

Evaluating Anthropometric Growth Endpoints with Z-Scores and Percentiles

Snehal Sanas, Pradeep Umapathi, Covance by Labcorp

ABSTRACT

Disease conditions in children can potentially affect a child's growth and development, hence an effective treatment for them is required to sufficiently demonstrate improvement, not only in disease condition but also in growth pattern. Unlike adults, assessment of drug safety and efficacy in children requires specific consideration of the impact of treatment on child growth.

Measuring overall child development can be a 'complex task', as it involves evaluating anthropometric measures like weight, height, head circumference and mid-upper arm circumference at different stages of development. Clinical trials involving pediatric populations need to have composite efficacy endpoints to account for the impact on growth. WHO and CDC have established worldwide anthropometric data standards against which a child's growth can be validated and conclusions can be drawn as to whether the child is growing correctly or has any growth issues.

This paper aims to understand the rationale behind data collected by WHO and CDC, what are Z-scores and percentiles, how to calculate Z-scores and percentiles, how to include this reference data into programs for statistical analysis and also how these are interpreted to evaluate growth. These standards have been used in clinical trials to demonstrate growth related drug efficacy, across various therapeutic areas as unique as rare congenital enzyme deficiencies to pediatric cardiology. This paper attempts to describe a case for implementing Z-scores and percentiles into clinical trials using a macro in SAS and also to touch base on how this approach is useful, not only in clinical trials but also in general assessment of a child's growth by pediatricians and health care providers.

INTRODUCTION

Pediatric illnesses have additional aspects to be addressed by treatments, compared to those in adults. Given the developing age of patients these treatments can potentially impact a child's growth and development. With children, physiology is constantly altering and upgrading. This changing physiology causes differences in the body's response to medication, compared with an adult. Thus, these treatments not only need to heal the pathophysiology, but also not to interrupt the growth processes. Pediatric treatments are required to sufficiently demonstrate improved or unaffected growth.

For such clinical trials, ICH Guidance E11 (Clinical Investigation of Medicinal Products in the Pediatric Population) and E11 (R1) (Addendum to ICH E11) has emphasized on determining possible effects on skeletal, behavioral, cognitive, sexual and immune maturation and development in pediatric patients. As a result, pediatric trials are required to have appropriate growth indicators as part of the composite efficacy endpoints to account for impact on growth.

The scope of this paper includes understanding and using Anthropometric Growth Indicators in Pediatric trials for assessing the effects on skeletal development of pediatric patients.

ANTHROPOMETRIC GROWTH INDICATORS

The term 'Anthropometric' comes from the Greek words Anthropos meaning 'Human' and matron meaning 'Measure' respectively.

Anthropometric measurements can be broadly categorized into measurements of Structural dimensions and measurements of Functional dimensions. Structural dimensions (Figure 1) are static body measurements such as height or weight. Whereas Functional dimensions (Figure 2) are dynamic measurements which gauge a person's ability to perform a particular action, such as the angle of shoulder rotation. The following are images illustrating these measurements:

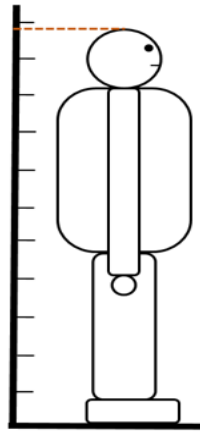


Figure 1: Height Measurement

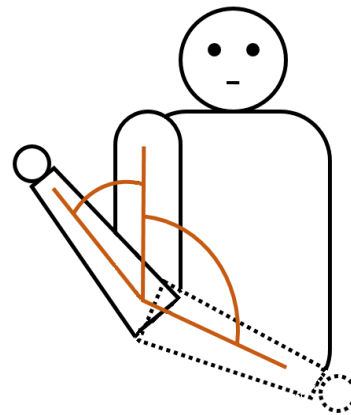


Figure 2: Shoulder Rotation Measurement

Measuring 'Anthropometric' growth is a complex task, as it involves monitoring multiple interdependent parameters. For example, let us consider a 3-year-old boy who weighs 10 kg and is 65 cm in height, however for his age the average weight of someone similar is approximately 11-18 kg and average height is approximately 89-103 cm. This apparently indicates underdevelopment compared with their expected height and weight, however is his current weight appropriate to his current height, is his weight properly distributed across his body, is his weight appropriate for his muscle and fat content, is his skeletal development proportionate, and how many children in a similar population are showing such a growth pattern. Answering all these question can help in concluding if the given boy is overall underdeveloped or his weight is appropriate but skeletal development is slow and so on.

To tackle this challenge, efforts have been made to provide guidance standards and reference databases so that growth can be compared and evaluated. In 1977 NCHS (National Center for Health Statistics, US) developed growth charts from reference data as a tool for pediatricians, so that child growth can be evaluated. In 2000 CDC (Center for Disease Control) further revised and upgraded these charts with additional parameters and based on the data collected from a wider national population. These charts were also adopted by WHO (World Health Organization) for international use, however there was a need to build up databanks considering various population groups around the globe, for having better accuracy in assessment of growth. The WHO conducted a Multicenter Growth Reference Study (MGRS) from July 1997 to December 2003. This study was carried out at 6 sites worldwide, Davis, California, USA; Muscat, Oman; Oslo, Norway; Pelotas, Brazil; Accra, Ghana; South Delhi, India. It involved a sample size of 8440 children who lived in socioeconomic conditions favorable to growth and where mobility was low. Data was recorded for the following anthropometric parameters; weight, recumbent length or height, head circumference, arm circumference, triceps skinfolds (aged ≥ 3 months), and subscapular skinfolds (aged ≥ 3 months).

After in-depth quality checks, data was analyzed and detailed validation reports, descriptive statistics tables and plots were produced. Growth indicators such as length/height-for-age, weight-for-age, weight-for-length, weight-for-height, body mass index-for-age, head circumference-for-age, arm circumference-for-age, triceps skinfold-for-age and subscapular skinfold-for-age were established from the statistical analysis of the collected database. Growth curves or growth charts with z-scores and percentiles for the above indicators were developed for multiple age groups gender-wise. The database and resulting growth curves and growth charts were released as standards by WHO in 2006. The following are some example of growth charts (Figure 3, Figure 4):

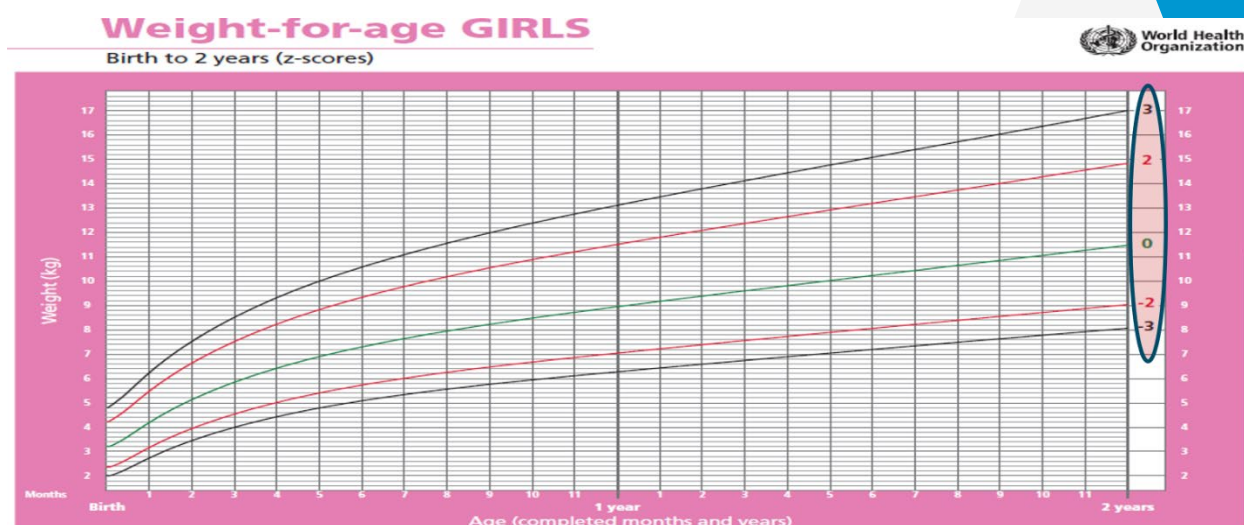


Figure 3: Z-scores Growth Chart

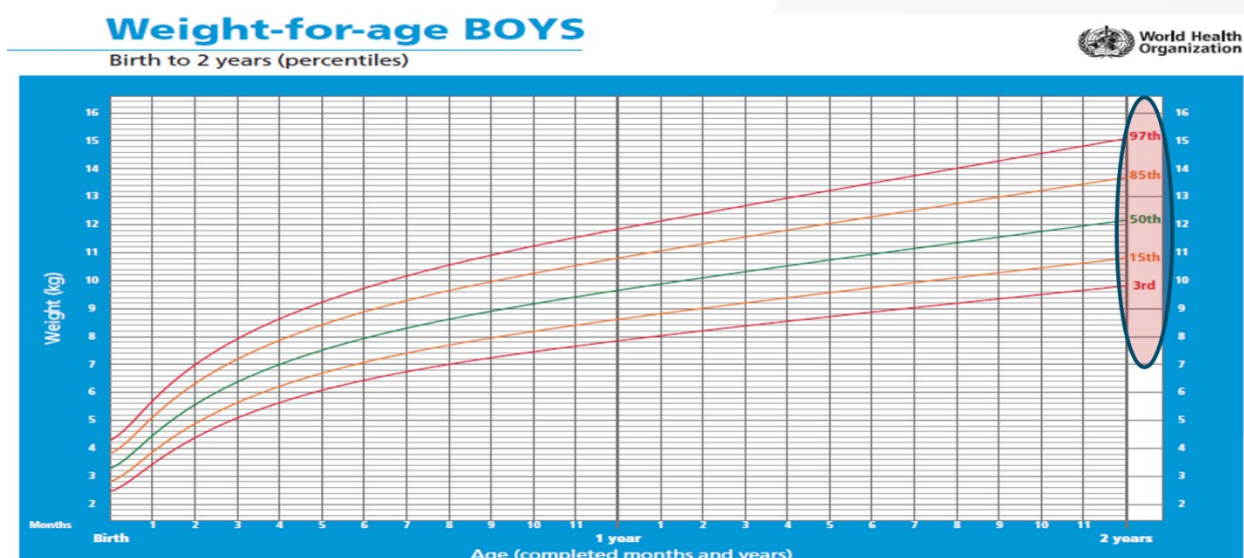


Figure 4: Percentiles Growth Chart

Z-SCORES AND PERCENTILES

The z-score is the deviation from the median value of the reference population, divided by the standard deviation of the reference population. Z-scores describe how far a measurement is from the median (average) measurement of the reference population.

A percentile is the value below which a percentage of the data falls. A percentile for an individual's measurement (such as height) indicates what percent of the reference population the individual's measurement would equal or exceed. For every z-score there is a corresponding percentile and vice versa. The following is a hypothetical data distribution plotted to illustrate z-scores and cumulative percentiles (Figure 5):

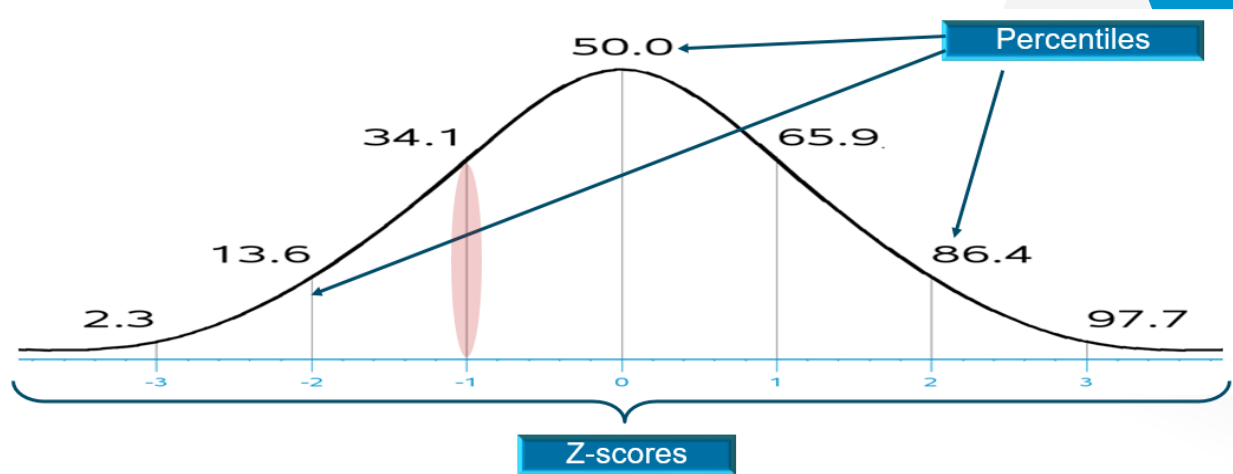


Figure 5: A normal bell shaped curve cut into Z-score segments

The z-score for a body measurement in this distribution is calculated as follows:

$$\text{z-score} = (\text{observed value}) - (\text{median reference value}) / \text{z-score of the reference population}$$

For example, assuming that the above distribution is for weights of girls aged 12 to 24 months with median reference value of weight as 9.5 kg and reference z-score as 1; for a 15-month old girl weighing 8.5 kg 'weight-for-age z-score' is calculated as;

$$\text{z-score} = (8.5 - 9.5) / 1 = -1$$

Z-score of -1 indicates weight related growth for the girl is less than average for her age and corresponding percentile of 34.1 indicates her weight-for-age growth equals or exceeds 34.1% of the studied reference population.

The analyzed data from WHO's MGRS when presented as a graph form a very user friendly tool to access growth for pediatricians, nurses and parents; below are some illustrative examples:

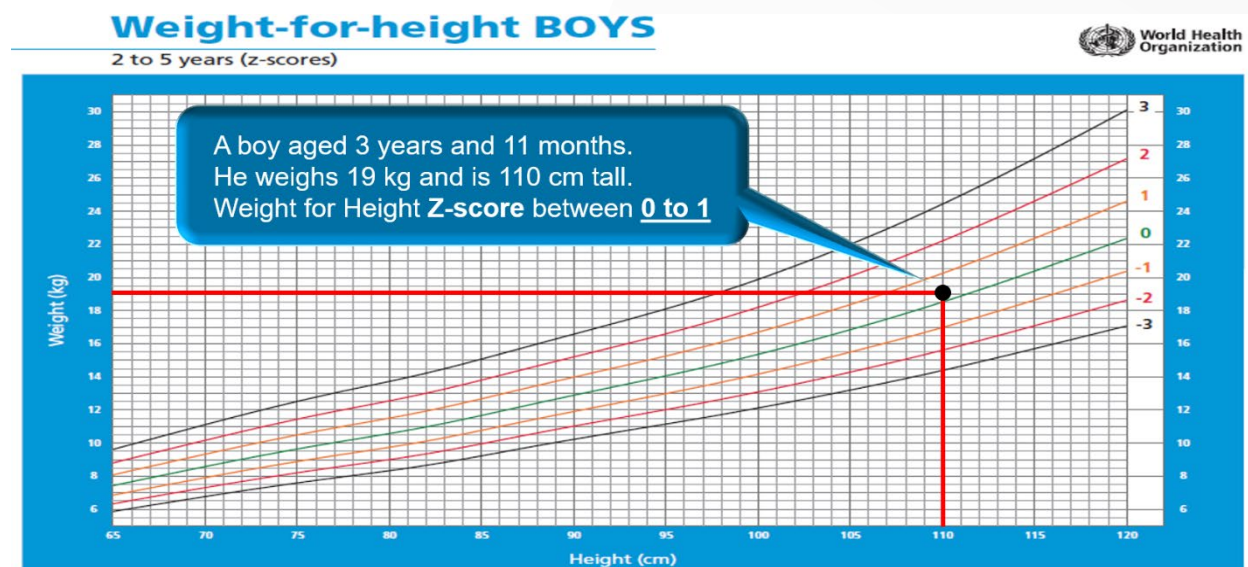


Figure 6: Interpretation of Z-score on Growth Chart

The above example (Figure 6) uses measurements of weight and height to get an approximate idea of the z-score and an overview clinical impression that the boy's weight for his height is over the average.

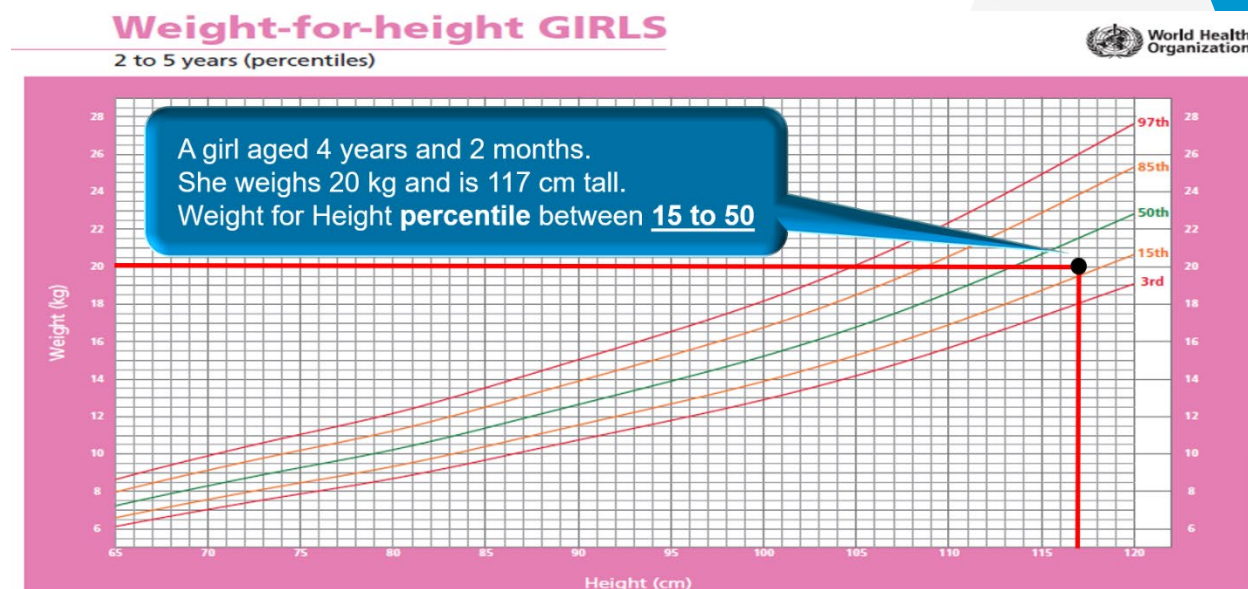


Figure 7: Interpretation of Percentile on Growth Chart

The above example (Figure 7) uses measurements of weight and height to get an approximate idea of the percentile and an overview clinical impression that the girl's weight for her height is between 15% and 50% of the reference population.

CLINICAL IMPLEMENTATION OF Z-SCORES AND PERCENTILES

As discussed above it is essential for clinical trial protocols to include anthropometric indicators as additional efficacy end points wherever appropriate. The following section describes methodologies to implement anthropometric evaluation as clinical end points.

For a hypothetical clinical trial of medicinal product 'X' being evaluated for indication 'Y' in a pediatric population falling in the age group of up to 2 years; the study protocol is designed to evaluate safety and efficacy of the medication for improving a pathological condition. Along with this the study also evaluates the impact of medication on the weight as well as height development of the participating population. Data is collected for weight and height of the patient over the course of treatment at the following time points: Day0/Baseline, every 15 days up to months 2, every other month up to month 20, and the end of treatment visit at month 24.

In order to utilize collected data of weight and height, z-scores can be calculated by using WHO's standard reference database and the resulting values can be summarized and presented using any necessary tables, listings and figures. For the purpose of processing any of the collected measurements from WHO's standard reference database, WHO has also provided a utility set containing a SAS executable macro 'igrowup_standard' and all required documentation to be able to implement this macro. This macro processes the collected data against data sets containing the WHO Child Growth Standards and produces the z-scores output files. The following flow chart provides the flow of data using this macro to generate z-scores of the collected data (Figure 8):

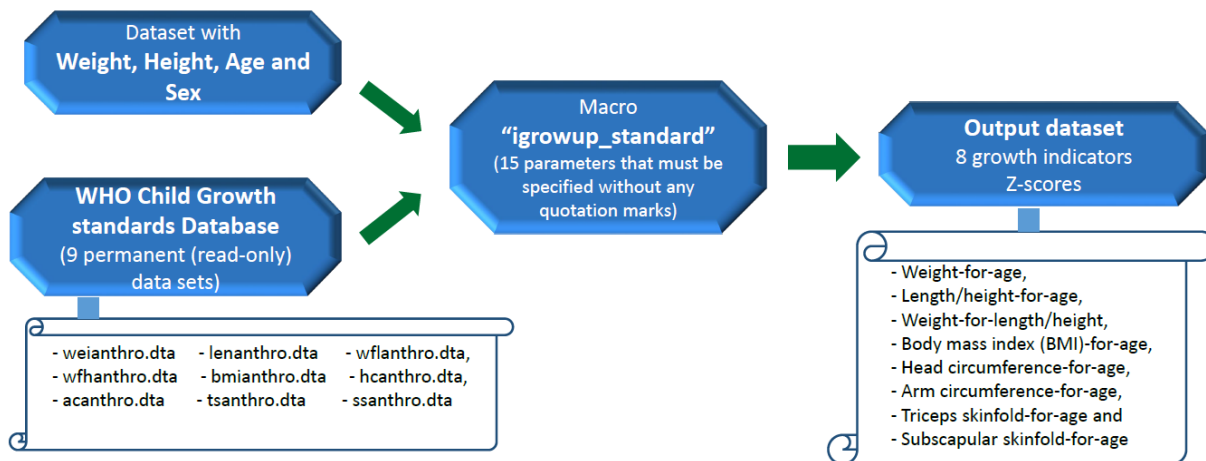


Figure 8: Data flow using WHO's 'igrowup_standard' macro

This macro has 15 parameters which indicate which anthropometric measurements are to be processed and calculates z-scores for the respective anthropometric measurements. The following is a sample call to invoke the macro followed by a description of the macro parameters:

```
%igrowup_standard (reflib= REFDATALIB,
                  datalib= OUDATALIB,
                  datalab= _AP,
                  sex= SEXN,
                  age= AGE_M,
                  ageunit= months,
                  weight=WEIGHT_Kg,
                  lenhei=HEIGHT_cm,
                  headc=,
                  armc=,
                  triskin=,
                  subskin=,
                  measure=,
                  oedema=,
                  sw=);
```

reflib: SAS Library/Directory with reference data.

datalib: SAS Library/Directory for input data / output data set.

datalab: Prefix for output files.

sex: Name of a variable containing sex information. If it is a numeric variable, its values must be, 1 for males and 2 for females. And if it is a character variable, it must be, "m" or "M" for males and "f" or "F" for females.

age: Name of a numeric variable containing age information. Age can be in either days or months.

ageunit: Unit of the age variable. It must be specified as either "days" or "months" (they are case sensitive).

weight: Name of a numeric variable containing body weight information, which must be in kilograms.

lenhei: Name of a numeric variable containing length (recumbent) or height (standing) information, which must be in centimeters.

headc: Name of a numeric variable containing the head circumference information, which must be in centimeters.

armc: Name of a numeric variable containing the mid-upper arm circumference information, which must be in centimeters.

triskin: Name of a numeric variable containing the triceps skinfold information, which must be in millimeters.

subskin: Name of a numeric variable containing the subscapular skinfold information, which must be in millimeters.

measure: Name of a character variable indicating whether recumbent length or standing height was measured. The values of this variable must be "I" or "L" for recumbent length, and "h" or "H" for standing height.

oedema: Name of the character variable containing oedema information. The values of this variable must be "n" or "N" for non-oedema, and "y" or "Y" for oedema.

sw: Name of a numeric variable containing the sampling weights.

Users must code any missing values as "." for numeric variables and as " " for character variables.

The output data sets from macro retains all the records and variables from input data set and adds on the following 19 variables derived by the macro (Table 1).

_agedays : calculated age in days for deriving z score	
_clenhei : converted length/height (cm) for deriving z score	
_cbmi : calculated bmi=weight / squared(_clenhei)	
_zwei : Weight-for-age z-score	_fwei : Flag for _zwei < -6 or _zwei > 5
_zlen : Length/height-for-age z-score	_flen : Flag for _zlen < -6 or _zlen > 6
_zwfl : Weight-for-length/height z-score	_fwfl : Flag for _zwfl < -5 or _zwfl > 5
_zbmi : BMI-for-age z-score	_fbmi : Flag for _zbmi < -5 or _zbmi > 5
_zhc : Head circumference-for-age z-score	_fhc : Flag for _zhc < -5 or _zhc > 5
_zac : Arm circumference-for-age z-score	_fac : Flag for _zac < -5 or _zac > 5
_zts : Triceps skinfold-for-age z-score	_fts : Flag for _zts < -5 or _zts > 5
_zss : Subscapular skinfold-for-age z-score	_fss : Flag for _zss < -5 or _zss > 5

Table 1: Z-scores output Data Set Variable name: Variable label

The variables containing z-scores are to be used to calculate percentiles. The z-scores and percentiles can be further listed, summarized and plotted as per the Statistical Analysis Plan. The following are example summary outputs:

Listing of z-scores and percentiles displayed subject wise can provide information on how subject's weight and height have changed over the course of treatment (Figure 9).

Listing of Weight for Age and Height for Age (Z-scores and Percentiles) by Subject

Visit	Weight (Kg)	Height (cm)	Weight for age (Z-score)	Weight for age (Percentile)	Height for Age (Z-score)	Height for Age (Percentile)
Subject : 005, Sex: Female, Age at the time of Enrollment: 25 months						
Day 0/Baseline	10.0	82.1	-1.3	9.7	-1.4	8.1
Month 0.5	10.6	82.6	-0.9	18.4	-1.3	9.7
Month 1	10.9	83.0	-0.7	24.2	-1.3	9.7
Month 1.5	11.2	83.7	-0.5	30.9	-1.2	11.5
Month 2	11.8	84.0	-0.2	42.1	-1.3	9.7
Month 3	12.0	84.9	-0.2	42.1	-1.2	11.5
Month 4	13.7	85.9	0.7	75.8	-1.2	11.5
Month 5	14.0	87.0	0.8	78.8	-1.0	15.9
Month 6	14.3	87.2	0.8	78.8	-1.2	11.5
Month 8	14.3	88.7	0.6	72.6	-1.2	11.5
Month 10	14.6	89.9	0.5	69.1	-1.2	11.5
Month 12	15.1	90.6	0.6	72.6	-1.3	9.7
Month 14	15.6	91.9	0.6	72.6	-1.3	9.7
Month 16	15.7	94.8	0.4	65.5	-0.9	18.4
Month 18	16.9	98.8	0.8	78.8	-0.2	42.1
Month 20	17.3	103	0.8	78.8	0.4	65.5
Month 24/EOT	16.9	105	0.3	61.8	0.4	65.5

Figure 9: Listing of Z-scores and Percentiles

Summary tables with descriptive statistics on z-scores and percentiles can provide understanding about the drug's effect on the overall study population (Figure 10).

Summary of Anthropometric (Weight for Age and Height for Age) parameters

Visit	n	Mean Weight for Age (Z-score)	Mean Weight for Age (Percentile)	Mean Height for Age (Z-score)	Mean Height for Age (Percentile)
Day 0/Baseline	10	-1.12	25.38	-1.17	22.15
Month 0.5	10	-1.09	25.97	-1.19	22.24
Month 1	10	-0.98	27.18	-1.14	22.16
Month 1.5	10	-0.71	31.92	-1.10	22.59
Month 2	10	-0.43	39.93	-1.07	23.37
Month 3	10	-0.57	39.38	-0.94	24.52
Month 4	10	-0.46	41.59	-0.91	25.04
Month 5	10	-0.32	45.23	-0.73	28.12
Month 6	10	-0.24	47.21	-0.61	31.40
Month 8	10	-0.27	46.50	-0.62	31.93
Month 10	10	-0.16	48.43	-0.63	32.51
Month 12	10	-0.06	50.89	-0.61	32.88
Month 14	10	0.04	53.46	-0.53	34.65
Month 16	10	0.00	51.80	-0.35	38.66
Month 18	10	0.11	54.80	-0.10	46.20
Month 20	10	0.27	59.68	0.14	54.08
Month 24/ EOT	10	0.17	56.19	0.09	53.42

Figure 10: Summary table of Z-scores and Percentiles

Percentile line plots by subject can visualize an individual subject's growth (Figure 11).

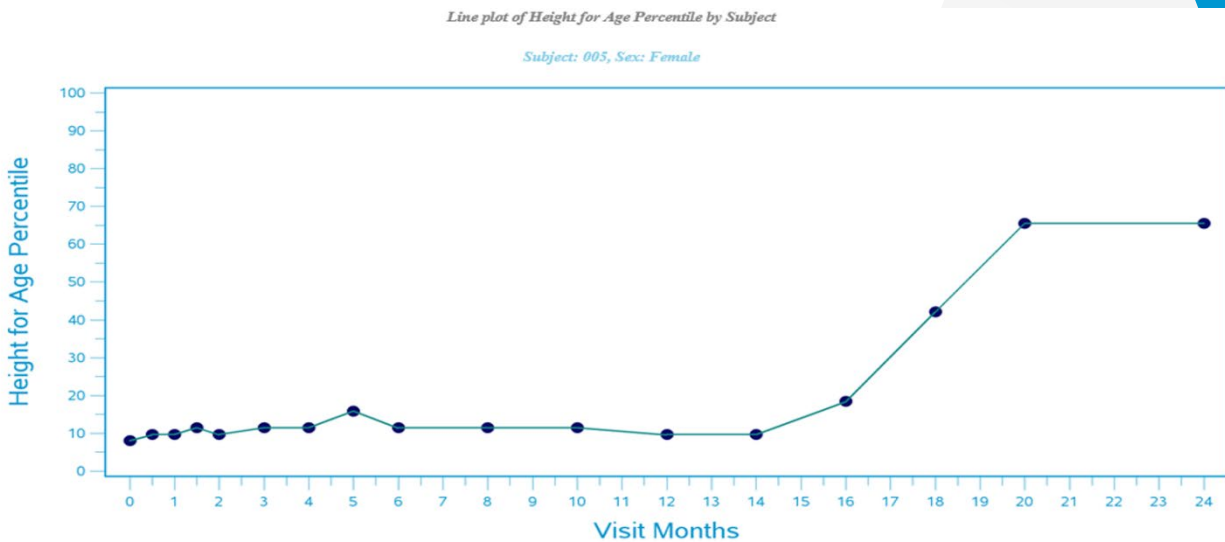


Figure 11: Line plot of Percentiles

Scatter plot of percentiles for study population can visualize trends of effect on growth of study population (Figure 12).

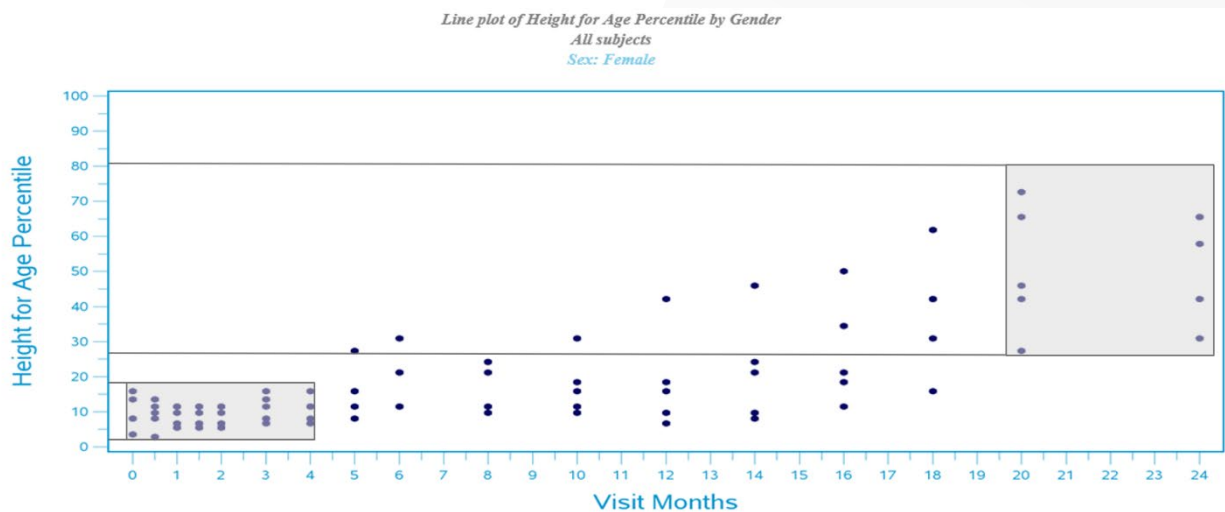


Figure 12: Scatter plot of Percentiles

MERITS

- Recording anthropometric measurements is an inexpensive approach to monitor effects on skeletal growth. Some of these measurements are routine in a clinical trial, such as height, weight.
- The tools required for data collection are easy to use and do not require any specialized skill.

- With these relatively easy to record measurements entire study population can be assessed for a given end point.
- WHO's standard database eliminates any need of multiple age or sex based normal ranges to be tabulated in data sets.
- As WHO's MGRS was conducted including global sample size and multiple groups, comparative assessment is possible.

LIMITATIONS

- As the WHO's MGRS was conducted in study populations living in socioeconomic conditions favorable to growth, over diagnosis of growth failure in children from developing countries is a possibility.
- This can also lead to incorrect diagnosis in children with non-supportive growth conditions.
- Regular updates to the WHO's database are required with further wider categorization of data on the basis of various population groups.
- More local growth databases specific to particular populations are required for more accurate assessment.

Following are some country specific databases utilized;

USA: CDC, WHO growth chart based assessment up 2 years

UK: WHO growth chart based assessment up 4 years

India: WHO growth chart based assessment, other local databases like Indian Academy of Pediatrics (IAP) are also available.

CONCLUSION

Z-scores and percentiles are useful for assessing growth related drug efficacy across various therapeutic areas. Z-scores and percentiles are also useful for the general assessment of child growth by pediatricians, health care providers, as well as for diagnosis of growth failure.

For children in developing age, z-scores and percentiles for growth indicators are sensitive to changes in pathological conditions and thus are an important tool to evaluate growth related efficacy of a medicinal product in pediatric trials.

REFERENCES

Training Courses and Instruction documents on Child Growth Assessment, World Health Organization. <http://www.who.int/childgrowth/training/en/>.

Multicenter Growth Reference Study (MGRS), World Health Organization. <http://www.who.int/childgrowth/publications/en/>

WHO Child Growth Standards STATA igrowup package. <http://www.who.int/growthref/tools/en/> and <http://www.who.int/childgrowth/software/en/>

Frequently Asked Questions About the 2000 CDC Growth Charts. https://www.cdc.gov/growthcharts/growthchart_faq.htm

Daniel K. Benjamin, Jr., Steven Hirschfeld, Coleen K. Cunningham and Ross E. McKinney, Jr. 2004. "Growth as a part of the composite endpoint in paediatric antiretroviral clinical trials." *Journal of Antimicrobial Chemotherapy*, 54, 701–703.

Vaman Khadilkar, Anuradha Khadilkar. 2011 Sep; 15. "Growth charts: A diagnostic tool." *Indian J. Endocrinol Metab.*, (Suppl3): S166–S171.

Henry Chubb, John M Simpson. 2012 Jul-Dec. "The use of Z-scores in paediatric cardiology." *Ann. Pediatr Cardiol.*, 5(2): 179–184.

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the authors at:

Snehal Sanas
Principal Statistical Programmer
Covance by Labcorp
snehal.sanas@covance.com

Pradeep Umapathi
Associate Director Statistical Programming
Covance by Labcorp
pradeep.umapathi@covance.com

Any brand and product names are trademarks of their respective companies.