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Using graphics to review and present PK/PD data for maximum impact

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ABSTRACT

Managing PK/PD data has always been a struggle, from reviewing the raw data to generating NONMEM datasets and presenting results based on them. The complexity is brought about by the wide range of data used, and the various time components that seem to be forever difficult to collect accurately. This paper will show how graphics in various forms based on the SDTM and NONMEM data can be used to review the quality of the raw data, and present the results that are both effective and memorable. It is always disheartening when people leave presentations without remembering the headline message. This paper will show how graphics can make the headline message both memorable, and something that is asked for in the future, bringing PK/PD data to the front at the time decisions need to be made.

INTRODUCTION

Graphics are always a powerful tool to report clinical trial data. It is also used widely to present and review the clinical trial data. During the process of generating the NONMEM data, these graphics can be very useful to identify a meaningful report or to identify any issues with the source data. However, it is always a struggle to find the correct place to use the graphics, for example too much use of graphics can be tedious. In the next few chapters, we will look into the places where we can use graphics for identifying issues in reporting with the maximum impact without compromising the valuable time, and overall improve the NONMEM generating process. Implementation of graphics during the preparation of PK/PD data for complex analysis means that the programmers as well as trial leaders can look past the 'big picture' and see the specific metrics that matter to their studies.

WHAT IS NONMEM DATA AND WHAT ARE THE ISSUES?

Population PK/PD analysis looks at PK and PD data in the body over time. These may be affected by many factors called covariates. What is important is that we know the value of these covariates at the time when the blood samples were taken for measuring the PK and PD results, and here lies the cause of all problems.

Studies are usually set up with either safety or efficacy in mind, not to collect PK or PD data. As a result, these data are cleaned for analysis in the clinical trial report, but not for creating NONMEM datasets. Laboratory data for example may be summarized by visit, and it may have been checked to make sure the visits are in chronological order, but what about whether they were done before or after dosing at that visit? This cross-checking between the various types of data is often missing from traditional checking processes and often leads to problems. Graphics can be a quick solution to these problems and

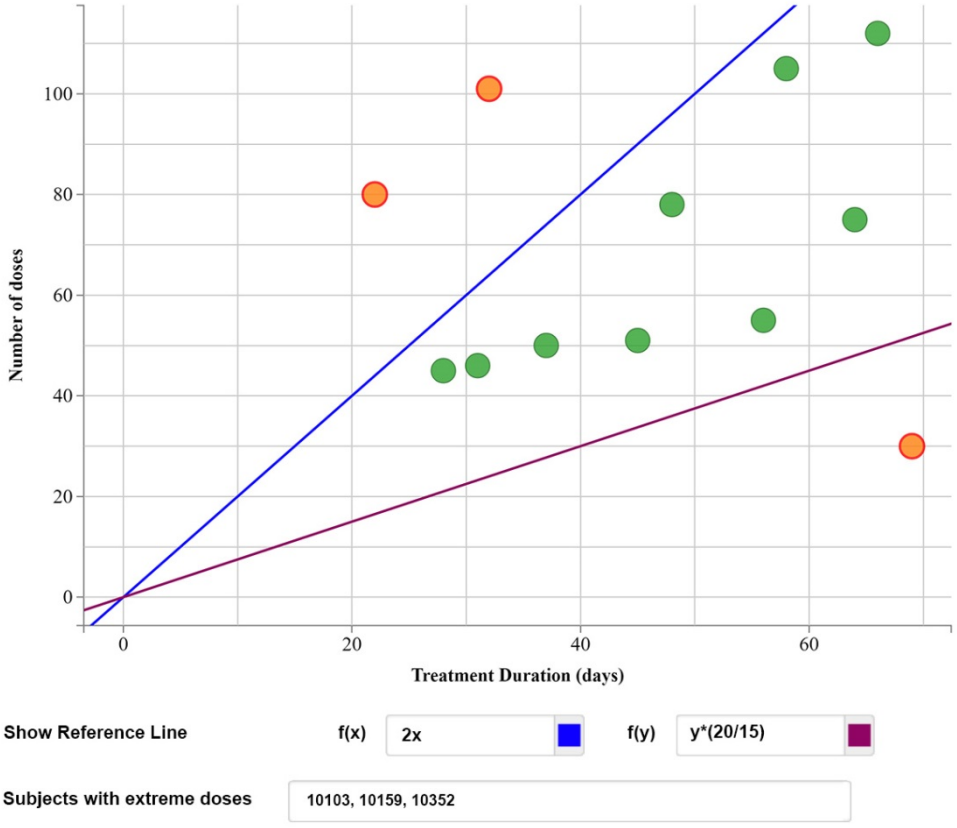
a programmer may avoid serious issues with very little effort by visualizing the real scenario rather than trying to understand the numbers.

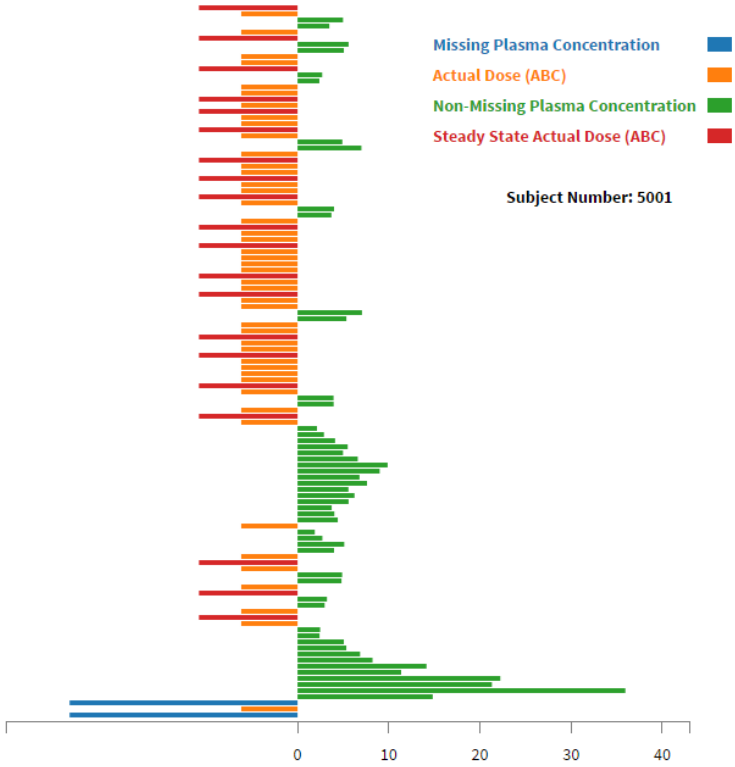
We tried to mimic the SAS ODS capability with some extra facility to select, filter and create charts easily. That will give ability to rerun and recreate the charts with any complex modification.

During the checking of the source datasets, we can easily identify the extreme and unexpected values and quickly identify the position of those values and compare with the situation/surroundings. This will give better estimates/ knowledge about the data rather than showing only numbers.

CHECK DOSING RECORDS

To check the extreme number of dosing according to the treatment duration for patients, we can plot the treatment duration with the number of dosing records. We can set a reference line which can be a straight line x=ay, where x is the number of dosing records taken by a patients and y is the duration of treatment period in day, month or year. 'a' is a constant which we can change to set the expected density of dosing records against treatment duration. We can set the maximum and minimum value for 'a' to check the extreme density of dosing against treatment duration. The extreme values will be presented in a different color and at the bottom of the graphics, patient numbers for these extreme values will be listed. And then we can check the dosing data for those specific patients.





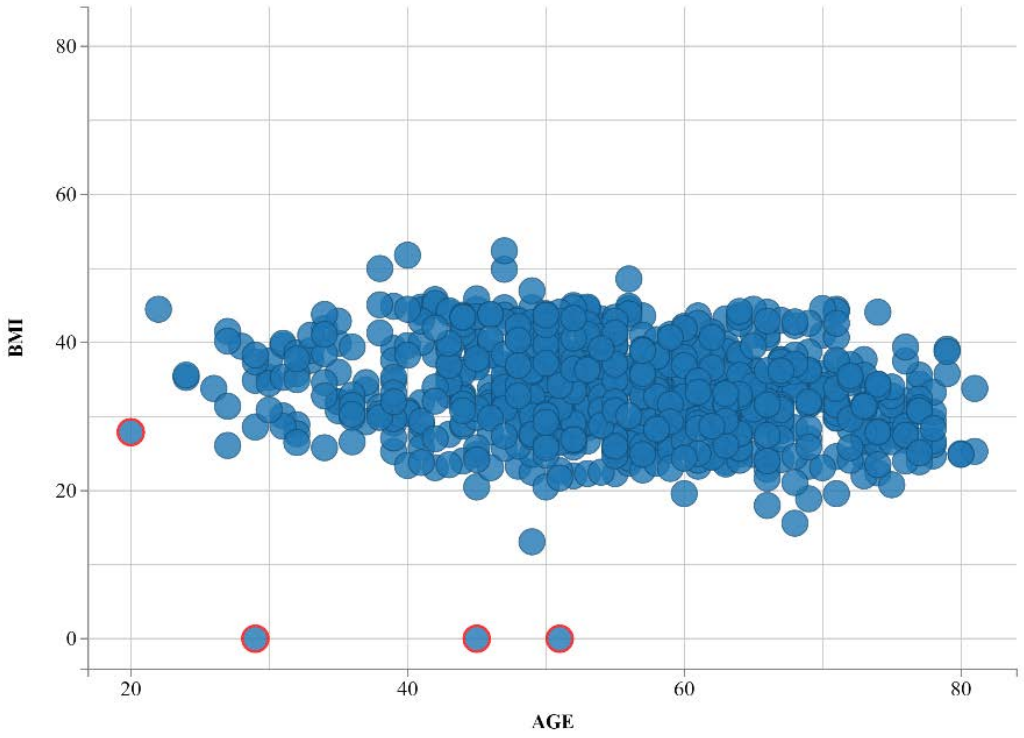
When we combine the dosing records with steady state and PK data, we can plot them by visit to identify any irregularities in the dosing records for a specific subject.

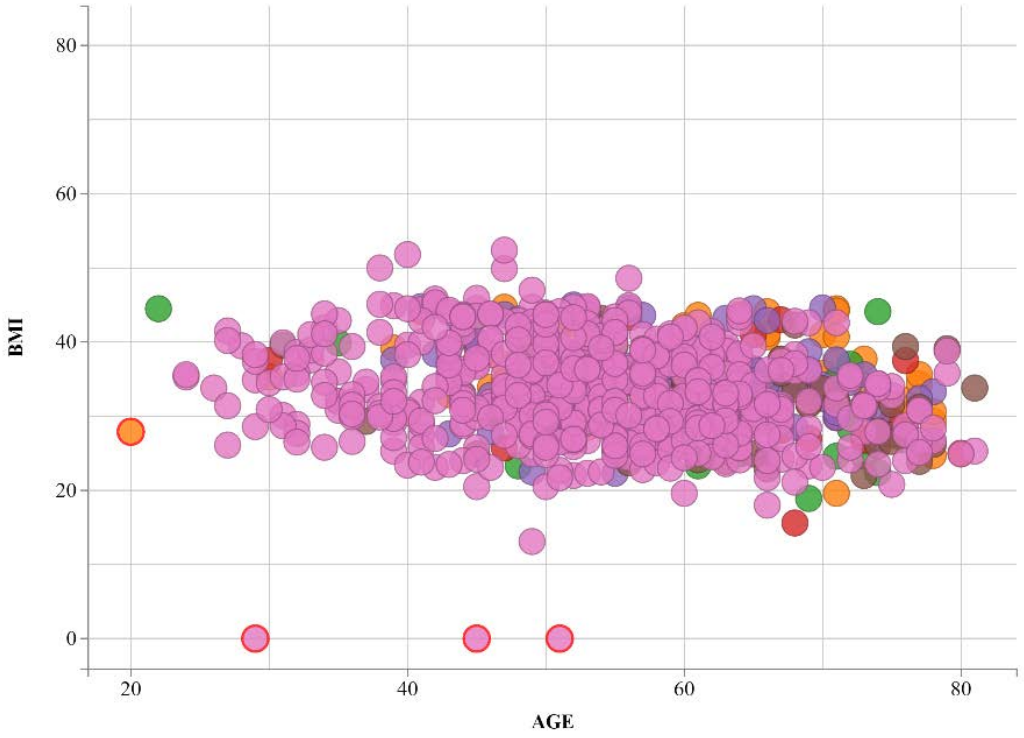
CHECK DEMOGRAPHIC COVARIATES

We can use a scatter plot for checking the demographic variables. If we produce a scatter plot for each subject, we may quickly identify any abnormalities in the variable values. It is also possible to check those values against a predefined set of ranges. If the programmer keeps the ranges fixed for different tests, then they can compare the situation after updating the datasets by replacing missing values or extreme values with predefined rules for the study. This before and after comparison gives a very good idea about the variable's validity after the modification. This also helps grow an impression of correctness by seeing the result instantly rather than waiting to complete the whole dataset and then check for abnormal values and update again.

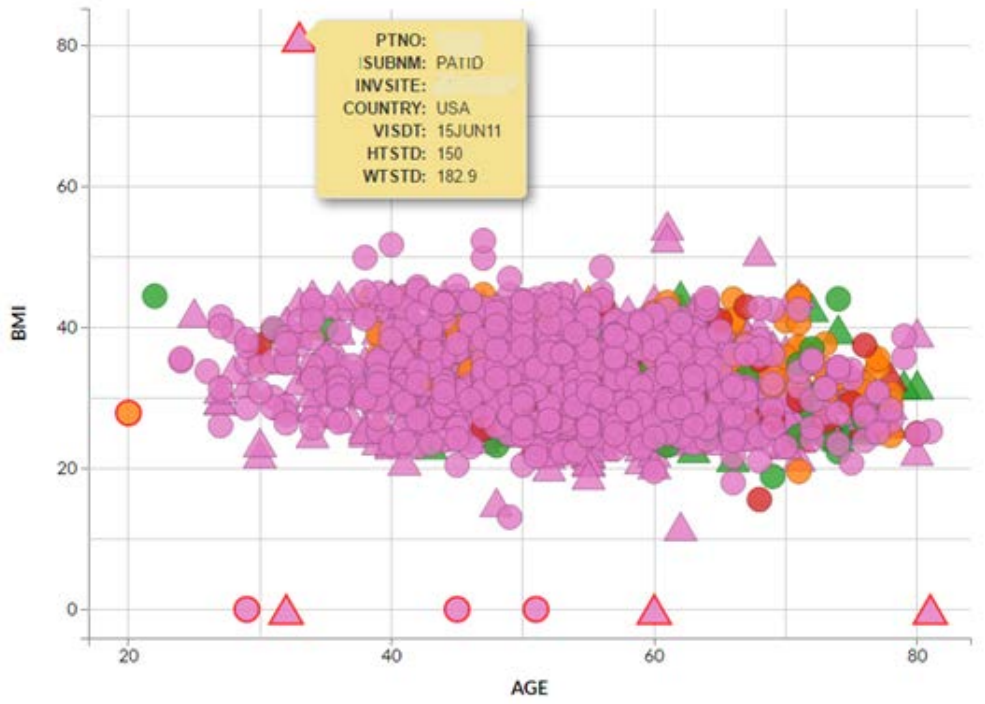
Demographic variables can be checked over time. We can also check the different doses against different demographic variables to identify any early data issues that may exist.

The graphics will allow the user to select the extreme values, allowing them to quickly identify the unique ID for the subject just by selecting those observations in the chart.

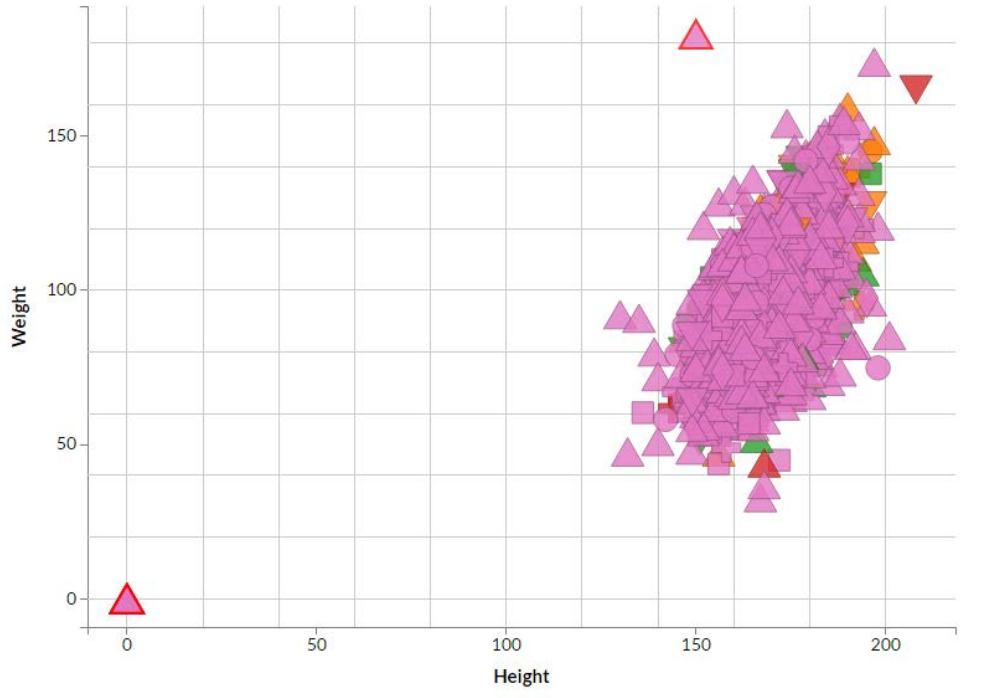




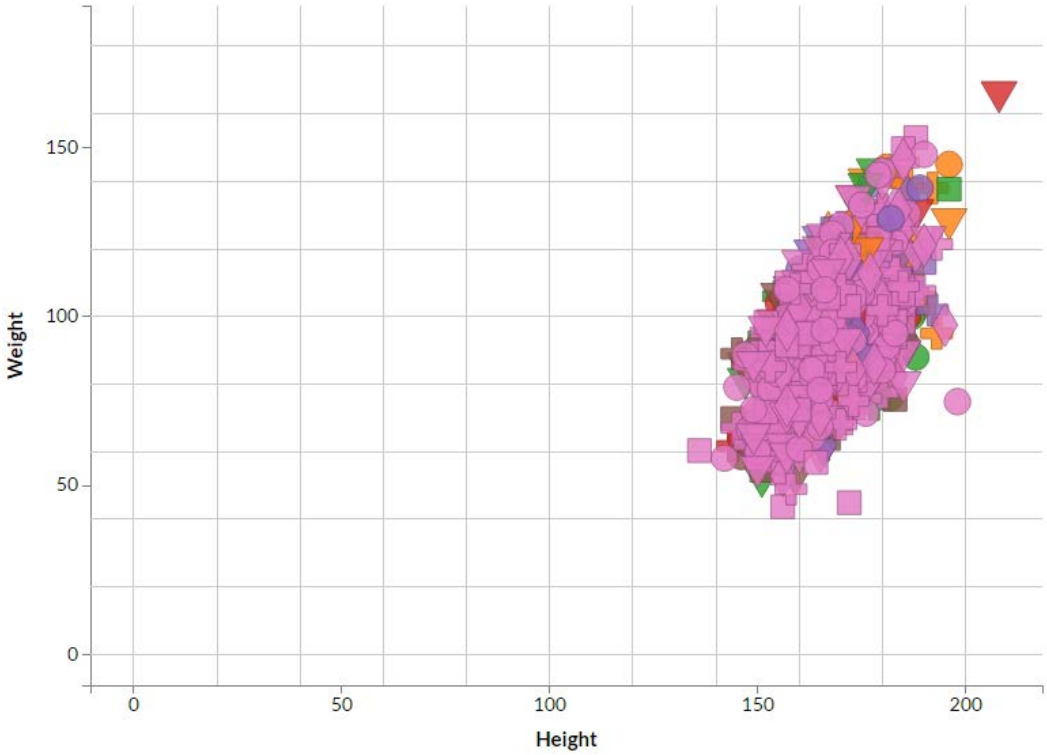
If we consider the age vs. BMI chart, we can quickly identify form the previous chart that at least three subjects might have abnormal BMI values, and who might need special treatment. The programmer can quickly notify the data managers regarding this issue.



A programmer can also quickly identify different attributes for a specific subject which needs attention. For example, in the above chart, hovering over a subject point can reveal information about a particular subject, which might be helpful to quickly identify and to take steps for specific subjects.



Above is another example, where we can clearly see that there are some issues with a few subjects. After handling those subjects' values based on the method described in the protocol, a programmer can recheck if those values are still causing issues or not.



In the above chart, this is the after-chart where all subjects who did not receive any treatment are removed. As a result, the programmer can take any necessary steps to remove such extreme values based on their merit.

CHECK ADVERSE EVENTS

Just after merging the adverse events data, a programmer can check the data at different time points, and check for any irregularities with the adverse events by plotting them in a timeline for each subjects. Besides this, a summary of adverse events can be plotted to identify any extreme or unusual values, which may help the user to identify early data issues. They can also be plotted together with CTs to see if any expected relationships are present.

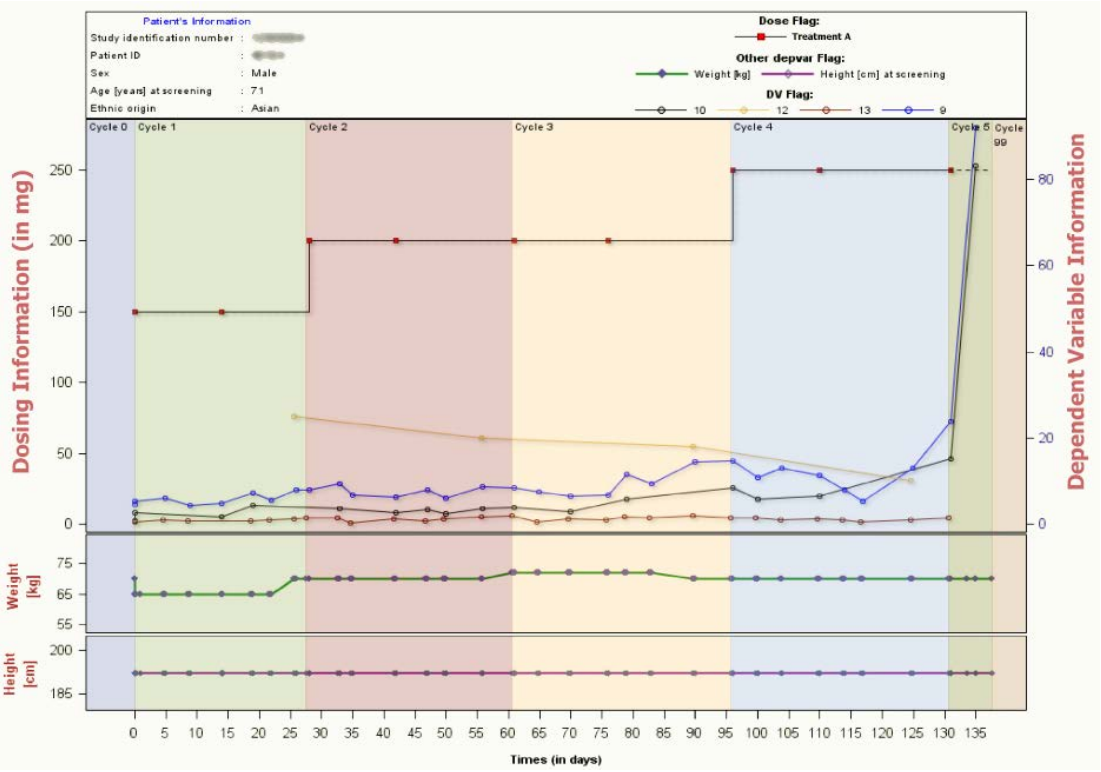
The programmer can also identify any missing time points for AEs in a timeline, when AEs are plotted against time. Then the programmer can check those timelines again when they have the updated data (after data issue is corrected) to ensure there are no more issues.

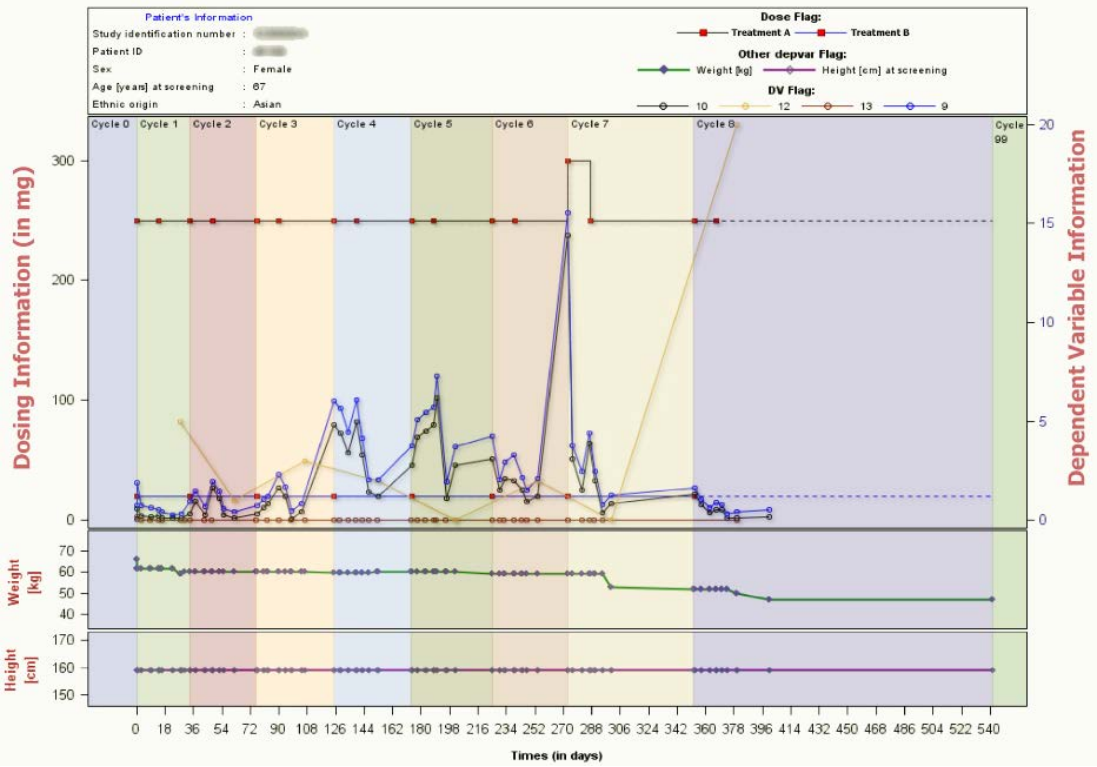
CHECK LABORATORY DATA

When any lab and dosing data is collected over time at different visits, then if the lab visit date is missing then this causes problems during the merge of the data. A programmer can identify early laboratory data issue by plotting each lab variables against each visits in a scatter plot. They can also use a density plot for the summarization, which can give an idea for any abnormalities. Further grouping can be applied to get the precise information and see as to which group the issue lies.

PATIENT PROFILE

When the NONMEM dataset is ready, the programmer can generate a patient profile to get an idea about each subject and quickly identify any issues which remain. It also gives a very good idea about the subjects' different information as demographic, dosing and laboratory and AE/CT are presented in a single chart, to get more knowledge about a subject. It is very easy to create this chart for different users. A programmer can also compare those different situations as they can generate these charts in little time.





CONCLUSION

Using graphical methods mentioned above, outliers can be easily identified in a sea of data. This means that the quality of the source data can be greatly improved, allowing for more accurate analysis results. The use of graphics also gives the analyst a complete overview of the data that is to be analysed, meaning that they are in a better position to develop a more accurate model of the data. As some of these graphics can provide a clear view of relationships between different covariates, the analyst will be able to draw better inference of the data.

Those preparing the NONMEM ready datasets for the Pharmacokineticist should consider providing a graphical interface or pre-prepared graphics together with the datasets. They will not only help the programmer provide a cleaner dataset, but the graphics can help the analyst review what they receive in a more informative manner.

CONTACT INFORMATION

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