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Drug exposure plot: Tailored approach to display ongoing data

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ABSTRACT

The 80/20 rule is driving business needs within Clinical Reporting. A major challenge we are faced to is the following: how can we minimize the 20% non-standard requests, that currently demand around 80% of our resources.

In early phase studies, where we are just starting to learn about the compound, this problem is particularly pronounced. We have found that we can best tackle this issue by providing tailored graphs that aim to address the scientific question. Such graphs are key to increase the data quality and facilitate decision making.

The drug exposure plot is a good example of programming insight to the study status for clinical teams. Several layers of information can be displayed (onset of particular events such as AE or tumor evaluations) on top of patient dosage administration history (dose change, interruption). It allows to display the combination of diverse collected or derived information and serves several purposes such as data transparency.

INTRODUCTION

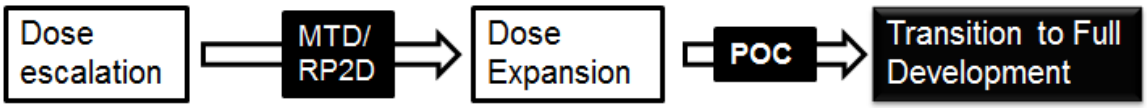
In early phase trials, the aim is to determine the appropriate right and safe dose level showing efficacy signals with acceptable safety and tolerability profile. Over the past years, adaptive study designs have been put in place to best assess these criteria. Despite a low number of patients in Phase I trials, we receive regular requests for data summary with ad-hoc additional information from the clinical team. Both clinical and programming teams have access to data but not with the same level of information/quality, our expertise is to provide pertinent and reliable outputs to the clinical team enabling decision making. The drug exposure plot presented hereafter is a good example as an insight of the study status to the clinical teams.

EARLY PHASE STUDIES

The aim is to move from laboratory experiments through clinical trials to point-of-care patient applications. Most of time, studies are first in human Phase I/II. The objective of dose escalation trial is to determine Maximum Tolerated Dose (MTD) and Recommended Phase 2 Dose (RP2D), with the intent to declare a Proof of Concept (POC). Once MTD/RP2D is declared, a dose expansion phase or the phase II part of the study starts which will trigger the PoC.

These decisions can cause some protocol amendments leading to new designs as it is challenging to expect what is somehow unexpected. This explains why early phase studies contain many exploratory analyses. Because of their exploratory nature, early phase studies may have few protocol amendments leading to new designs (new regimen tested to improve patient compliance, new arms in dose expansion/phase II part). Indeed it is challenging to expect what is somehow unexpected.

Classic design:



MTD=Maximum tolerated dose; RP2D=Recommended phase 2 dose; POC=Proof of concept

During the escalation phase, in order to determine the MTD, clinicians need to understand the effect of the drug and the subject's tolerance but they also need to ensure that dose has been taken as planned. Early efficacy findings are of interest in order to find the best balance between tolerability and efficacy.

More exploratory, more reporting activities, less planning

Oncology Translational Medicine (Early Phase in Oncology) working methods are different from what is called Full Development; the number of patients is lower in early phase (around 25~100), but the number of reporting events is much higher. In order to better know the molecule, its interaction with any potential combined drug, the attention is focused on exploratory activities. It implies an expertise from a programmer's point of view, in the different data assessments (in-depth efficacy knowledge, as well as PK for example) to ensure appropriate data derivation.

The most important part of the reporting is done prior to the data base lock. It involves working on ongoing database which are not 100% clean and complete.

An analysis plan is defined at the study start, but it is subject to changes due to the impact of the protocol amendments and the increase in compound/study treatment knowledge. Hence, the initial focus is not on the final Clinical Study Report, the initial priorities are to anticipate any exploratory analyses and to try to understand what the clinicians' needs are.

TYPICAL CLINICAL QUESTIONS TO THE STATISTICAL / PROGRAMMING TEAM:

The first objective is to show safety outcome and to understand the effect of the compound on subjects. A common request can be split in primary and secondary area of interest:

Primary: 'Display the drug administration'

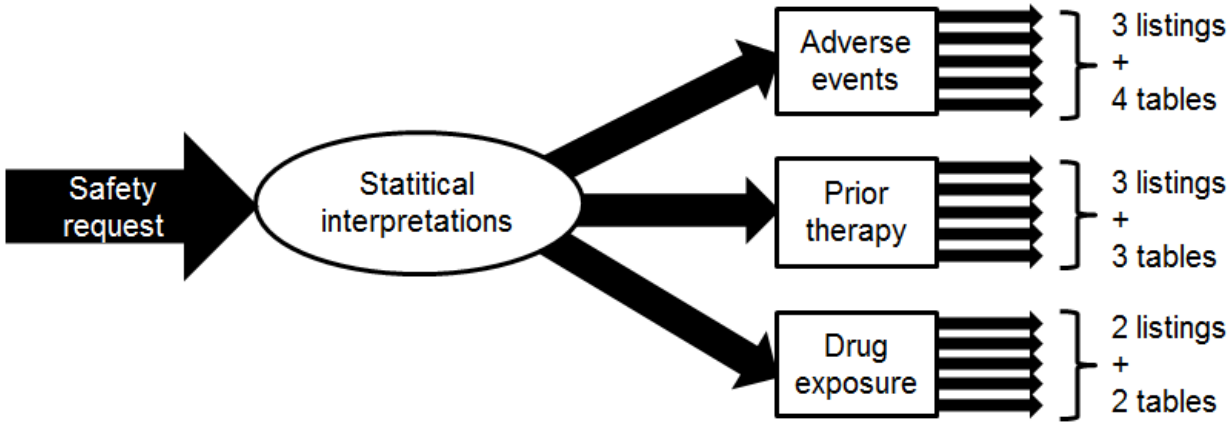
- How long does a patient stay on study?
- How often does a dose interruption and/or a dose reduction occur?

Secondary: Additional cross analysis with efficacy response / adverse event / reason for end of treatment:

- What is the relation between exposure and the reason for treatment discontinuation?
- What is the link between the occurrence of one particular adverse event and the associated dose level?
- What is the effect of a dose reduction on the efficacy response?
- …

The More outputs there is, the less clear the information is:

The usual approach to answer the questions above would be to split the request in multiple sub categories (adverse events, drug exposure, prior therapies, etc…) and then to produce the corresponding standard outputs as shown below.
As a result, the content and the purpose of the request are spread, making it harder to interpret.



For example, it's simple to highlight the most critical adverse events in a classical AE summary table. It is however harder to show the relationship between the occurrence of the event and the intake of a dose.

Investigation subject by subject:

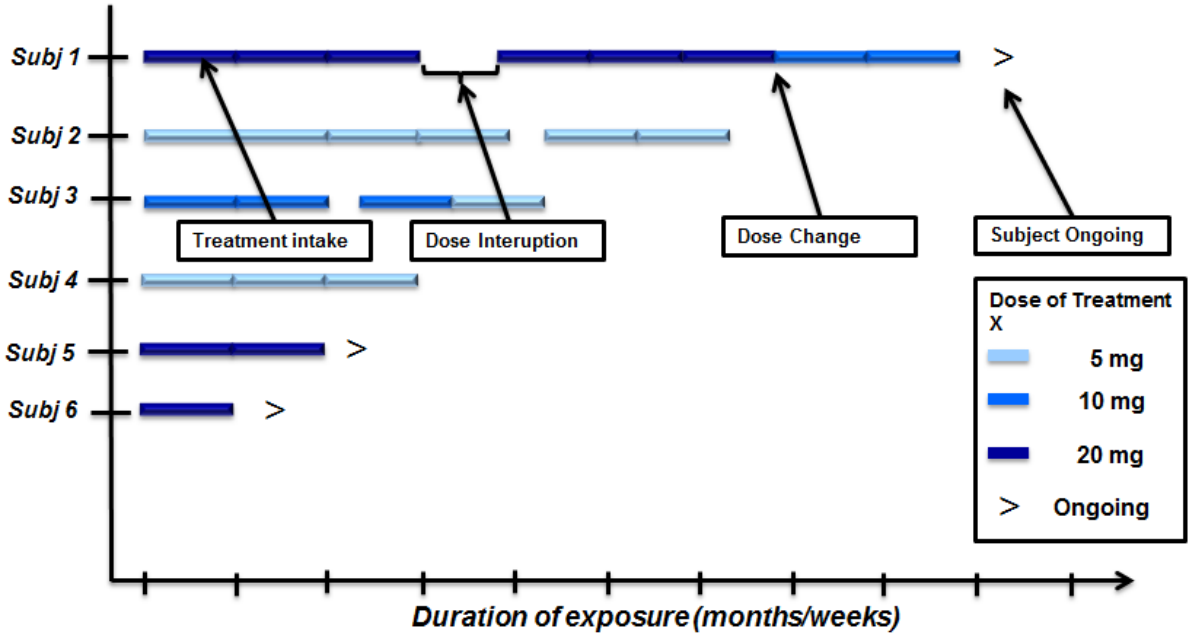
The fact that Phase I trials do not contain so many patients becomes an asset for the individual data representation and review. Clinicians often need to go back to the individual source listings to investigate case by case, any risk or safety trend. Although linked to the CRF, These listing are not always convenient and could lead to a huge number of pages to review.

In this context, we needed to develop new outputs and go beyond our standards to deliver more pertinent information, condensed, with the potential to be interpreted at a glance.
The drug exposure plot is one of the examples of this programming insight.

DRUG EXPOSURE PLOT

Taking into account all the aspects and constraints described above, it seemed obvious we needed one graph to display patient level information.

Main purpose: Display the treatment administration record:



In this graph, the subject id is on the y-axis and the duration of exposure is on x-axis. Each 'bar' represents the exposure to the drug, while the color specifies the different dose level. This allows immediate review of patient compliance to study treatment.

By displaying the study day/weeks/months instead of the associated dates on the x-axis, we can compare the exposure of the different patients. Adding marker for patients ongoing or not allows quick review of potential early drop outs in particular dose levels

Note that the exposure displayed in the graph is dependent on the regimen the dose was given. Typically, for a daily dosing, the exposure stops at the time of the last dose received. For a weekly dosing, the exposure stops 7 days after the last dose received.

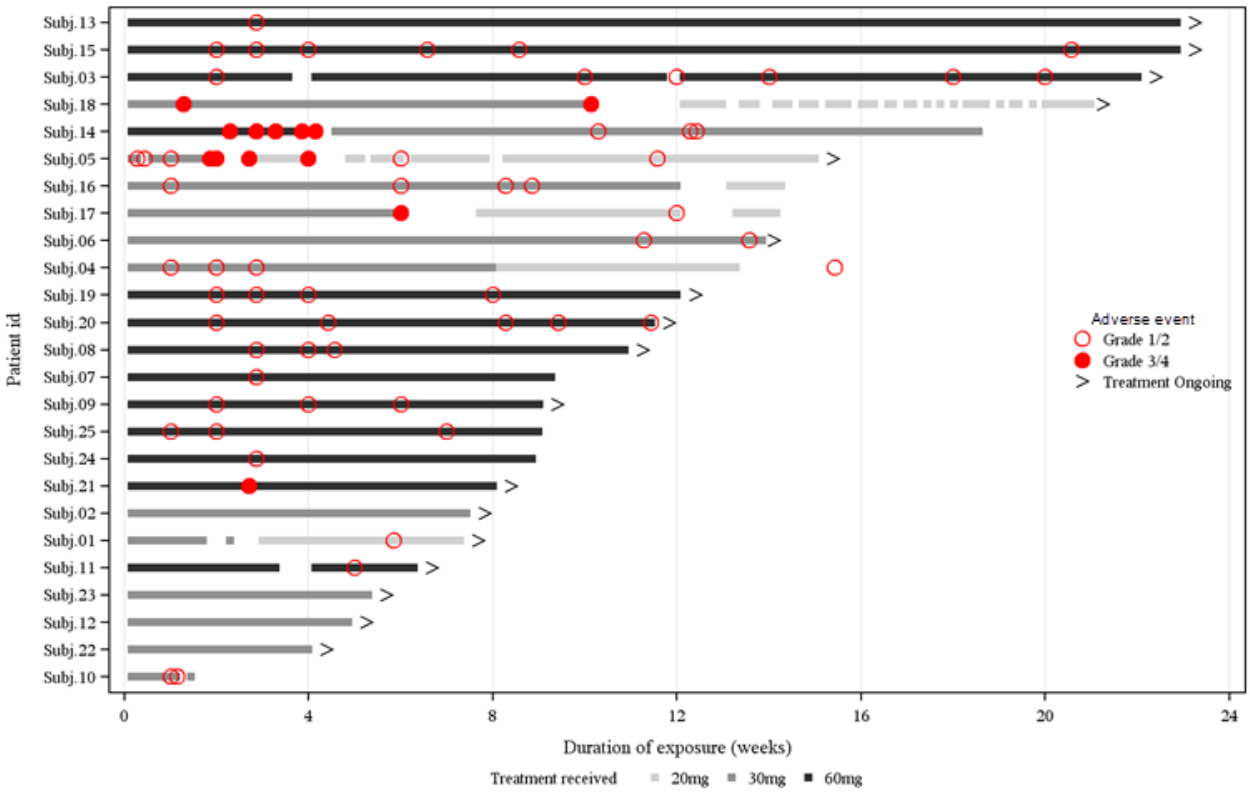
With those basic statements displayed, we have already completed the primary area of interest:

- The overall 'lifecycle' by subject:
  - Duration of exposure
  - Which dose levels?
- Dose interruption:
  - When?
  - How often?
  - Duration of the interruptions
- Dose Change:
  - When?
  - Related to the dose level?

Secondary area of interest: Two examples of Additional events:

Example 1 - Safety: Drug exposure plot and adverse event by 'severity grade'

On top of the overall drug exposure that we have just described, the plot below is displaying the occurrence of a particular adverse event of interest, making an emphasis on the Grade 3/4 adverse events. According to the protocol, the occurrence of such a Grade 3/4 adverse event should lead to a dose decrease.



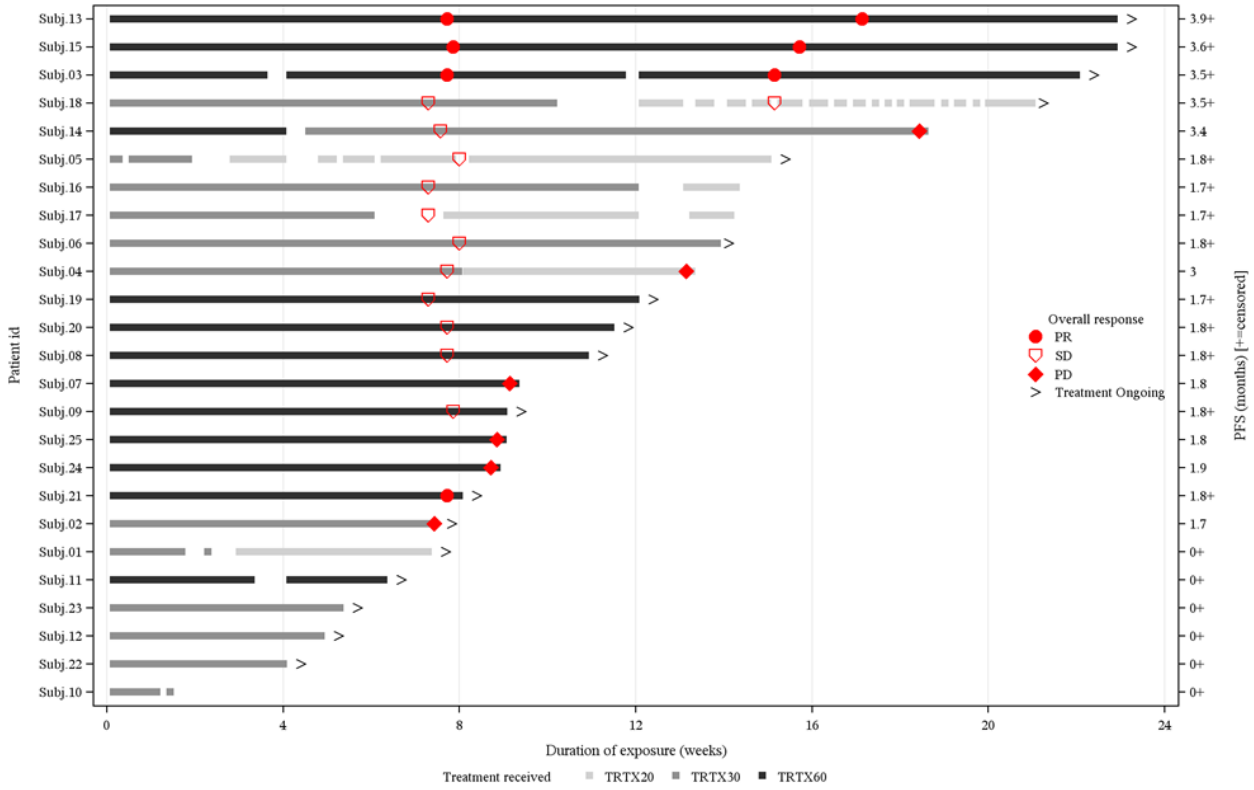
- Subjects 18, 14, 05 and 17 have grade 3/4 adverse events which are leading to a dose decrease

- Investigate potential protocol deviations, data issue, programming issue, etc :
  - Subject 18 and 21 have a grade 3/4 AE in the first four weeks with no dose change.
  - Subject 16, 04 and 01 have dose decrease not related to AE.
  - Subject 04 has an adverse event out of his exposure

- Subject 18 has a lot of interruptions after 12 weeks

Example 2 - Efficacy: Drug exposure plot and Recist overall response

As per protocol, every two months, the evolution of tumor lesions is assessed. Then they are categorized by a level of response: Complete response (CR) > Partial Response (PR) > stable disease (SD) > progressive disease (PD). The patient should discontinue after a PD.



- Check potential protocol deviation:
  - A patient should discontinue after a Progressive disease (PD)**:**
    Why subject 02 is still ongoing after a PD?
  - The response evaluations should be done every two month
    Why subject 04 has his second assessment earlier (13 weeks instead of 16) than planned?
    Why subject 14 has his second assessment later (19 weeks instead of 16) than planned?

- First efficacy interpretations:
  Subjects 13, 15 and 03 have the longest exposure to study drug and partial responses (PR) and are still ongoing. That could give an idea of the potential effect at TRTX60 on efficacy responses.

- Identify the patient without any assessments:
  Subject 11, 23, 12, 22 and 10 haven't completed at least two months yet

- Check consistency between PFS reported and exposure /response data

SAS Procedure

The objective is to develop a SAS program with the following features:

- Live data: Need to be re-run several time on different data cuts
- Template and not a macro due too many complex design
- Subject level information: Subject ID needs to be visible
- Cosmetic: Color, symbol, label, order and legend label needs to be defined by the user
- The layout should be same across pages

Proc SGPLOT syntax:

```
Proc SGPLOT data  = input dataset ;

        Scatter Y= Subject ID X= Treatment group1
                /Markerattrs=(symbol=squarefilled size=5 color=color1) legendlabel="treatment label1"
                name="trt1";
        Scatter Y= Subject ID X= Treatment group2
                /Markerattrs=(symbol=squarefilled size=5 color=color2) legendlabel="treatment label2"
        name="trt2";                    :
                                        :
                                        :

        Scatter Y= Subject ID X=Secondary category1
                / Markerattrs=(symbol=symbol1 size=9 color=red) legendlabel="Category label1" name="cat1";
        Scatter Y= Subject ID X=Secondary category2
                / Markerattrs=(symbol=symbol2 size=9 color=red) legendlabel="Category label2" name="cat2";
                                        :
                                        :
                                        :
        Scatter Y= Subject ID X=Ongoing variable
                 /Markerattrs =(symbol=greaterthan  size=7 color=black) legendlabel='Treatment Ongoing'
        name='ong';

        Keylegend "trt1" "trt2" … /location=outside position=bottom noborder title='Treatment received'
        titleattrs=(size=7) valueattrs=(size=7);
        Keylegend "cat1" "cat2"… 'ong'/ location=inside position=right noborder title="category label" titleattrs=(size
        =7) valueattrs=(size =7);

        *Xaxis statement;
        *Yaxis statement;

run;
```

Transforming multiple dots into a bar:

If, at first sight, it looks like a bar chart, one 'bar' is actually a succession of dots (filled square).

One filled square represents one day with a treatment intake, seven successive squares represent one full week of daily dosing, etc…

For this reason, we are using the Scatter statement. Why do we have so many of them in the above syntax?

One scatter statement per Dose level:

Subj_ID	Start	End	Duration	Dose level (mg)	Study day (start)	Study day (end)
A	05.09.2014	07.09.2014	3	20	1	3
A	08.09.2014	08.09.2014	1	0	4	4
A	09.09.2014	12.09.2014	4	10	5	8
A	15.09.2014	15.09.2014	1	10	11	11
A	16.09.2014	18.09.2014	3	5	12	14

1. Expend each non-zero dosing to create one record per subject, per study day. **The zero dosing are excluded as they are not being displayed in the plot.**

2. Transpose the study day by dose level to create a new variable per dose level which contains the coordinate of the dot (= study day)

Subj_ID	Start	End	Duration	Cumulative duration	Dose level (mg)	Trt5	Trt10	Trt20
A	05.09.2014	05.09.2014	1	1	20			1
A	06.09.2014	06.09.2014	1	2	20			2
A	07.09.2014	07.09.2014	1	3	20			3
A	09.09.2014	09.09.2014	1	5	10		5	
A	10.09.2014	10.09.2014	1	6	10		6	
A	11.09.2014	11.09.2014	1	7	10		7	
A	12.09.2014	12.09.2014	1	8	10		8	
A	15.09.2014	15.09.2014	1	11	10		11	
A	16.09.2014	16.09.2014	1	12	5	12		
A	17.09.2014	17.09.2014	1	13	5	13		
A	18.09.2014	18.09.2014	1	14	5	14		

3. In the SGPLOT, apply one scatter statement per dose level with a different color, legend label and name.

```
Scatter Y= Subj_ID X= Trt5  /Markerattrs=(symbol=squarefilled size=5 color=GREYE0)
        legendlabel="5 mg" name="doslvl1";
Scatter Y= Subj_ID X= Trt10 /Markerattrs=(symbol=squarefilled size=5 color=GREYA0)
        legendlabel="10 mg" name="doslvl2";
Scatter Y= Subj_ID X= Trt20 /Markerattrs=(symbol=squarefilled size=5 color=GREY50)
        legendlabel="20 mg" name=" doslvl3";
```

4. Legend: Call the names of previous scatter statement in the desired order:

```
Keylegend "doslvl1" "doslvl2" "doslvl3"
      /location=outside position=Top noborder titleattrs=(size=7) valueattrs=(size=7);
```

One Scatter statement per event category (e.g. Adverse event + ongoing flag):

a. One event should be associated to one specific study day.
   a. An adverse event is defined by the day it started
   b. An ongoing flag is defined by the exposure end date

AE Panel

Subj_ID	Grade cat	AE Grade	Start	Study day
A	1	3	07.09.2014	3
A	2	4	15.09.2014	11
A	1	1	18.09.2014	14

Treatment panel

Subj_ID	Ongoing	Treatment start	Treatment end	Study day	Displayed study day*
A	Yes	07.09.2014	18.09.2014	14	15

*Study day +1 in order to have it after avoid overlapping the exposure bar

b. Transpose the study day as for the dose level and 'set' the datasets to the main one:

Subj_ID	Start	End	Duration	Cumulative duration	Dose level (mg)	Trt5	Trt10	Trt20	AE1	AE2	Ong
A	05.09.2014	05.09.2014	1	1	20			1			
A	06.09.2014	06.09.2014	1	2	20			2			
A	07.09.2014	07.09.2014	1	3	20			3			
A	09.09.2014	09.09.2014	1	5	10		5				
A	10.09.2014	10.09.2014	1	6	10		6				
A	11.09.2014	11.09.2014	1	7	10		7				
A	12.09.2014	12.09.2014	1	8	10		8				
A	15.09.2014	15.09.2014	1	11	10		11				
A	16.09.2014	16.09.2014	1	12	5	12					
A	17.09.2014	17.09.2014	1	13	5	13					
A	18.09.2014	18.09.2014	1	14	5	14					
A										3	
A										11	
A									14		
A											15

c. In the SGPLOT, apply one scatter statement per variable transposed with a different symbol, legend label and name if many category

```
Scatter Y= Subj_ID X= AE1
        /Markerattrs=(symbol=circlefilled size=9 color=RED) legendlabel="grade 1/2"
        name="_ae1";
Scatter Y= Subj_ID X= AE2
        /Markerattrs=(symbol=starfilled size=9 color=RED) legendlabel="grade 3/4"
        name="_ae2";

Scatter Y= Subj_ID X= Ong
        /Markerattrs=(symbol=greaterthan size=7 color=Black)
         legendlabel="Treatment ongoing" Name= "_Ong";
```

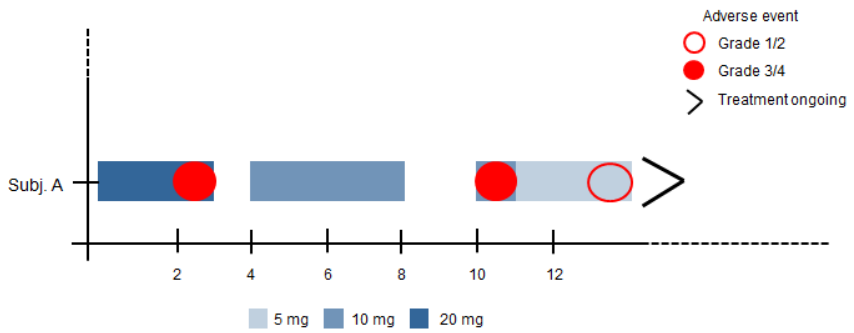
d. Legend: Call the names of previous scatter statement in the desired order:

```
  Keylegend "_ae1" "_ae2" "_Ong"
/LOCATION=inside position=right noborder title="Adverse event" TITLEATTRS=(Size=7)
VALUEATTRS=(Size=7);
```

Final input dataset, procedure and output for subject A:

Subj_ID	Trt5	Trt10	Trt20	AE1	AE2	Ong
A			1			
A			2			
A			3			
A		5				
A		6				
A		7				
A		8				
A		11				
A	12					
A	13					
A	14					
A					3	
A					11	
A				14		
A						15

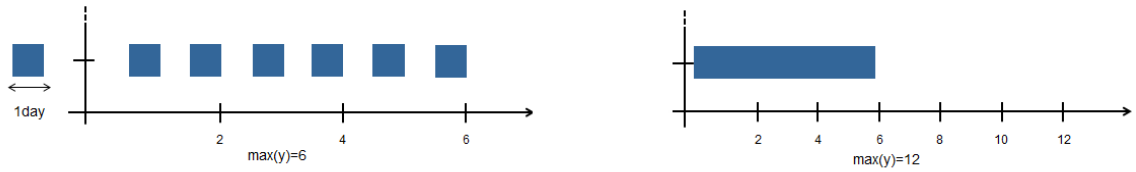
```
Proc sgplot= final_input_dataset;
        Scatter Y= Subj_ID X= Trt5
                /Markerattrs=(symbol=squarefilled size=5 color=GREYE0) legendlabel="5 mg"
                name="doslvl1";
        Scatter Y= Subj_ID X= Trt10
                /Markerattrs=(symbol=squarefilled size=5 color=GREYA0) legendlabel="10 mg"
                name="doslvl2";
        Scatter Y= Subj_ID X= Trt20
                /Markerattrs=(symbol=squarefilled size=5 color= GREY50) legendlabel="20 mg"
                name=" doslvl3";
        Keylegend "doslvl1" "doslvl2" "doslvl3"
                /location=outside position=Top noborder titleattrs=(size=7) valueattrs=(size=7);

        Scatter Y= Subj_ID X= AE1
                /Markerattrs=(symbol=circlefilled size=9 color=RED) legendlabel="Grade 1/2"
                name="_ae1";
        Scatter Y= Subj_ID X= AE2
                /Markerattrs=(symbol=starfilled size=9 color=RED) legendlabel="Grade 3/4"
                name="_ae2";
        Scatter Y= Subj_ID X= Ong
                /Markerattrs=(symbol=greaterthan size=7 color=Black)
                 legendlabel="Treatment ongoing" Name= "_Ong";
        Keylegend "_ae1" "_ae2" "_Ong"
                / location=inside position=right noborder title="Adverse event"
                titleattrs=(Size=7) valueattrs =(Size=7);
        /*Xaxis …*/
        /*Yaxis …*/
Run;
```



X/Y Axis, Control the formatting of the graph:

- X axis: Control the maximum value of durations of exposure:

  To prevent SAS from adjusting automatically the layout, we have fixed the size of the dots. We need to control the size of the x-axis to ensure that a succession of squares looks like a bar.



  Without any control, SAS automatically sets the size of the x-axis to a value a bit higher than the maximum x (example on the left) and it doesn't look like a bar anymore. As we are controling the size of the squares, we can define the corresponding minimum size of the x-axis, in order to get a bar. In the example on the right above, it is set to minx=12.

  Finally, we are defining the length of the x-axis (length_x) as the maximum value between minx and the maximum duration of exposure.

```
Xaxis  label= "Duration of exposure label"  values= (0 to &length_x. by 2) GRID
       valueattrs=(size=7) labelattrs=(size=8);
```

- Y axis: Control the number of patients displayed

  - We define a maximum number of subjects per page. This number also depends on the size of the filledsquare (e.g. for a filled square of size 5, we can display a maximum of 25 subjects)
  - We calculate the number of pages required to present all patients
    nb_page = ceil(total number of patient / 25);
  - Each subject is re-assigned a number corresponding to the corresponding rank it is presented in the output (1 for the patient with the longest duration, 2 for the second longest, etc..)
  - The original subject ID is then displayed using a format (e.g. 1 = subj 13 , 2 = "Subj. 15))

  do i=1 to nb_page by 1;

  min_sbj,=(nb_page - i)*25;
  max_sbj=(nb_page - i)*25+24

  Proc sgplot=final;

  .
  … *Sgplot statements* …
  .

  Yaxis label= "*Subject id label*" values= (***min_sbj*** to ***max_sbj*** by 1)
  valueattrs=(size=7) labelattrs=(size=8);

  run;
end;

➔ Advantage of controlling format by fixing constant values:
  - The layout will be exactly the same throughout pages
    - Same scale across pages
    - All subject exposure are correctly displayed
  - Avoid incorrect automatic adjustment by SAS

LIMITATIONS AND IMPROVMENTS:

Why can't we do a "push button" macro?

The sgplot procedure can easily be included in a macro but due to the variety of designs and their complexities, the way we derive and we display the data is often directly impacted:

- Combination of treatments:
  A subject is taking a combination of two treatments or more, how should it be displayed?
  We can either choose:
  - To present them in two bars within the same page
  - To present them on two different pages
  - To combine them in one bar but we then need to think about the meaning of a dose change / interruption.

- Many different dose levels:
  We used the color to categorize the different dose levels. In early phase studies, it is common to have more than ten different dose levels. In this case, it does not make sense to display all of them. Based on discussions with the clinical team, we can, for example, decide
  - To pool different dose levels together
  - To use different colors to identified only the dose changes (e.g. one color when the dose is taken as planned, one lighter dose for an actual dose lower than the planned dose, etc…)

- Impact of the treatment regimen:
  In a simple case where the regimen is 'OD/QD' (daily dosing), we know that one dot corresponds to one day of exposure. However the exposure for other regimens can be trickier to represent (e.g. 'daily day during two weeks followed by one week of rest'). In those cases, we need to review carefully the definition of the exposure and especially the consideration of the rest period..

Area of improvement:

- Attribute Map: Control attributes of each category (color, symbol, label, …) outside the graph procedure
- SGPLOT restriction: Use GTL to program the graph procedure (a good start would be to generate the GTL template with the option TMPLOUT= in the SGPLOT)

CONCLUSION:

The clinical teams are using the exposure plot to perform some of their data review and also for many presentations (internals and externals) to support their decision making.
In order to accommodate to the constraints caused by live data and non-standard study designs, it was decided to implement this plot in a very controlled manner.
With clinicians' inputs, this plot is generated for all types of study designs and all different combination of exposure information with any other type of events, making this plot one of our most popular and powerful graphs in early phase studies.

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