Measuring Growth and Evaluating Pubertal Development in Pediatric Clinical Trials

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
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Measuring Growth and Evaluating Pubertal Development in Pediatric Clinical Trials Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to assist sponsors in monitoring growth and, when appropriate, pubertal development in clinical trials that enroll pediatric participants with rare and common diseases. This guidance provides recommendations for the most appropriate methods for measuring and recording growth and evaluating pubertal development for evaluation of safety.

This guidance does not address use of growth or pubertal development data to support primary evidence of efficacy in growth disorders (e.g., primary growth deficiency, disorders of pubertal development such as precocious puberty or delayed puberty). Sponsors should further discuss with the appropriate review division how to establish efficacy for such drugs.[2]

This guidance does not address evaluation of nutritional status. This guidance does not address statistical methods for analyzing growth or pubertal developmental data.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance has been prepared by the Division of Diabetes Lipid Disorders and Obesity, the Division of Pediatrics and Maternal Health, and the Division of Rare Diseases and Medical Genetics in the Office of New Drugs in the Center for Drug Evaluation and Research, the Office of Pediatric Therapeutics, and the Center for Biologics Evaluation and Research at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and biological products unless otherwise specified.

II. BACKGROUND

In general, pediatric clinical trials should include accurate, serial measurements and recordings of growth parameters if an investigational drug has the potential to affect growth or pubertal development. Typically, growth is assessed using measurements of weight and linear growth (length and height), and when appropriate, head circumference. Additional measurements and calculations may be needed in certain pediatric age groups and disease populations, as discussed further in section III., Measurements of Growth and Pubertal Development. Typically, pubertal development is assessed using clinical phenotyping. Accurately identifying the onset and progression of puberty is essential for accurate interpretation of growth data.

III. MEASUREMENTS OF GROWTH AND PUBERTAL DEVELOPMENT

A. Growth Measurements

1. General Considerations

Sponsors should consider the following for measuring growth in pediatric participants enrolled in clinical trials:

- Develop a protocol for training investigators and trial site personnel responsible for collecting growth parameters and conducting physical examinations and include procedures for determining a trial participant's age, obtaining growth measurements, instrument calibration, and evaluation of pubertal development.

- Avoid self-reported growth measurements because they may not be sufficiently accurate, consistent, and reliable for data collection. Growth measurements assessed outside of established trial sites may be acceptable if the measurements are taken by a trained health care professional using appropriate and calibrated instruments.

- In general, collect and record growth measurements for a minimum trial duration of 12 months. Sponsors should discuss alternative trial durations with the appropriate review division and consider any potential safety concerns related to the drug for the intended patient population.

- Keep pediatric participants who discontinue the study treatment in the trial to continue to obtain their growth measurements. Measurements obtained after treatment discontinuation may be useful for ensuring the reliability and interpretability of analyses and results.

a. Reducing measurement error

To reduce measurement error, the sponsor should include procedures and practices in the protocol, such as the following:

- Outline procedures for calibration of measuring instruments (e.g., calibration timing relative to measurement, calibration frequency).

- Document how measurements are obtained (e.g., for weight, use of tared weight, documenting type of scale, clothing; for height, use of recumbent or standing methods of measurement) and how to address challenges in obtaining measurements (e.g., uncooperative child, assistive technology).

- For trials involving multiple treatment arms, blind trial site personnel to each trial arm. For single-arm trials, the sponsor should discuss with the appropriate review division how the trial could be designed to avoid biased measurement of growth parameters.

- Because of diurnal variations in height and weight, schedule study visits and/or perform growth measurements at the same time of day unless justification is provided.

b. Determining age

Appropriately determining a participant's age is important for accurate and consistent documentation of growth. Sponsors should consider the following when determining age:

- For participants 3 years of age and older, calculate and use the chronological age to the nearest month and year.

- For participants younger than 3 years of age, consider whether the participant was born at term (37 weeks gestation or later) or preterm (before 37 weeks gestation).

  For participants born at term, sponsors should consider the following calculations for age:

  i. For participants older than 12 months of age, calculate age to the nearest month.

  ii. For participants from three to 12 months of age, calculate age in completed weeks or months.

  iii. For participants less than 3 months of age, calculate age in completed weeks.

  For participants born preterm, sponsors should consider the following for calculating age:

  i. Determine the gestational age (GA) at birth (e.g., based on the first day of mother's last menstrual period (LMP), prenatal ultrasonography, history of assisted reproduction, postnatal physical exam), and document the method for determining GA.

ii. Document both the chronological and corrected age[3] for each growth assessment until participants have transitioned from corrected to chronological age. Given a lack of consensus about thresholds of transition from corrected to chronological age, sponsors should provide data to support or justify the selected age correction strategy.

c. Using standardized charts

Sponsors should plot anthropometric measurements based on age and sex using the appropriate standardized charts for the trial population.

Unless justification is provided to support using an alternative approach for growth measurement, sponsors should consider the following for pediatric participants enrolled in U.S. trial sites:

- For participants born at term (37 weeks gestation or later):

  i. Two years of age and older, use the Centers for Disease Control and Prevention (CDC) growth charts.[4]

  ii. Birth to younger than 2 years of age, use the World Health Organization (WHO) growth charts.[5]

- For participants born prematurely (before 37 weeks gestation):

  i. Born at 22 to 36 6/7 weeks GA, use the Fenton[6,7] preterm infant growth chart.

[3] Definitions of terms for corrected age include *gestational age* (GA; completed weeks) that means time elapsed between the first day of the last menstrual period and the day of delivery; *chronological age* (days, weeks, months, or years) that means time elapsed from birth; *postmenstrual age* (PMA; weeks) that means GA plus chronological age; and *corrected age* (CA; weeks or months) that means chronological age reduced by the number of weeks born before 40 weeks of gestation.

[4] See the CDC's Clinical Growth Charts web page available at https://www.cdc.gov/growthcharts/clinical_charts.htm.

[5] See Department of Health and Human Services, CDC, 2010, Use of World Health Organization and CDC Growth Charts for Children Aged 0–59 Months in the United States, MMWR, 59 (No. RR-9):1–15, available at https://www.cdc.gov/mmwr/PDF/rr/rr5909.pdf.

[6] See Fenton TR and Kim JH, 2013, A Systematic Review and Meta-Analysis to Revise the Fenton Growth Chart for Preterm Infants, BMC Pediatr, 13:59.

[7] See Olsen IE, Groveman SA, Lawson ML, Clark RH, and Zemel BS, 2010, New Intrauterine Growth Curves Based on United States Data, *Pediatrics,* 125(2):e214–e224.

ii. Born at 28 weeks to 36 6/7 weeks GA, use the International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) preterm postnatal growth standards as an alternative to Fenton.[8,9]

iii. Once a child reaches the term equivalent (40 weeks or later) postmenstrual age, transition to use of the WHO growth charts.

For trials conducted outside the United States, sponsors should use growth charts based on normative data for the trial population, when available.

When disease-specific growth charts (e.g., for Down syndrome, achondroplasia) are available, sponsors should use both standardized and disease-specific growth charts.

2. Weight Assessment

Sponsors enrolling pediatric participants in clinical trials should consider incorporating the following considerations in the trial protocol regarding weight assessment:

- Use a scale with an electronic (i.e., digital) reading that allows for adjusting the scale to zero prior to weighing the pediatric participant.
- Place the scale on a flat, hard, and even surface.
- Calibrate all scales used during trials at a standardized time before each study visit.
- Record weight for participants weighing more than or equal to 5 kilograms (kg) to the nearest 0.1 kg; for neonates weighing less than 5 kg, recording weight to the nearest 10 grams.
- Address in the protocol how weight will be assessed in participants who are technology-dependent (e.g., ventilator-dependent), device-dependent (e.g., gastrostomy tube), or require assistive technology (e.g., orthotics, prostheses, wheelchairs). Techniques to consider include the following:

  — If the technology can be safely removed[10], weigh the participant without the technology.

[8] See the Global Health Network International Fetal and Newborn Growth Consortium for the 21st Century's Postnatal Growth of Preterm Infants on the INTERGROWTH-21st website available at https://intergrowth21.tghn.org/standards-tools/.

[9] See Villar J, Giuliani F, Barros F, Roggero P, et al., 2018, Monitoring the Postnatal Growth of Preterm Infants: A Paradigm Change, Pediatrics, 141(2):e20172467.

[10] Risk(s) associated with these measurements in participants who require a supportive device may need to be considered by institutional review boards in their subpart D determinations (21 CFR part 50, subpart D, Additional Safeguards for Children in Clinical Investigations).

191 — If the technology cannot be safely removed, measure the weight of the participant
192 with the technology and subtracting its estimated weight (based on device
193 specifications). Include a source document that captures the weight of the technology
194 and the scale weight, which would be the first recording of the data value. Record
195 this calculated weight (i.e., the weight of the participant minus the weight of the
196 technology) as the participant's weight. In addition, document the weight of the
197 participant with the technology and the estimated weight of the technology.
198
199 • Weigh the participant in an examination gown and underwear, and remove all other
200 clothing including shoes and socks. Sponsors should have trial site personnel document
201 the clothing worn when weight is measured and consider the following:
202
203 — When a participant uses diapers, weigh the participant in a freshly changed diaper.
204
205 — In preterm neonates, weigh the participant without a diaper or adjust the scale to zero
206 to account for the diaper weight, prior to weighing the pediatric participant.
207
208 • Weigh participants using a standing scale once they are able to independently stand still.
209
210 • Consider the following techniques to measure weight in participants 2 years of age and
211 older who cannot stand independently:
212
213 — When the pediatric participant must be held by an adult, set the scale to zero to
214 account for the adult's weight, weigh the adult holding the pediatric participant and
215 record the weight.
216
217 — Use chair scales, bucket scales, wheelchair scales, or bed scales as appropriate for the
218 intended patient population.
219
220 • In participants with conditions that may result in fluid retention, document edema
221 describing the location and degree of edema, using objective descriptors when possible
222 (e.g., grade 1 to 3 ascites; 1+ to 4+ pretibial, pedal, presacral peripheral edema), that are
223 based on definitions agreed upon with the appropriate review division and specified in
224 the protocol.
225
226 • Weigh dialysis-dependent participants after dialysis.
227
228 *3. Linear Growth (Length and Height) Assessment*
229
230 Sponsors should consider the following for measuring length and height in pediatric participants
231 enrolled in clinical trials:
232
233 • Measure recumbent length in participants from birth to less than 2 years of age using a
234 length board (or infantometer) with a fixed head piece, horizontal backboard, and an
235 adjustable foot piece. The length board should be placed on a flat, stable surface.
236

- Measure standing height in participants 2 years of age and older using a stadiometer mounted at a right angle between a level floor and against a straight, vertical surface.

- When transitioning from recumbent length to standing height measurements in participants between 2 to 3 years of age, measure both length and height.

- Measure linear growth to the nearest 0.1 centimeter (cm).

- Before measuring linear growth, remove shoes, hats, hair ornaments, and braids whenever possible because these items will interfere with accurate linear growth measurement.

- Measure linear growth three times at each study visit to improve accuracy and consider the following:

  — Repeat measurements that are not clinically plausible (e.g., height measurement that is lower than the height measured at the previous or prior study visits).

  — Calculate the mean of the three linear growth measurements.

  — Record individual growth measurements and the mean of the measurements.

  — Use the mean value in linear growth analyses.

- Provide details in the protocol on any alternative strategies that will be used for evaluating linear growth in trials enrolling pediatric participants with conditions that may affect measurement of linear growth (e.g., contractures, genetic syndromes including skeletal dysplasia, scoliosis). For participants who are not cooperative with linear growth measurements, sponsors should consider an adjustment strategy based on recommendations by WHO[11] or other professional health organizations.

4. Head Circumference Assessment

Sponsors should consider the following for measuring head circumference in pediatric participants enrolled in clinical trials:

- Measure head circumference (HC) using a nonelastic tape measure.

- Measure HC in all participants *younger than* 2 years of age or until sutures are fused.

- Measure HC in participants 2 years of age and older in some clinical situations (e.g., neurocognitive impairment, microcephaly, macrocephaly, diseases that affect neurodevelopment) and in trials investigating therapeutics that may cause neurotoxicity.

[11] See the Child Growth Standards web page on the WHO website at https://www.who.int/tools/child-growth-standards/standards.

- Measure HC at the maximum diameter of the head (the glabella to the occiput) and to the nearest 0.1 cm. Abnormal head shape (e.g. craniosynostosis, positional plagiocephaly, microcephaly) should be documented.

- Measure HC three times at each study visit to improve accuracy and also consider the following:

  — Repeat measurements that are not clinically plausible.
  — Calculate the mean of the three HC measurements.
  — Record individual HC measurements and the mean of the measurements.
  — Use the mean value in HC analyses.

5. Other Considerations

Sponsors should also consider the following when enrolling pediatric participants in clinical trials:

- Confirm diagnoses for genetic disorders affecting growth with molecular or cytogenetic testing to ensure use of appropriate growth charts and accurate interpretation of anthropometric data.

- Discuss collection of relevant family history data (e.g., growth and puberty patterns) with the appropriate review division.

Note that FDA currently does not recognize biomarkers as validated assessments of growth.

B. Pubertal Development

Sponsors enrolling pediatric participants in clinical trials should use a sexual maturity rating (e.g., Tanner Staging) to evaluate and document pubertal development at baseline (i.e., trial entry) and at regular intervals based on the potential safety concerns associated with the drug and the pubertal development stage of the pediatric participant. Sponsors should also consider the following:

- Discuss with the appropriate review division the appropriate intervals for evaluation of pubertal development.

- Sexual maturity ratings should be based on both breast and pubic hair changes in females and on both genital and pubic hair changes in males. Evaluation of genital changes in males should include an assessment of testicular volume using an orchidometer.

- Discontinue or do not initiate pubertal development assessments when the participant has completed puberty (i.e., Tanner 5). FDA also recommends the following:

— Train investigators and examiners on how to conduct sexual maturity ratings. Whenever possible, the same trial health care professional should evaluate pubertal development.

— Identify and record the age at menarche for female participants.

C. Other Measurements

1. Skeletal Age

Sponsors should consider the following recommendations when assessing skeletal age in pediatric participants enrolled in clinical trials:

- Evaluate skeletal maturation by validated assessments and tools to provide information about skeletal maturity compared to chronological age. Potential bone age assessments include imaging of the following:

  — For hand and wrist bones, using the following:

    - X-ray (Greulich and Pyle method, Tanner-Whitehouse method, Gilsanz and Ratibin atlas, or computer-assisted skeletal bone age systems)
    - Ultrasound
    - Magnetic resonance imaging

  — For knee joints, using X-ray (O'Connor knee scale)

- Discuss the appropriate bone age assessments for the trial participant population with the appropriate review division.
- Use the same validated methodology or instrument for all participants throughout the trial to improve consistency and accuracy. Sponsors can consider alternative methods if adequate validation is demonstrated.
- For consistency, reassess all readings with a blinded, single central reader, when using reader dependent methods, to limit interreader reliability issues intrinsic to these methods. Sponsors should use the results from the single central reading as the primary data source for analyses.
- For body proportions, discuss with the appropriate review division the need for additional measurements in pediatric participants with specific diseases known to be associated with disproportionate growth (e.g., Marfan syndrome, skeletal dysplasia).

2. Dual-Energy X-ray Absorptiometry Scan

Depending on the study population, sponsors that enroll pediatric participants in clinical trials can use dual-energy X-ray absorptiometry (DXA) scans to monitor bone mineral density, bone mineral content, and body composition. Sponsors should discuss the conduct of DXA scans with the appropriate review division.