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Monitoring Child Growth and Safety Profile using Growth Charts

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ABSTRACT

In child nutritional trials, graphical presentation of subject-level anthropometric parameters over time is useful to visualize child growth trajectory according to age. The trajectories of selected anthropometric parameters are usually evaluated with reference to a growth chart developed using growth standards, such as World Health Organization (WHO) child growth standards. Growth charts provide expected percentile values of the anthropometric parameters based on children of same gender and age-group from the general population. It is usually important in child nutritional trials to monitor the child growth for potential effect of study product feeding, adverse events and concomitant medications. This paper describes step-by-step procedure for plotting subject-level trajectory of an anthropometric parameter during the trial period on the growth chart developed using WHO child growth standards. The chart also displays details of onset of adverse events as well as intake of concomitant medications. It uses PROC GPLOT and SAS Annotate facilities.

INTRODUCTION

Human growth can be divided into the phases of fetal, infant, childhood and pubertal growth. These phases overlap in time and interact with each other, and consequently the growth and development during one phase may influence the other. This potentially makes monitoring of child growth during infancy clinically important. For example, there is evidence that rapid rate of weight gain during infancy may lead to obesity later in the childhood and could result in cardiovascular diseases later in the life [1].

A typical child growth chart consists of smooth curves of an anthropometric parameter (e.g., weight, height, upper arm circumference) plotted against age or another anthropometric parameter. The curves represent a set of percentile values (e.g., 97th, 90th, 75th, 50th, 25th, 10th and 3rd percentiles) or values corresponding to standard deviation scores (e.g., 1, 2, 3 SD above/below reference mean or median value) of the parameter based on data of same gender at various ages based on local or multi-country general population.

For child nutritional trials, it is usually important to monitor child growth for various anthropometric parameters with reference to child growth charts developed using child growth standards based on local or close to local population. When local population based child growth standards are not available, often the World Health Organization (WHO) child growth standards, developed based on multi-country data, is preferred as the reference [1]. To monitor individual study subject's growth in context of an anthropometric parameter, measurement values of the parameter are plotted on the corresponding child growth chart of that parameter (e.g., using WHO child growth standards) and compared with its 50th percentile curve across various time points (age at the measurement collection time points). If the subject's own measurement values systematically fall above the 50th percentile of the growth chart, it is inferred that the subject had gained weight more than expected according to the reference population and vice versa. However, it may not be considered as clinically significant weight gain (or loss) unless the subject's own weight crosses the pre-specified higher (or lower) percentile of the growth chart (e.g., 75th percentile) or pre-specified margin of standard deviation score (e.g., 2 SD) above (or below) the 50th percentile value. Usual expectation is that subjects should stay relatively consistent in their growth pattern. In nutritional trials, adverse events and/or intake of concomitant medications could also affect child growth. Hence, often clinicians are interested to see onset of adverse events (AEs) and intake of concomitant medication on the subject-level trajectory of anthropometric parameters during the trial period. In this paper, our aim is to demonstrate a step-by-step procedure for plotting subject-level trajectory of an anthropometric parameter on a growth chart developed using the WHO child growth standards and also displaying onset of AEs and intake of concomitant medications with their descriptions on the same chart. The final chart would look like the graph below:

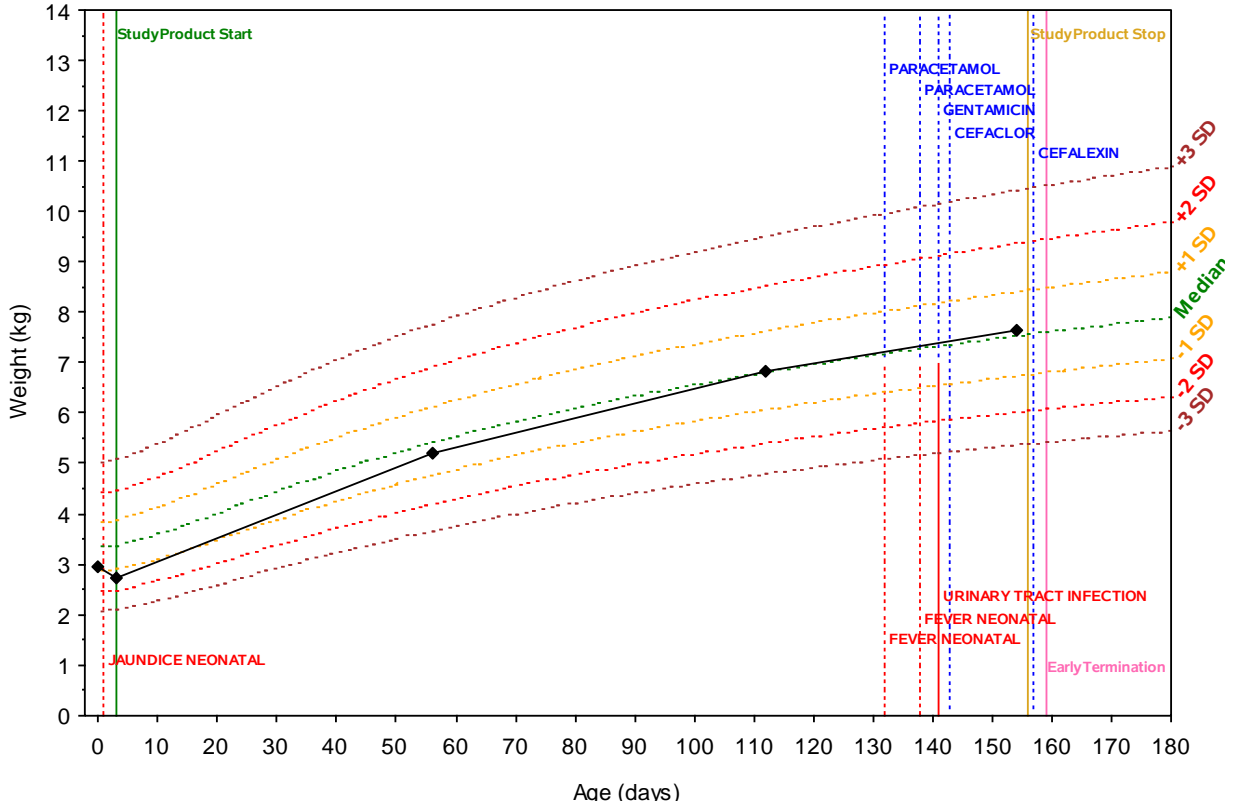


Figure 1: Subject's weight over age with reference to the WHO child growth standards

The bottom most dotted curve touching at -3 SD on the secondary Y-axis shows reference values for weight-for-age according to WHO child growth standards corresponding to -3 SD below 50th percentile value. Similarly, the other dotted lines show expected weight-for-age at various standard deviation scores higher/below 50th percentile value for the same gender children in the general population. The black solid line is the subject's own weight trajectory over the trial period. Texts in red color show adverse event description and adjacent red vertical dotted lines show corresponding adverse event onset time-points. Similarly, the texts and vertical dotted lines in blue color show information on intake of concomitant medications.

KEY WORDS: Growth charts, Safety profile, PROC GPLOT, Axis statement, Symbol statement, SAS annotation.

DATA OVERVIEW

In this paper, we are considering body weight as the anthropometric parameter of interest for male children (SEX=1) during birth to 180 days of age.

1. For plotting WHO child growth standards reference lines (median and ± 3 SD, ± 2 SD, ± 1 SD from median), we need dataset 'weianthro.sas7bdat' having variables SEX, AGE, L, M, S (explained later in detail). This can be downloaded from *WHO Child Growth Standards - SAS igrowup* package from the WHO website [2].
2. To get the subjects safety profile as well as body weight variable in to one dataset, we require:

Dataset A: Subject level dataset with unique subject identifier (USUBJID), gender (SEX), date of birth (BRTHDT) and other study product related information - study product start date (TRTSTDT), study product stop date (TRTENDT), early study termination date (EARLDT);

1	USUBJID	SEX	BRTHDT	TRTSTDT	TRTENDT	EARLDT
2	101	1	6-Mar-2012	9-Mar-2012	9-Aug-2012	12-Aug-2012

Dataset B: Adverse events dataset with USUBJID, AE onset date (AESTDT), AE preferred term (AEPT), a flag variable (AESER) to indicate an AE as a serious adverse event (SAE) where (AESER='YES' for SAEs);

1	USUBJID	AESER	AESTDT	AAPT
2	101		7-Mar-2012	Jaundice neonatal(AE)
3	101		16-Jul-2012	Fever neonatal(AE)
4	101		22-Jul-2012	Fever neonatal(AE)
5	101	YES	25-Jul-2012	Urinary tract infection(SAE)

Dataset C: Concomitant medications dataset with USUBJID, concomitant medication start date (CMSTDT); concomitant medication generic name (CMTERM);

1	USUBJID	CMSTDT	CMTERM
2	101	16-Jul-2012	PARACETAMOL
3	101	22-Jul-2012	PARACETAMOL
4	101	25-Jul-2012	GENTAMICIN
5	101	27-Jul-2012	CEFACTOR
6	101	10-Aug-2012	CEFALEXIN

Dataset D: Anthropometric dataset with USUBJID, subject weight in kg (WT) and weight measurement date (WTDT) for each weight data collection study visits.

1	USUBJID	WT	WTDT
2	101	2.94	6-Mar-2012
3	101	2.72	9-Mar-2012
4	101	4.91	1-May-2012
5	101	6.34	26-Jun-2012
6	101	7.13	8-Aug-2012

In the each of the above datasets (A, B, C, D), add a variable AGE using formula $AGE = VARDT - BRTHDT$. Here *VARDT* represents TRTSTD, TRTENDT, and EARLDT for dataset A; AESTDT for dataset B; CMSTDT for dataset C and WTDT for dataset D. In order to add AGE variable corresponding to variables TRTSTD, TRTENDT, EARLDT one dataset, one may need to first create three datasets, say A1, A2 and A3 with AGE variable corresponding to TRTSTD, TRTENDT, EARLDT and then merge in to single dataset using AGE as 'by' variable. During this process, do create 3 flag variables (SPSTART, SPSTOP, and EARLTERM) with the value 'YES' to indicate value in AGE variables either correspond to TRTSTD, TRTENDT or EARLDT. Merge the updated dataset A, B, C and D into a single dataset, say ALL, using AGE as 'by' variable. The dataset ALL would have the structure displayed below:

1	USUBJID	SEX	AGE	SPSTART	SPSTOP	EARLTERM	WT	AAPT	AESER	CMTERM
2	101	1	0				2.94			
3	101	1	1					Jaundice neonatal		
4	101	1	3	Yes			2.72			
5	101	1	56				5.21			
6	101	1	112				6.83			
7	101	1	132					Fever neonatal		PARACETAMOL
8	101	1	138					Fever neonatal		PARACETAMOL
9	101	1	141					Urinary tract infection	YES	GENTAMICIN
10	101	1	143							CEFACTOR
11	101	1	154				7.63			
12	101	1	156		Yes					
13	101	1	157							CEFALEXIN
14	101	1	159			Yes				

PROGRAMMING OVERVIEW

CONSTRUCTION OF WHO GROWTH STANDARDS REFERENCE LINES

WHO growth standards are developed to provide standard deviation scores (also called Z-scores) using on LMS method [3]. WHO growth standards provide values of L, M and S parameters for series of age-groups for both male and female children. Thus, by supplying subject's weight, age and gender to LMS method formula, $Z\text{-score} = [(Weight/M)^{-1}]/(L*S)$, one can obtain Z-score. It is useful to assess whether the subject weight is higher or lower than the median weight of children from general population with same gender and age-group, and to what extent. Alternatively, we can also calculate weight corresponding to a given Z-score using formula $Weight = M(1 + L*S*Z\text{-score})^{1/L}$ and compare with subject's weight. For comparing subject's weight at various study visits, we use the later approach. We calculate the weights corresponding to 0, ±1, ±2 and ±3 WHO child growth standards Z-score for male population at ages corresponding time from birth to the study visits. These serve as WHO child growth standards reference lines. The line corresponding to 0 Z-score represents 50th percentile (median) of population weight for male children.

Below are sample data steps to calculate weights for plotting the reference lines:

```
libname _reflib "C:\WHO\igrowup_sas";
data sdz(keep=SEX AGE sd:);
  set _reflib.weianthro(where=(SEX=1 and AGE le 180));
  array sdx(7) sd3neg sd2neg sdneg sd0 sdlpos sd2pos sd3pos;
```

```

do _i=-3 to 3;
  sdx[_i+4]=m*((1+_i*1*s)**(1/l));
end;
run;

```

Now, the reference lines are plotted using PROC GPLOT statements mentioned as below:

```

proc gplot data=sdz gout=myplot;
  plot (sd3neg sd2neg sd1neg sd0 sd1pos sd2pos sd3pos)*AGE/overlay frame
  name="sdplt";
run;
quit;

```

Below is a sample output:

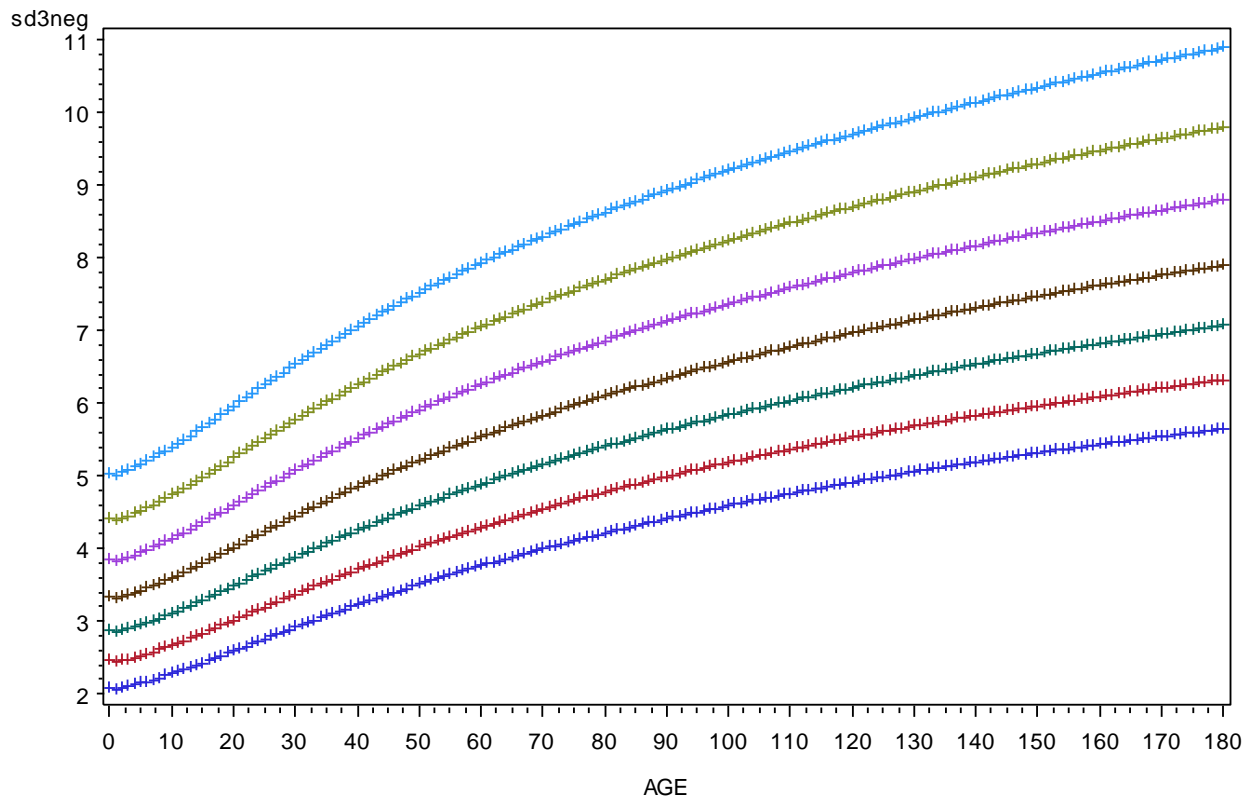


Figure 2: Using GPLOT procedure with OVERLAY option, we can plot multiple variables against the single time variable (AGE) in same graph

The display settings of the plotted reference lines can be changed using SYMBOL statements mentioned below:

```

symbol1 interpol=spline width=1 color=brown line=33;
symbol2 interpol=spline width=1 color=red line=33;
symbol3 interpol=spline width=1 color=orange line=33;
symbol4 interpol=spline width=1 color=green line=33;
symbol5 interpol=spline width=1 color=orange line=33;
symbol6 interpol=spline width=1 color=red line=33;
symbol7 interpol=spline width=1 color=brown line=33;

```

Here SYMBOL1 is used for sd3neg, SYMBOL2 is for sd2neg and so on as mentioned in the PROC GPLOT step above.

The X and Y axis display characteristics can be adjusted by adding AXIS statements mentioned below:

```
axis1 order=(0 to 180 by 10) major=(height=.3) length=87 pct minor=none
offset=(1,0) label=(height=1 'Age (days)');
axis2 order=(0 to 14 by 1) minor=(height=.2 number=1) offset=(0,0) label=( angle=90
height=1 'Weight (kg)');
```

Now the PLOT statement should be updated in the PROC GPLOT statements above to reflect the changes in axis settings. It should be now:

```
plot (sd3neg sd2neg sdlneg sd0 sdlpos sd2pos sd3pos)*AGE / overlay frame
name="sdplt" haxis=axis1 vaxis=axis2;
```

Below is the sample output after updating PLOT statement.

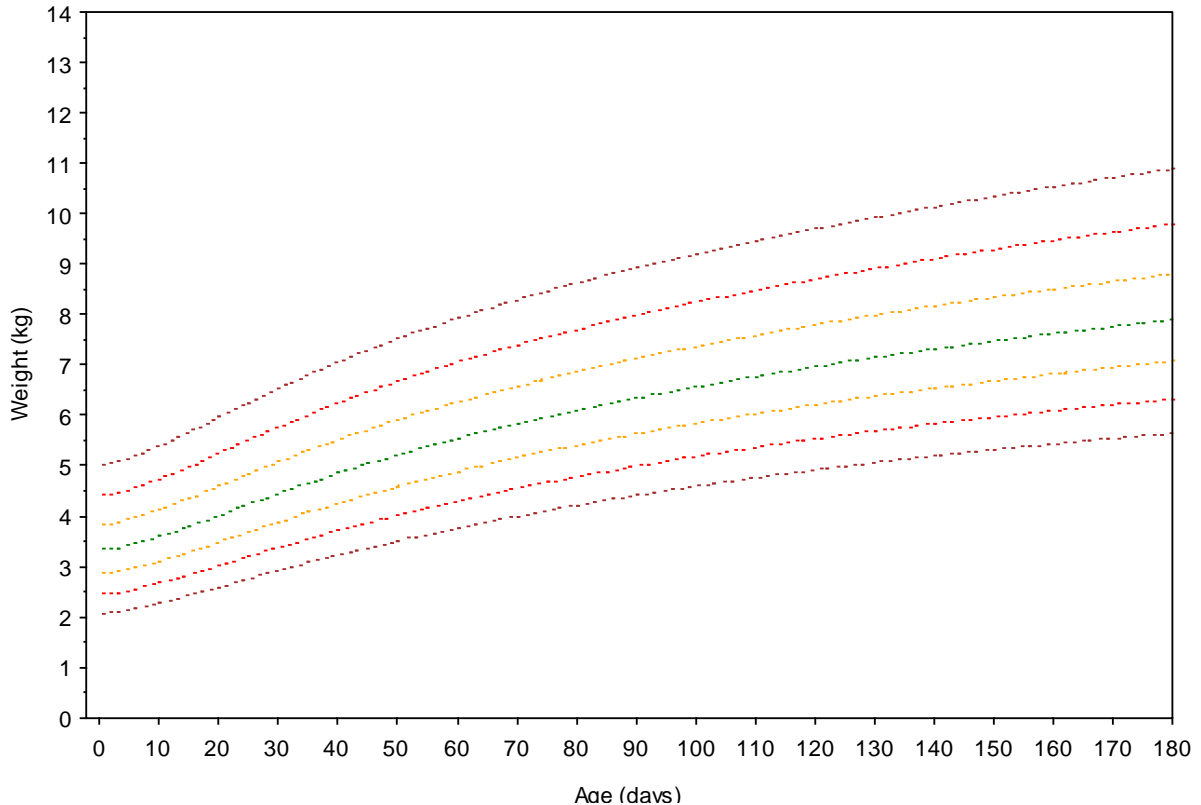


Figure 3: Modified the display settings by SYMBOL and AXIS statements

Now, we name the reference lines with the same color using the annotation facility.

```
/* Create the Annotate data set LINETEXT */
data linetext;
length function color $ 10 text $ 30 style $ 25;
retain xsys '2' ysys '1' hsys '1' position '6' size 1;

set all end=last;
style = "'Albany AMT/bold'";
cborder='';

if last then do;
xsys='2'; ysys='2'; hsys='3'; position='6'; size=2.5;
x=age; angle=50;
y=sd3neg; text=' -3 SD'; color='brown'; output;
y=sd2neg; text=' -2 SD'; color='red'; output;
y=sdlneg; text=' -1 SD'; color='orange'; output;
y=sd0; text=' Median'; color='green'; output;
```

```

y=sd1pos; text=' +1 SD'; color='orange'; output;
y=sd2pos; text=' +2 SD'; color='red'; output;
y=sd3pos; text=' +3 SD'; color='brown'; output;
end;
run;

```

Again, the PLOT statement in the PROC GPLOT step should be updated to reflect the above changes:

```

plot (sd3neg sd2neg sd1neg sd0 sd1pos sd2pos sd3pos)*AGE / overlay frame name="sdz"
      haxis=axis1 vaxis=axis2 annotate=linetext;

```

Below is the sample output after updating PLOT statement.

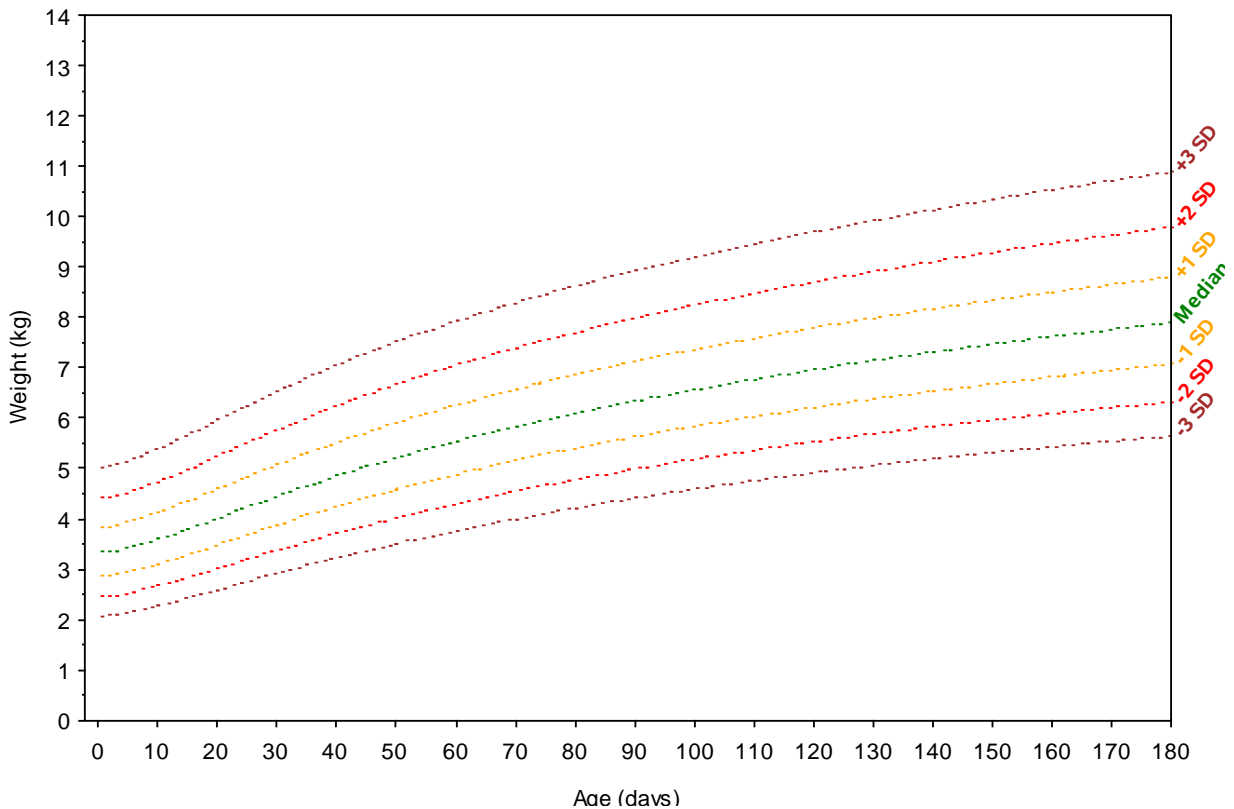


Figure 4: Added reference line legends on secondary vertical axis with the same colors as the lines

ADDING SUBJECT WEIGHT AND SAFETY PROFILE

Now it's time to add subject information on the plot. For this, the standard deviations dataset (SDZ) should be merged with subject profile dataset (ALL) by AGE. It also requires adding the subject weight variable (WT) to the PLOT statement. Moreover, additional SYMBOL statement should be added to change the display of subject weight line to solid black line connected by dots - representing the subject's weight measured at that age. The SYMBOL statement could be:

```

symbol8 interpol=join width=1 color=black line=1 v=diamondfilled;

```

and updated PLOT statement should be:

```

proc gplot data=all1 gout=myplot;

```

```
plot (sd3neg sd2neg sd1neg sd0 sd1pos sd2pos sd3pos wt)*AGE / overlay frame
name="sdplt" haxis=axis1 vaxis=axis2 annotate=linetext;
```

Below is a sample output after updated PLOT statement.

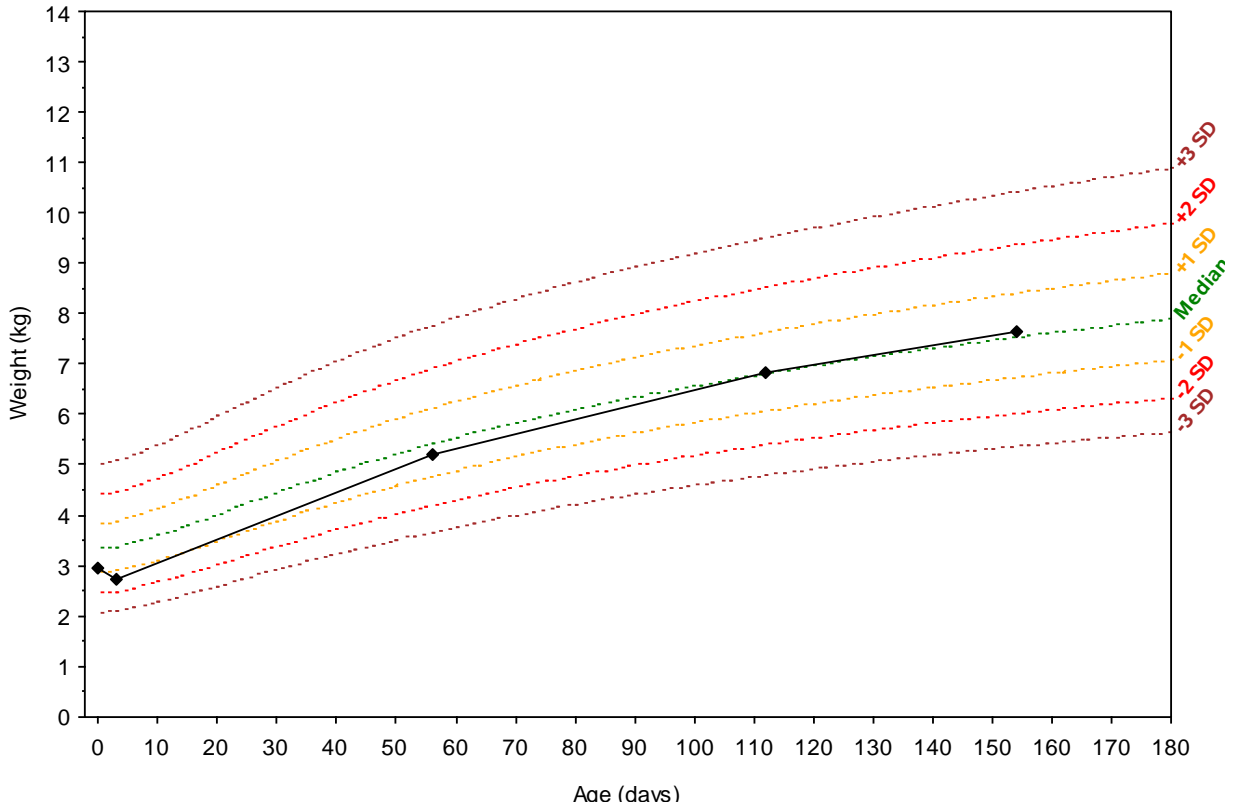


Figure 5: Added subject's weight in the plot

Now we add the subject exposure and safety information on the above chart. Study product start (SPSTART), study product stop (SPSTOP) and early termination (EARLTERM) information are represented by solid vertical lines of different colors at age of their occurrence.

AE preferred term (AEPT) and CM generic name (CMTERM) are represented by dotted vertical lines of red and blue colors respectively at age of their occurrence.

Serious adverse events (AEPT at AESR='YES') are represented by solid vertical lines with the same color as AEPT. In case an AE start date and CM start date occur on the same day, both shares the same line. CM terms are displayed in downward step style from the top of the chart area. (S)AE terms are displayed in upward step style from bottom of chart area. Please see Figure 1.

The above information can be added in the chart by amending the annotate dataset as below:

```
/* Create the Annotate data set LINETEXT */
data linetext;*(drop=age sex sd:);
length function color $ 10 text $ 30 style $ 25;
retain xsys '2' ysys '1' hsys '1' position '6' size 1;

set all end=last;
style = "'Albany AMT/bold'";
if SPstart ne '' then do;
  function='move'; x=age; y=0; output;
  function='draw'; x=age; y=100; size=.1; color='Green'; line=1; output;
```

```

function='label'; x=age+.5; y=97; size=2.2; color='Green'; angle=0;
text=strip('Study Product Start'); output;
end;
if SPstop ne '' then do;
function='move'; x=age; y=0; output;
function='draw'; x=age; y=100; size=.1; color='Goldenrod'; line=1; output;
function='label'; x=age+.5; y=97; size=2.2; color='Goldenrod'; angle=0;
text=strip('Study Product Stop'); output;
end;
if earlterm ne '' then do;
function='move'; x=age; y=0; output;
function='draw'; x=age; y=100; size=.1; color='hotpink'; line=1; output;
function='label'; x=age+.5; y=7; size=2.2; color='hotpink'; angle=0;
text=strip('Early Termination'); output;
end;
cborder='';
if aeptx ne '' then a+1;
if cmptx ne '' then c+1;

/* AE and CM both occurs at same age*/
if aeptx ne '' and cmptx ne '' then do;
if aeptx ne '' and aeser ne '' then do;
function='move'; x=age; y=0; output;
function='draw'; x=age; y=50; size=.1; color='Red'; line=1; output;
function='label'; x=age+.8; y=5+(a*3); size=2; color='Red'; angle=0;
text=uppercase(strip(aeptx)); output;
end;
else if aeptx ne '' then do;
function='move'; x=age; y=0; output;
function='draw'; x=age; y=50; size=.1; color='Red'; line=2; output;
function='label'; x=age+.8; y=5+(a*3); size=2; color='Red'; angle=0;
text=uppercase(strip(aeptx)); output;
end;
if cmptx ne '' then do;
function='move'; x=age; y=51; output;
function='draw'; x=age; y=100; size=.1; color='Blue'; line=2; output;
function='label'; x=age+.8; y=95-(c*3); size=2; color='Blue'; angle=0;
text=uppercase(strip(cmptx)); output;
end;
end;

/* AE or CM occurs at different ages*/
else do;
if aeptx ne '' then do;
if aeptx ne '' and aeser ne '' then do;
function='move'; x=age; y=0; output;
function='draw'; x=age; y=100; size=.1; color='Red'; line=1; output;
function='label'; x=age+.8; y=5+(a*3); size=2; color='Red'; angle=0;
text=uppercase(strip(aeptx)); output;
end;
else if aeptx ne '' then do;
function='move'; x=age; y=0; output;
function='draw'; x=age; y=100; size=.1; color='Red'; line=2; output;
function='label'; x=age+.8; y=5+(a*3); size=2; color='Red'; angle=0;
text=uppercase(strip(aeptx)); output;
end;
end;
if cmptx ne '' then do;
function='move'; x=age; y=1; output;
function='draw'; x=age; y=100; size=.1; color='Blue'; line=2; output;
function='label'; x=age+.8; y=95-(c*3); size=2; color='Blue'; angle=0;
text=uppercase(strip(cmptx)); output;
end;
end;

```



```

end;

if last then do;
  xsys='2'; ysys='2'; hsys='3'; position='6'; size=2.5;
  x=age; angle=50;
  y=sd3neg; text=' -3 SD'; color='brown'; output;
  y=sd2neg; text=' -2 SD'; color='red'; output;
  y=sd1neg; text=' -1 SD'; color='orange'; output;
  y=sd0; text=' Median'; color='green'; output;
  y=sd1pos; text=' +1 SD'; color='orange'; output;
  y=sd2pos; text=' +2 SD'; color='red'; output;
  y=sd3pos; text=' +3 SD'; color='brown'; output;
end;
run;

```

The PROC GPLOT statement with the update annotated dataset would give the chart displayed in Figure 1. Similar charts can be prepared for female subjects and other anthropometric parameters.

CONCLUSION

The paper presented a step-by-step procedure for plotting a subject level trajectory of an anthropometric parameter values on the population based growth chart. The chart also displays information on potential covariates affecting the subject's growth such as study product start/stop date, onset of adverse events, intake of concomitant medications. This subject level chart could be useful for monitoring the subject's growth in the context of selected anthropometric parameter during the trial period, especially in child nutritional trials. This idea can be extended to other therapeutic areas and/or clinical monitoring - such as monitoring laboratory values over time with reference to normal ranges.

REFERENCES

- [1] Stettler N, Zemel BS, Kumanyika S, Stallings VA. Infant weight gain and childhood overweight status in a multicenter cohort study. *Pediatrics* 2002;109(2):194-199.
- [2] The WHO Child Growth Standards (<http://www.who.int/childgrowth/en/>, accessed on 7th April 2014).
- [3] Cole TJ. The LMS method for constructing normalized growth standards. *European Journal of Clinical Nutrition* 1990;44(1):45-60.

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