335	2,9 [2,8;3,0] *296 (88,4)*	HR: 0,635 [0,536; 0,752] p < 0,0001 + 1,5 Monate

Output 1: Time-to-Event output

(1) Overall Survival endpoint.

(2) Median Survival Time.

(3) Lower and Upper Confidence Intervals of the Median Survival Time.

(4) Number of patients with the events, and the percentage of patients.

(5) Hazard Ratio.

(6) Lower and Upper Confidence Intervals of the Hazard Ratio.

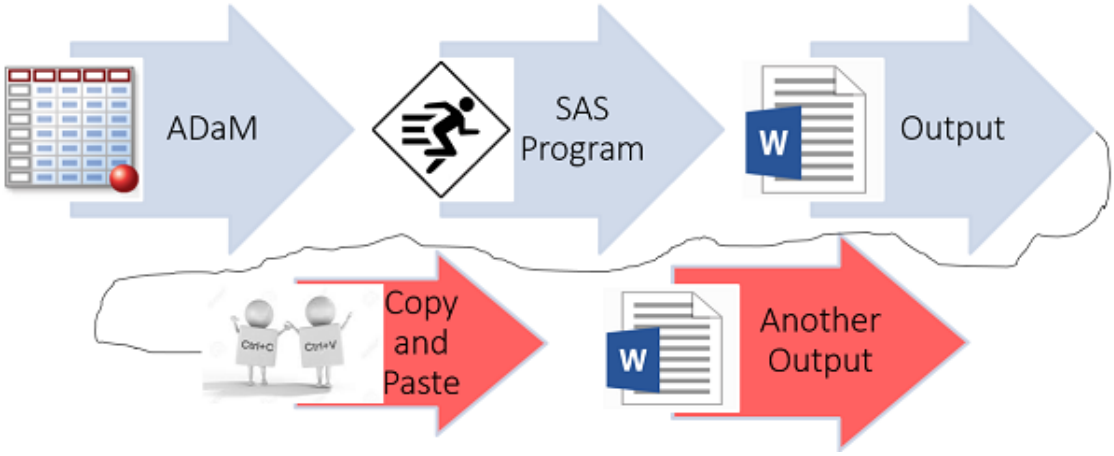
(7) Log-Rank p-value.

(8) Progression-free Survival endpoint.

You will notice that in Output 1, there are a lot of commas where you will expect to see decimal places, for example the value of 9,6 (instead of 9.6) for the Median Survival Time in the Ramucirumab + Paclitaxel Group. The format difference is an idiosyncrasy of the German dossier submission.

INEFFICIENCIES IN CREATION OF PREVIOUS GERMAN DOSSIER

The standard method of creating the tables needed for the German Dossier submission, was to copy the values from the necessary tables which were in the Clinical Study Report (CSR) and then paste those values into the tables needed for German Dossier submission. The problem with this approach is that, it is manual, repetitive and prone-to-error. Output 2 illustrates the previous process.

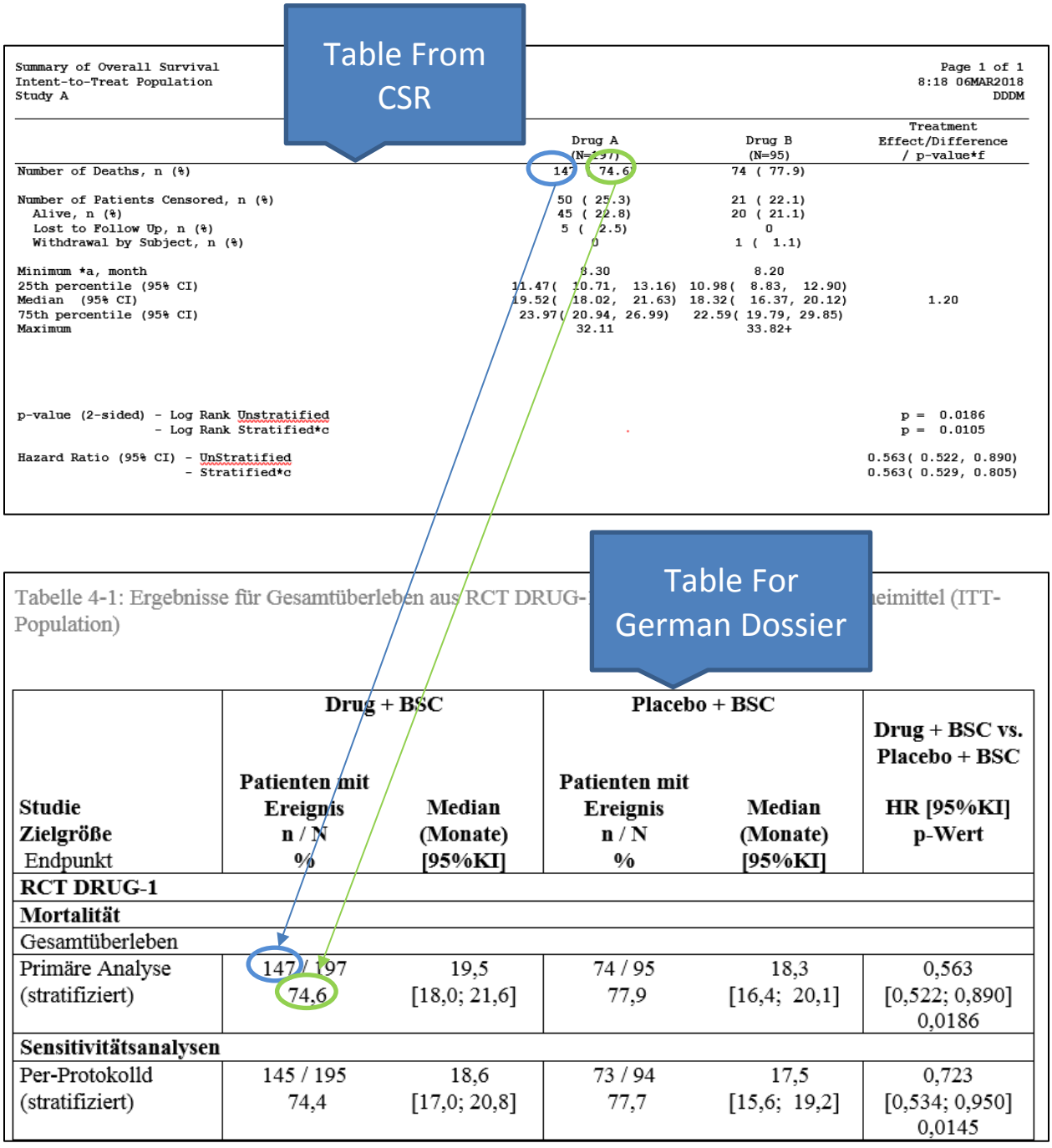


Output 2: Previous Process

TIME TO OVERALL SURVIVAL EXAMPLE

Let us imagine that there was interest in the Time-to-Overall Survival, which is generally the case. Typically, SAS would read in the ADTTE dataset, and the LIFETEST procedure, along with the PHREG procedure would calculate the necessary Kaplan Meier estimates, and Hazard Ratios. Then the REPORT procedure would create the Time-to-Overall Survival output according to the specifications. The Time-to-Overall Survival output would then be included in the CSR. The first section of Output 3 shows an example of the standard Time-to-Overall Survival output.

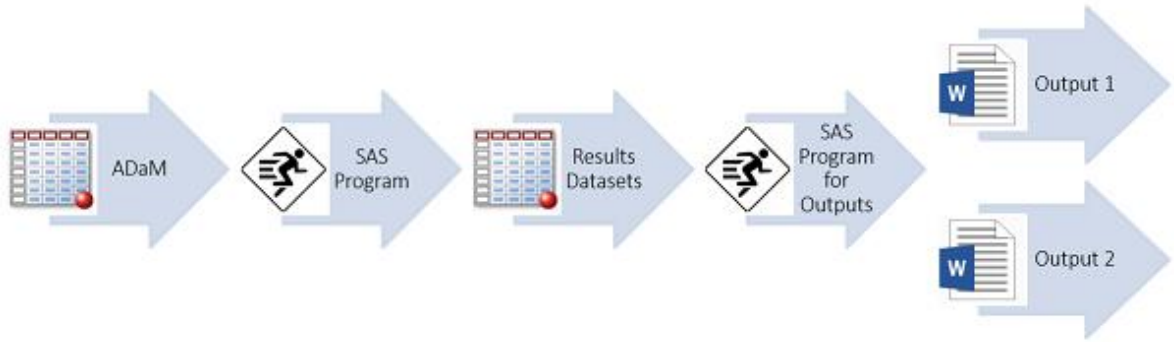
The format required for the German Dossier is different from the format required for the CSR. Therefore typically someone working in the German Dossier team, such as a medical writer, would create an empty German Dossier table i.e. a table without any values but which was in the right format, and then they would open a copy of the CSR and find the endpoint which they were interesting in, and then copy and paste that value into the German Dossier table shell. Output 3 illustrates this process.



Output 3: Copy and Paste Example

IMPROVEMENTS IN CREATION OF CURRENT GERMAN DOSSIER

As mentioned before, copying and pasting between documents is prone-to-error. It is also inefficient. In addition, decimal places need to be changed to commas and vice versa. Output 4 below shows how it is possible to add more automation in the German Dossier process, and use SAS to create the German Dossier tables, instead of copying and pasting manually.



Output 4: Current Process

Using the Time-to-Overall Survival output again, in the current process, SAS will store the necessary Kaplan Meier estimates, and Hazard Ratios into a SAS (results) dataset. Then SAS will directly create the tables in the right format for the German Dossier (Output 1), and also for the CSR (Output 2).

You may be wondering how this is possible, and so we will look at some SAS Code.

USEFUL CODE FOR GERMAN DOSSIER OUTPUTS

Program 1 uses the SQL procedure to extra the calculated data needed for the outputs (from the temporarily imported datasets), such as the Median Survival Time and the Hazard Ratios. Then Program 1 formats the values in the correct format, such as using commas instead of decimal places.

```
* Median;
proc sql;
  select (scan(trstat1, 1, "(")), scan(trstat2, 1, "(") into :Median1_&dataset,
:Median2_&dataset
  from &dataset.
  where term = "Median  (95% CI)";
quit;
options LOCALE=German_Germany;
Median1_dataset = put(input("&&&Median1_&dataset", best.), nlnum5.1);
```

(1) (2) (3)

Program 1: Extracting Data and Formats

(1) A macro variable is used for the dataset because usually different datasets are created for different endpoints. A so generally there are separate datasets which contain the Median time-to-event, and the Hazard Ratios for Overall Survival, Progression Free Survival, and Overall Survival using a different population flag.

(2&3) These format the values into the format needed for the German Dossier, i.e. using commas instead of decimal places, so a number originally displayed as 74.6 will be displayed as 74,6.

Program 2 below shows an example of how the TEMPLATE procedure controlled the output margins. It is not necessary to write the code for the templates from scratch. The template below was based on the STYLES.RTF template. To see a template style, for example STYLES.RTF you can use the follow code, and then view the template in the log window:

```
proc template;
  source styles.rtf;
run;
```

```
proc template;
  define style Styles.rtf_gd;
    parent = styles.rtf;
      *style body from body /
        marginleft = 34.5mm marginright = 34.0mm
        margintop = 18.2mm marginbottom = 14.2mm;
       /* Creating own margins */
        style body from body /
        marginleft = 1in marginright = 1in
        margintop = 1.5in marginbottom = 1in;
run;
```

Program 2: Output Format – Margins and Font Sizes

Program 3 below is some of the Proc REPORT code. This code helps to remove some of the borders (by making the right borders have the color white), and makes certain section of the report have bold text. For example, if you look at Output 5, you will notice that the 1st, 2nd and 5th rows have all got bold text and they only have one right border,

```
compute gd_description;
    if order in (1, 2, 5) then do;
         call define(_row_,"style", "style={borderrightcolor =
           white font_weight=bold}");
    end;
    else if order = 3 then do;
         call define(_row_,"style", "style={borderrightcolor =
           white}");
    end;
endcomp;

compute HR_pvalue;
    if order <= 3 or order = 5 then do;
         call define(_col_,"style", "style={borderrightwidth=1
           borderrightcolor = black}");
    end;
endcomp;
compute Median1;
    if order = 4 or order > 5 then do;
         call define(_col_,"style", "style={borderrightwidth=1
                       borderrightcolor = black}");
    end;
endcomp;
```

(1) (2) (3) (4)

Program 3: Producing Reports – Controlling Borders and Font Weight

(1) Makes the font bold, and makes the defines that the right borders are colored in white, for all the columns in the 1st, 2nd and 5th rows.

(2) Defines that the right borders are colored in white, for all the columns in the 3rd row.

(3) In order to have one right border colored in black, and therefore have the appearance of a border, this code puts a black border on the right hand side of the HR p-value column, for the rows that needed it, i.e. the rows less than 3 and the 5th row.

(4) This code separates the two treatments by putting a black border on the right hand side of the Median column of the active drug.

Output 5 was created directly from a SAS program, and this is more efficient than using the previous copy and paste process.

Tabelle 4-1: Ergebnisse für Gesamtüberleben aus RCT DRUG-1 mit dem zu bewertenden Arzneimittel (ITT-Population)

Studie Zielgröße Endpunkt	Drug + BSC Patienten mit Ereignis n / N %	Drug + BSC Median (Monate) [95%KI]	Placebo + BSC Patienten mit Ereignis n / N %	Placebo + BSC Median (Monate) [95%KI]	Drug + BSC vs. Placebo + BSC HR [95%KI] p-Wert
RCT DRUG-1					
Mortalität					
Gesamtüberleben					
Primäre Analyse (stratifiziert)	147 / 197 74,6	19,5 [18,0; 21,6]	74 / 95 77,9	18,3 [16,4; 20,1]	0,563 [0,522; 0,890] 0,0186
Sensitivitätsanalysen					
Per-Protokolld (stratifiziert)	145 / 195 74,4	18,6 [17,0; 20,8]	73 / 94 77,7	17,5 [15,6; 19,2]	0,723 [0,534; 0,950] 0,0145

Output 5: Example Output

CONCLUSION

It is better to automate the process as much as possible, then to use the copy and paste method. This is because the copy and paste method is prone-to-error and takes a lot of time, and it is quite repetitive.

By using results datasets, in conjunction with German formats, Proc SQL, Proc TEMPLATE, and Proc REPORT, you can create German Dossier outputs, in the appropriate format.

It is better to work with the team that are creating the ADaMs as soon as possible. This is because, it will be much easier then to include variables which are needed for the German Dossier. Such as German Translation Text of Adverse Events.

There are further automations that can be done, for example automating the text that goes in front and beneath the table. These will be the next steps, because apparently the text above or below the tables is quite standard.

REFERENCES

Gemeinsame Bundesausschuss. (2019, 03 28). *Gemeinsame Bundesausschuss*. Retrieved from Gemeinsame Bundesausschuss: https://www.g-ba.de/english/

CONTACT INFORMATION

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