Evaluating Anthropometric Growth Endpoints with Z-Scores and Percentiles

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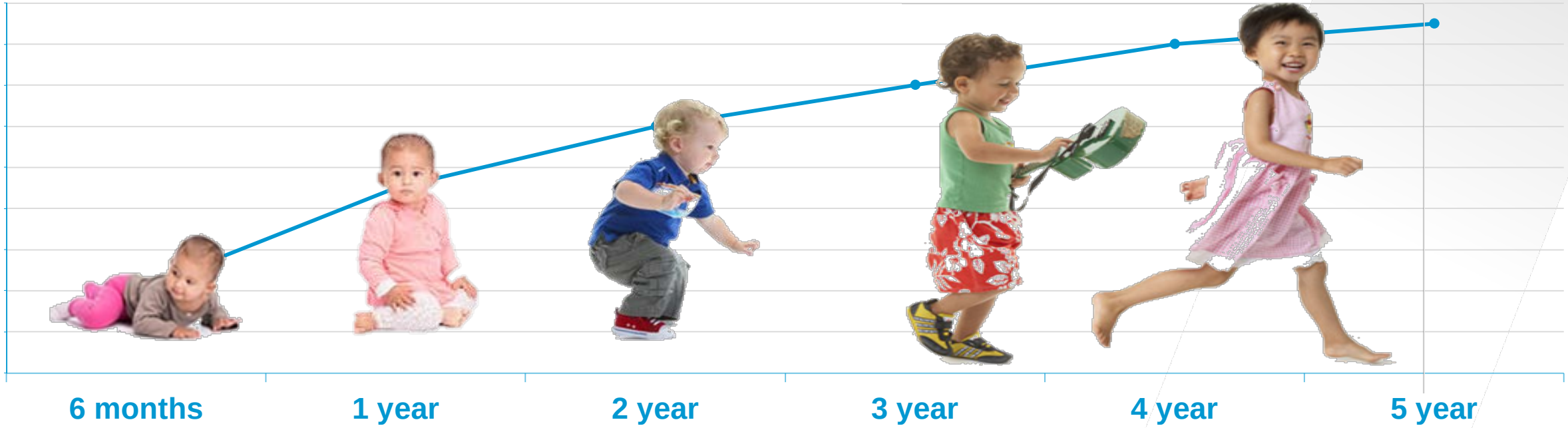
Agenda

By the end of the this presentation you will have known:

- ***Importance of growth evaluation in pediatric trails***
- ***Complexity of measuring Anthropometric Growth***
- ***WHO Growth database and Growth charts***
- ***Z-scores and Percentiles***
- ***Clinical Implementation as efficacy end points***
- ***Merits and Limitations***



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Growth Evaluation in Pediatric Trials

- **Pediatric illnesses can affect a child's growth & development**.
- Changing physiology of a child causes **difference in body's response to medicine as compared to that in an adult**.
- Pediatric Treatments should **sufficiently demonstrate improved or unaffected growth.**
- **ICH Guidance E11** (Clinical Investigation of Medicinal Products in the Pediatric Population) has emphasized on determining **possible effects on skeletal, behavioral, cognitive, sexual, and immune maturation & development** in pediatric patients.
- Pediatric trails should to have **growth indicators as a part of composite efficacy endpoints** to account for impact on growth.

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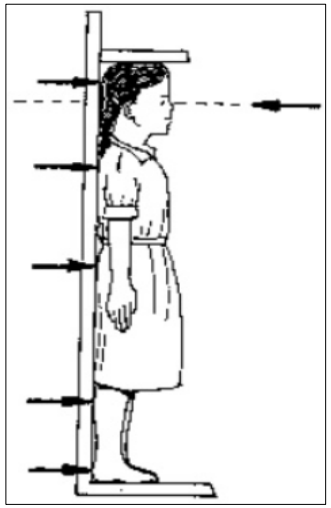
Growth Evaluation in Pediatric Trials

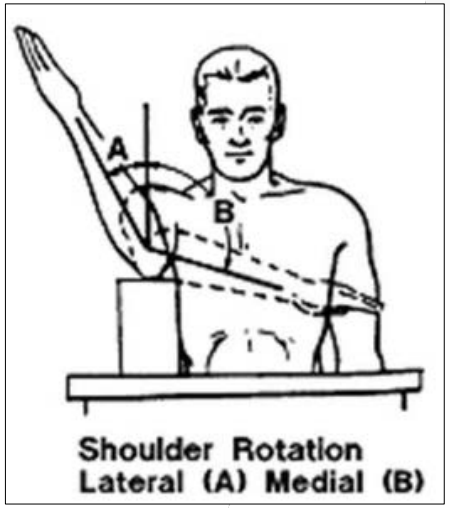
- The scope of this presentation will include assessment of **Anthropometric Growth in Pediatric Patients**.

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

Structural ("static") dimensions



Functional ("dynamic") dimensions



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Complexity of measuring Anthropometric Growth

Raj, Age: 3 years,
Height: 65 cm (2.13 ft)
Weight: 10 kg

Expected
Height : 89.1 - 103.1 cm (2.92 to 3.38 ft)
Weight: 11.43 – 18.07 kg

Longer height

Weight per height

Appropriate Growth

Growth monitoring
A COMPLEX TASK

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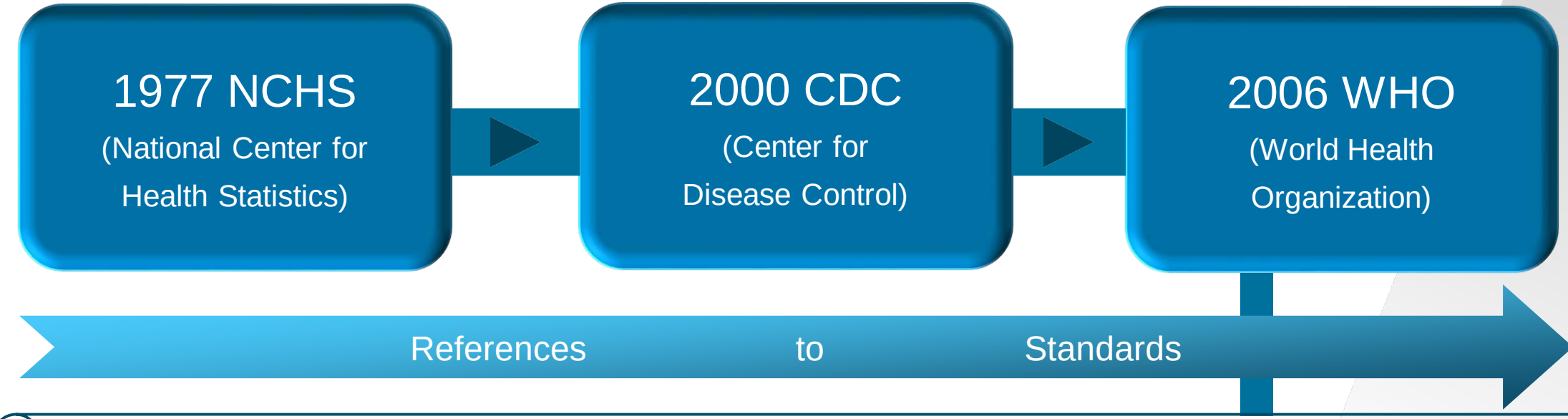
Growth Databases: References & Standards

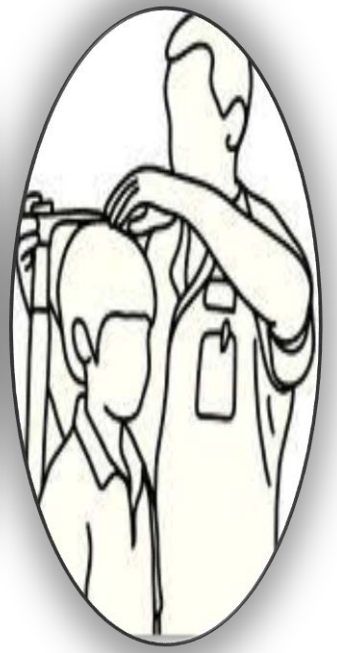


Multicenter Growth Reference Study (MGRS) (July 1997–December 2003):

- **Sites:**
  Davis, California, USA;
  Muscat, Oman;
  Oslo, Norway;
  Pelotas, Brazil;
  Accra, Ghana
  South Delhi, India.
- **Sample Size**: Total 8440 children.
- **Data collected for :**
  Weight,
  Recumbent length or height,
  Head circumference,
  Arm circumference,
  Triceps skinfolds (aged ≥ 3 months),
  Subscapular skinfolds (aged ≥ 3 months).
- The study populations lived in socioeconomic conditions favorable to growth.

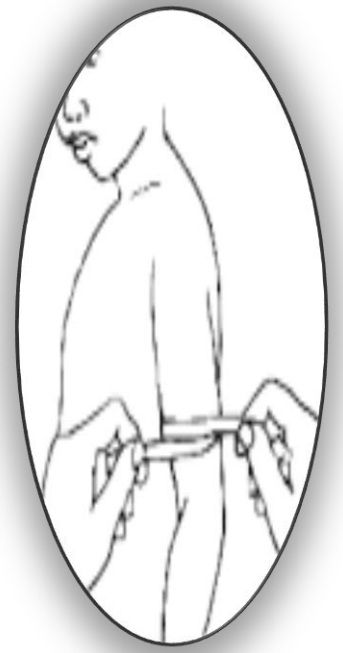
WHO Growth Database and Growth Charts

- Following are various Anthropometric Measurements and respective Indicators

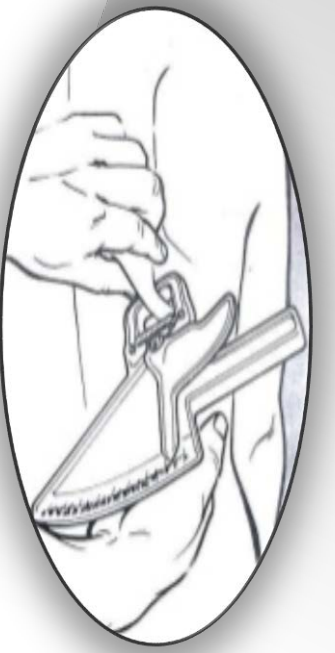
Weight-for-age, Length/height-for-age
Weight-for-length/height
BMI-for-age

Head circumference-for-age



Arm circumference-for-age

Triceps skinfold-for-age



Subscapular skinfold-for-age

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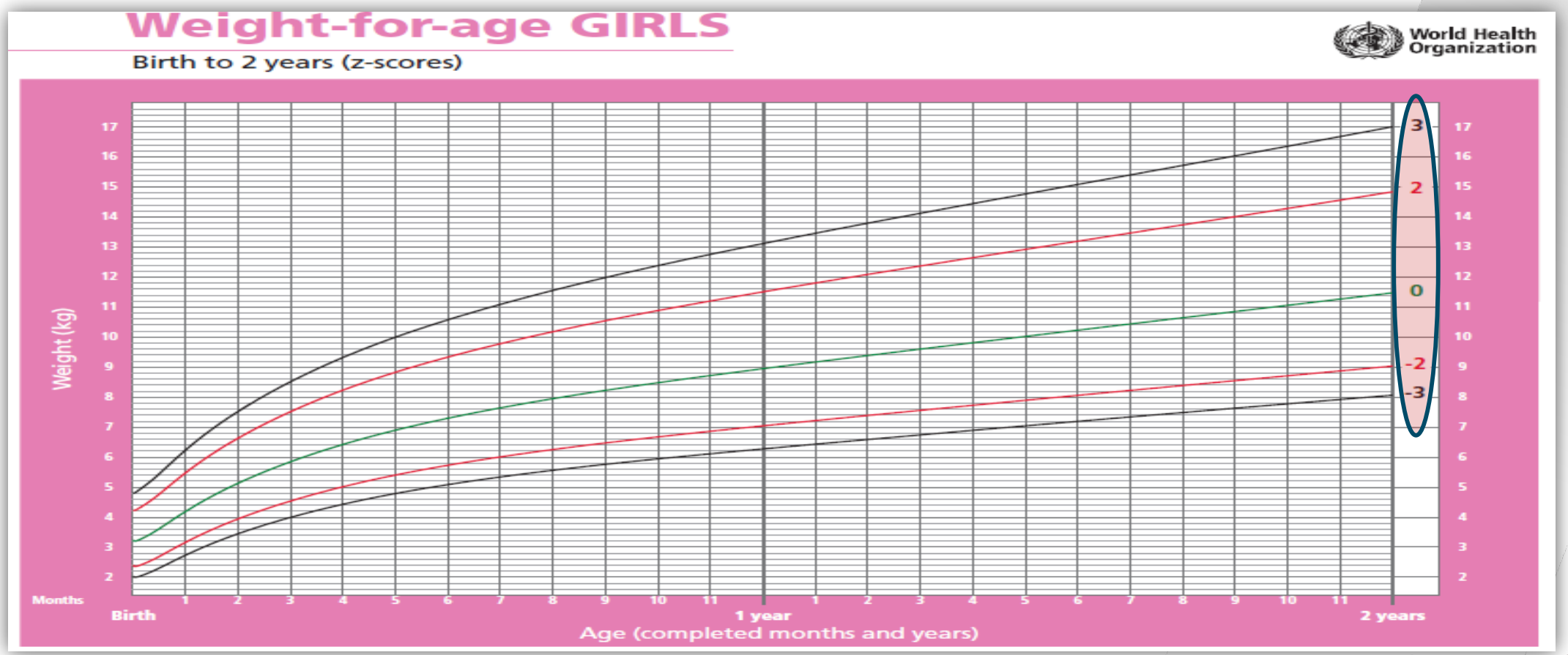
WHO Growth Database and Growth Charts

- From data collected in **MGRS, Z-scores for various anthropometric indicators are calculated and growth charts are developed.**

Example Growth Chart 1:



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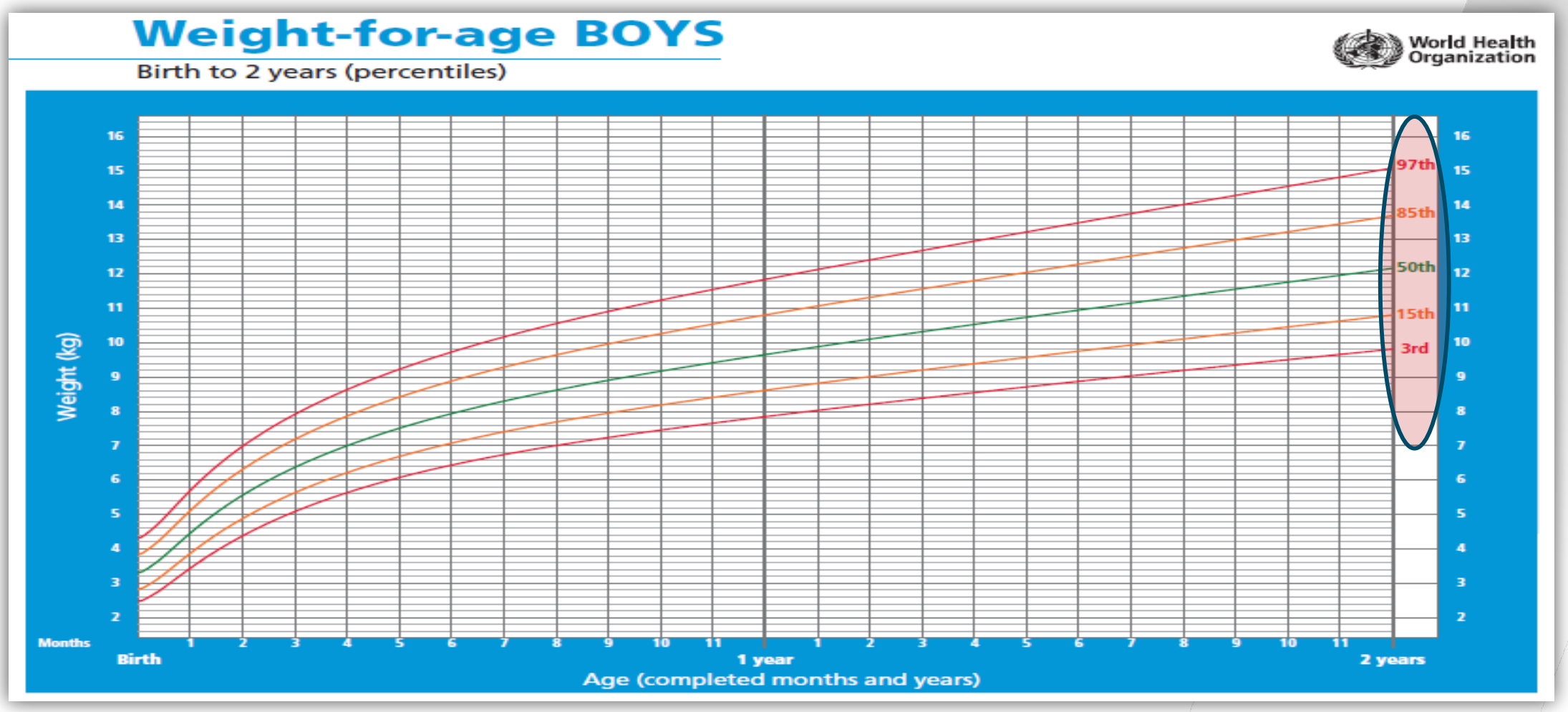
WHO Growth Database and Growth Charts

- **Example Growth Chart 2:**



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Z-scores and Percentiles

Z-scores

- Describes how far a measurement is from the median (average) measurement.

$$z-score_{ia} = \frac{x_{ia} - m_a^r}{sd_a^r}$$

Percentiles

- Indicates what percent of the reference population, the individual would equal or exceed.

$$percentile = \frac{n\left(x_{ia} \geq x_a^r\right)}{N_a^r} 100$$

For every Z-score there is a corresponding percentile and vice versa.

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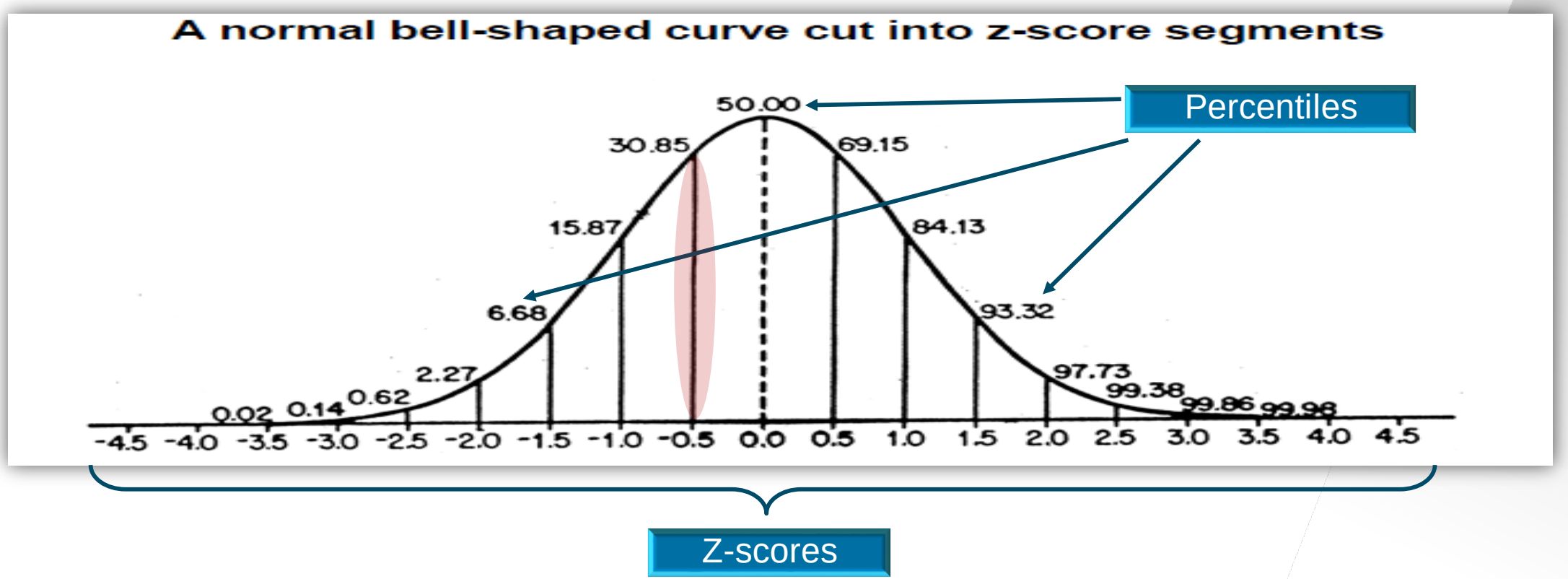
Z-scores and percentiles



Example:

- 12-month-old baby girl weighs 9.0 kg
- In reference sample,
  - Median weight is **9.5 kg**
  - Standard deviation is **1.0**

$$\text{Z-Sore (W/A)} = \frac{(9.0\text{-}9.5)}{1} = -0.5$$

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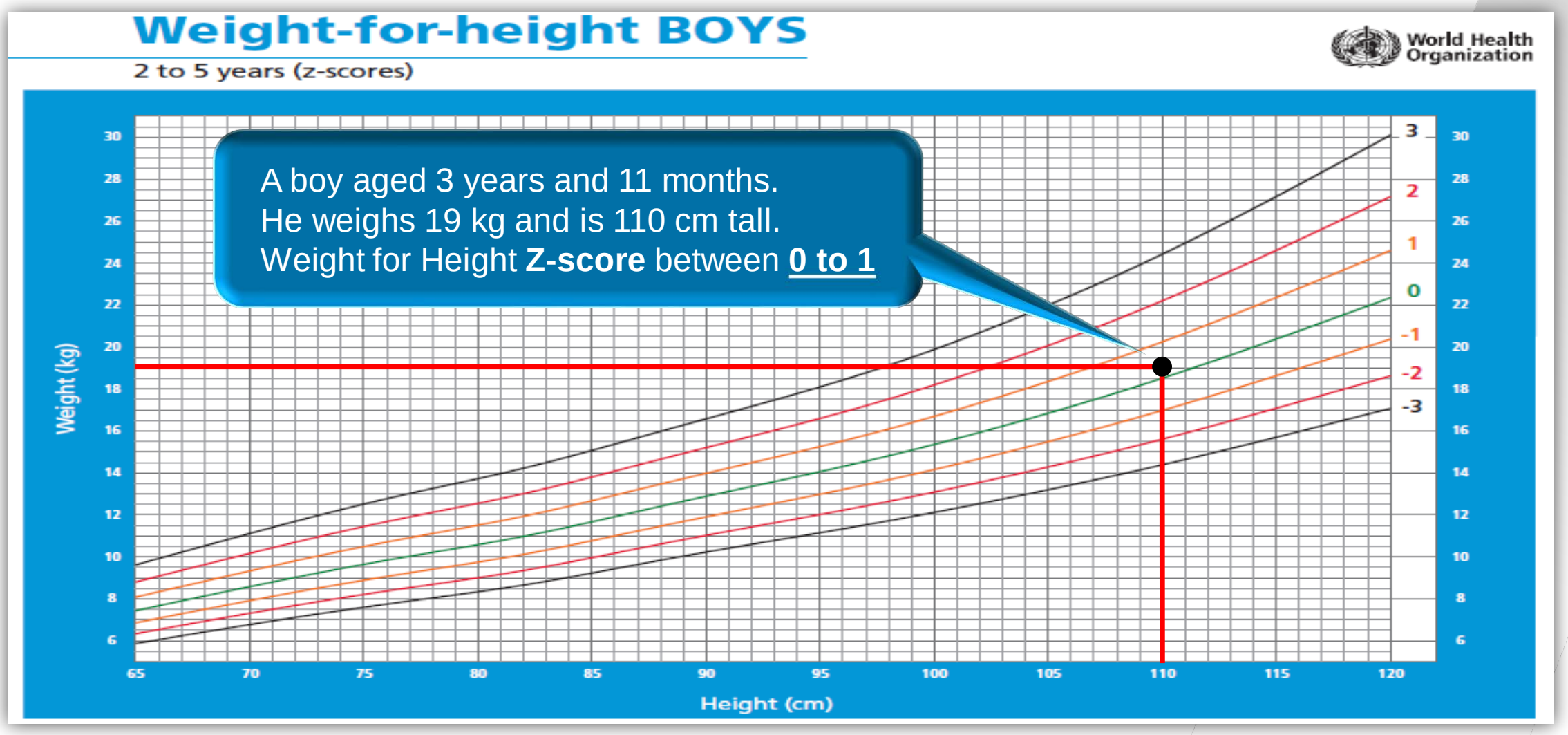
Interpretation of Z-score on Growth Chart



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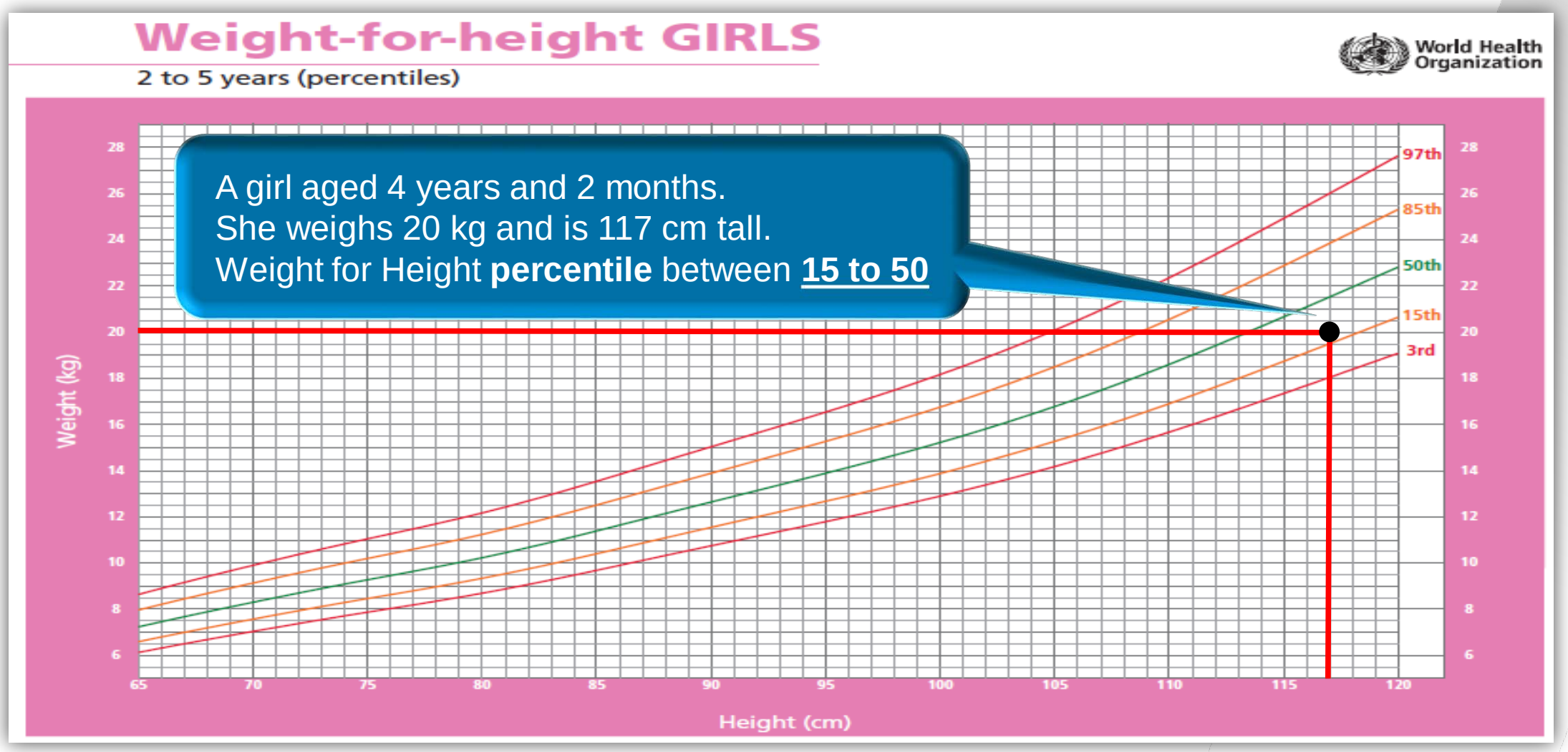
Interpretation of Percentile on Growth Chart



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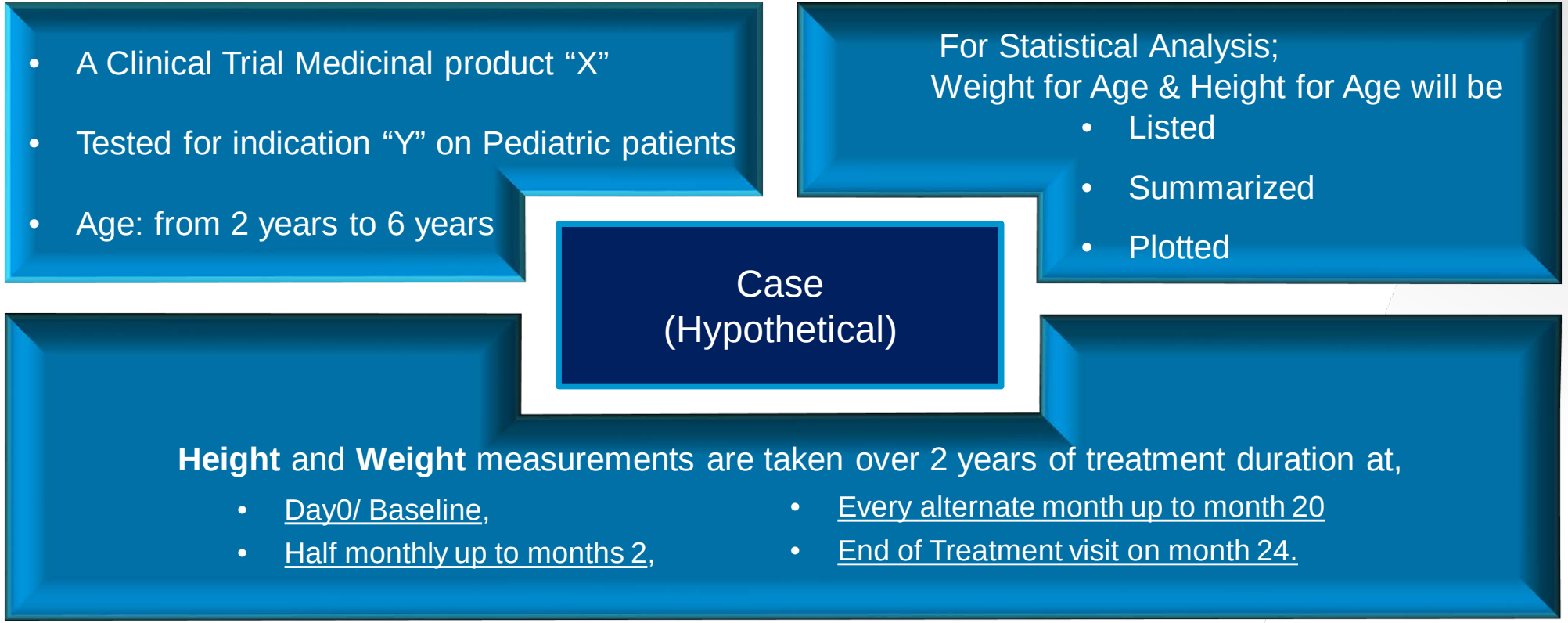
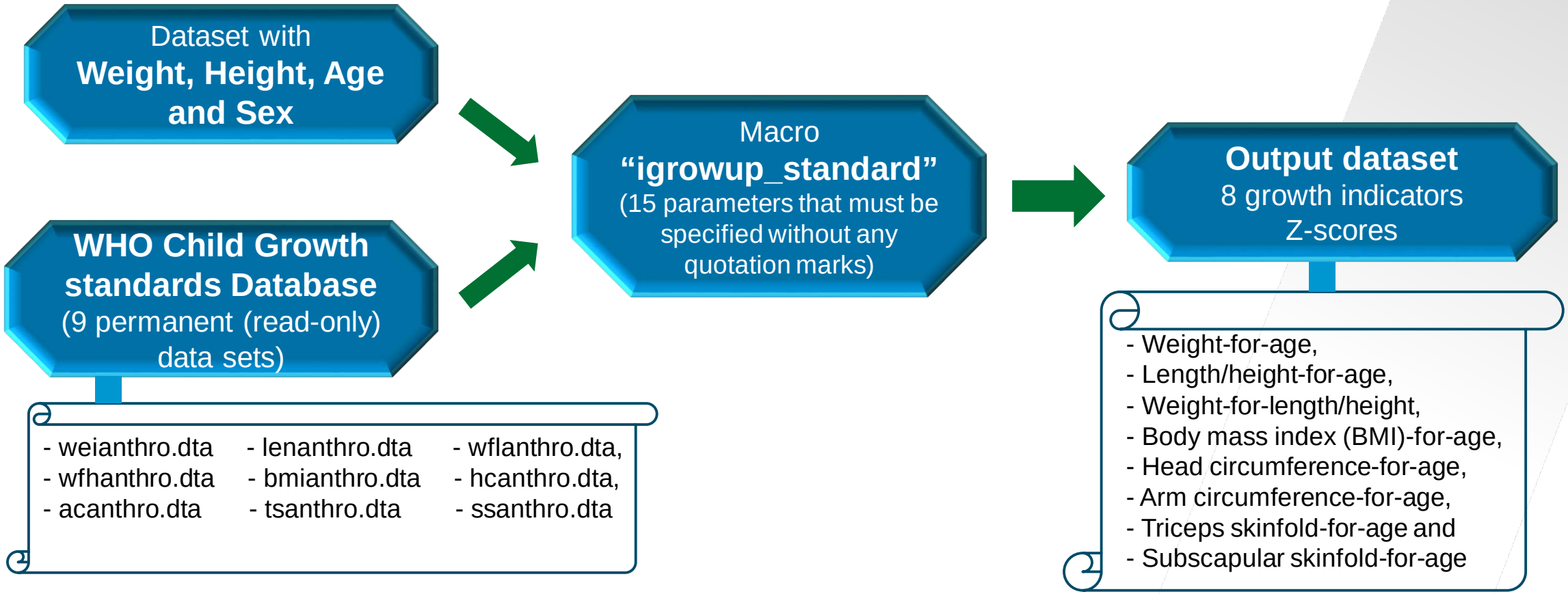
Clinically Implementing Z-scores and Percentiles

- It is essential for Clinical protocols to include **Anthropometric indicators as additional efficacy end points** where ever appropriate.



Clinically Implementing Z-scores and Percentiles

- To calculate Z-scores and Percentiles from the collected data, it needs to be processed using **macro "igrowup_standard"** provided by WHO to be used with **reference database**.



Clinically Implementing Z-scores and Percentiles

- Following is sample call to the macro;

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

Directory with reference data

Directory for input data / output data set

Sex variable name
1 for males and
2 for females

Prefix for output files

Numeric Age variable (either days or months)

Unit of age
"days" or "months"
(**case sensitive**)

Name of a numeric variables containing;
- Body weight in kilograms
- Length (recumbent) or height (standing) in centimeters
- Head circumference in centimeters
- Mid-upper arm circumference in centimeters
- Triceps skinfold in millimeters
- Subscapular skinfold in millimeters

Character variable for recumbent length or standing height ("l" or "L" OR "h" or "H")

Character variable with Oedema information ("n" or "N" OR "y" or "Y")

Numeric variable with sampling weights

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Clinically Implementing Z-scores and Percentiles

- The output data set from macro **retains all the records and variables from input data set** and adds on the following **19 variables** derived by the macro:

Variable name : Variable label

_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 _zwe i> 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 _zwf l> 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	: Tricpes 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

- 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 Statistical Analysis plan.

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Clinically Implementing Z-scores and Percentiles

A basic listing of Z-scores and Percentiles plotted subject wise can provide information on how subject's Weight and Height have chaged over the course of treatment.

Listing 1

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

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Clinically Implementing Z-scores and Percentiles

Summary tables with descriptive statistics on Z-scores and Percentiles can provide understanding about the drug's effect on overall study population.

Table 1

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

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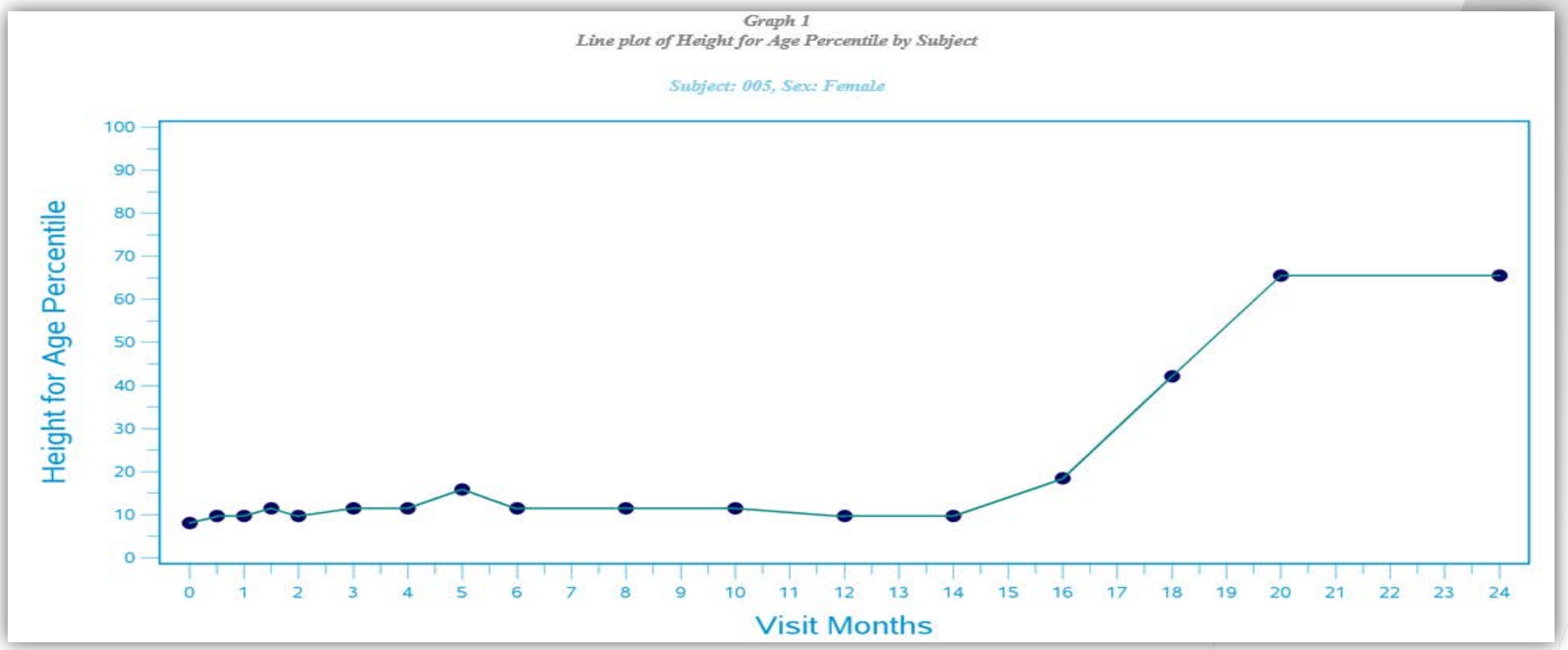
Clinically Implementing Z-scores and Percentiles

Percentile line plots by subject can visualize an individual subjects growth.



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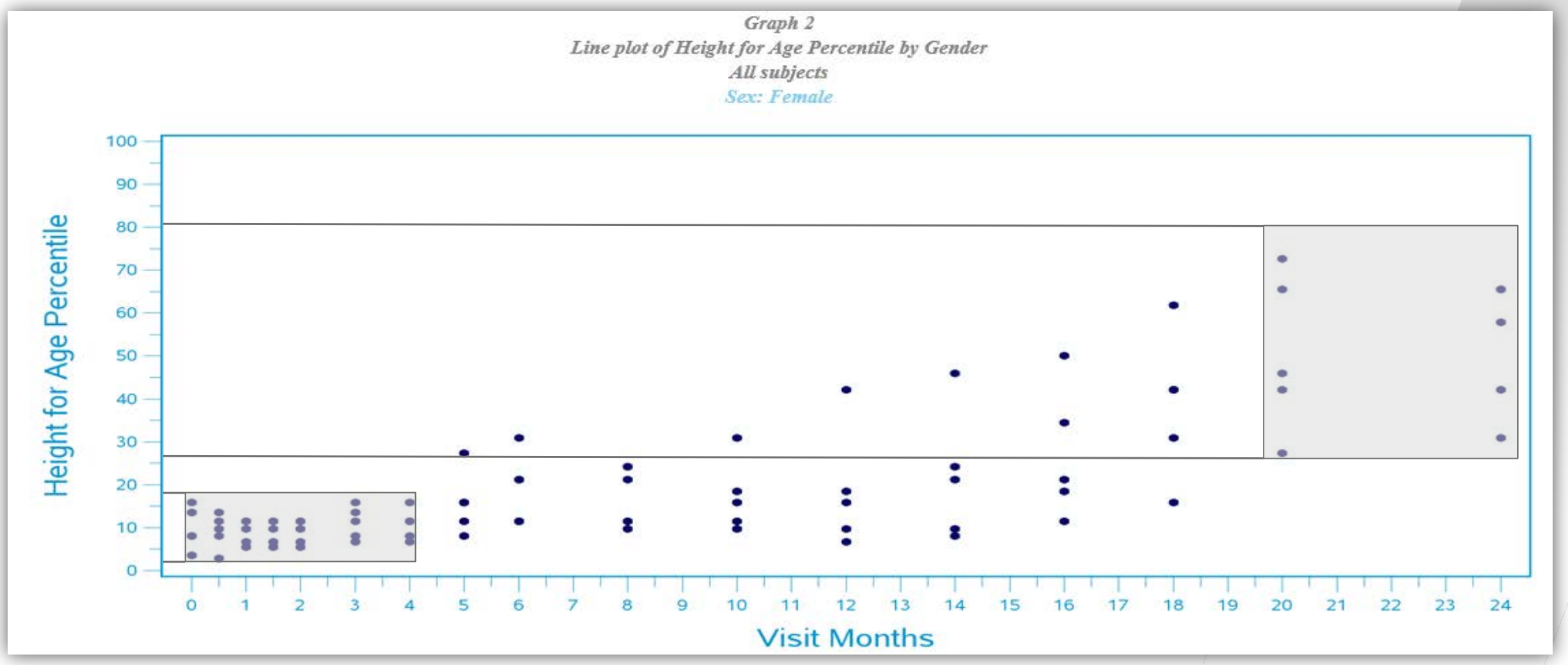
Clinically Implementing Z-scores and Percentiles

A scatter plot for percentiles for study population can visualize trends of effect on growth of study population.



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Merits

- ✓ Inexpensive way to monitor effect.
- ✓ Tools are easy to use.
- ✓ Entire study population can be assessed.
- ✓ No need of multiple age or sex based normal ranges.
- ✓ Comparative assessment is possible.

Limitations

- ✓ Over diagnosis of growth failure in children from developing countries.
- ✓ Incorrect diagnosis in children with non-supportive growth conditions.
- ✓ Regular updates to database are required.

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Other Growth Databases

- More local growth databases specific to particular population are required for more accurate assessment.
  - 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.

- Research efforts are being made for developing specific growth data for Chinese, Japanese population.

Conclusion

- Z-scores and Percentiles have been used for assessing growth related drug efficacy across various therapeutic areas as;
  - Congenital enzyme deficiencies
  - Cardiology
  - Retroviral infections
  - Nephropathy etc.

- Z-scores and Percentiles are also regularly used for;
  - General assessment of child growth by pediatricians, health care providers.
  - Pediatric diagnostic of growth failure.

For children in developing age, Z-scores and Percentiles for growth indicators are ***sensitive to changes in pathological condition*** and thus are ***important tool to evaluate growth related efficacy of medicinal product in Pediatric trials***.

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Thank you!

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