**INTERPRACTICE-21st**

Implementing the INTERGROWTH-21st Preterm Postnatal Growth Standards



**Project Protocol**

International Preterm Postnatal Growth Standards Consortium

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17. **Project Summary**

The Project aims to: a) promote optimal postnatal growth of preterm infants until 6 months post-term and b) standardise growth measurement in selected populations around the world, based on implementation of the INTERGROWTH-21st international standards and evidence-based feeding recommendations.

Specifically, we wish to identify healthcare institutions that provide care to preterm babies and infants and establish an online community of health professionals who are able to apply the feeding protocol and monitor preterm postnatal growth using the INTERGROWTH- 21st standards.

We plan to implement the growth monitoring and feeding protocols in selected, leading neonatal units and, ultimately, gain high-level health policy support for these practices. The combination of using recommended feeding practices and international standards to monitor postnatal growth and development should help to: a) avoid nutritional patterns that may be associated with childhood overweight and obesity, and b) improve the growth, development and survival of preterm infants.

1. **The INTERGROWTH-21st Project**

The package of clinical tools produced by the **INTERGROWTH-21st Project** aims to standardise how to assess and monitor the growth, nutritional status and neurodevelopment of the 130 million babies born every year in the world.1 The tools are helping to improve health outcomes and reduce the number of avoidable infant deaths, especially amongst the world’s most vulnerable populations.

The INTERGROWTH-21st Projectwas carried out by the International Fetal and Newborn Growth Consortium for the 21st Century, a multidisciplinary network of more than 300 doctors and scientists from 27 institutions in 18 countries worldwide. Coordinated by the University of Oxford, it is the largest collaborative venture to-date in the field of maternal and newborn health research.

Supported by the Bill & Melinda Gates Foundation, the INTERGROWTH-21st Project comprised a set of inter-related studies, involving 60,000 mothers and infants across five continents. A rich body of data on health, growth and nutrition was gathered across the first 1,000 days of life (from conception to age 2) so as to extend into the fetal period the existing WHO Child Growth Standards, which are used in over 140 countries worldwide to monitor the growth of children from birth to age 5.

The INTERGROWTH-21st Project adopted the same conceptual, methodological and analytical approaches as the study that produced the WHO Child Growth Standards. Healthy, well-nourished women, free of disease, living in a clean environment and receiving good antenatal care were recruited.2 Their babies were shown to grow in a similar way in the womb and achieve a similar size at birth, irrespective of their race or ethnicity, or where they were living.3 From these findings, in keeping with WHO recommendations, a set of fully integrated, ‘prescriptive’ standards were produced, all from the same cohort of healthy mothers, describing how babies *should* grow, which perfectly complement the existing WHO Child Growth Standards.

The clinical tools, **the Global Perinatal Platform for Growth and Development in the 21st Century**, include: (a) international standards for clinical assessment and monitoring of growth and development over the first 1,000 days; (b) the first phenotypic classification system for preterm birth and impaired fetal growth, and (c) simplified tests for assessing cognitive development in the field at age 2 in any cultural setting. These tools constitute the only comprehensive, scientifically-based platform for delivering targeted, effective interventions to reduce infant morbidity and mortality, growth disturbances and neurodevelopmental disability.

The last component recently published in the *BMJ* presents **international standards for measuring symphysis-fundal height** that should be provided to every pregnant woman in the world as a simple, inexpensive, screening tool to detect impaired fetal growth.1 Although most clinicians already measure the distance from the fundus of the womb to the pubic symphysis with a tape measure to assess fetal growth, they do so in a non-standardised manner using a variety of different charts. The *BMJ* paper describes a standardised method for measuring the symphysis-fundal height, presents the new international charts, and recommends actions to be taken when disturbances in fetal growth are suspected.

The whole INTERGROWTH-21st package, which consists of seven components, is a powerful vehicle for full integration of maternal, newborn and child care across the world. The other six components are:

1. Routine **nutritional assessment** of all pregnant women, using international weight gain during pregnancy standards.4
2. Accurate **gestational age dating** in early pregnancy,5 and for women initiating antenatal care late,6 with ultrasound tools adapted to primary care settings to improve both the antenatal and postnatal management of preterm babies, e.g. for timely treatment with corticosteroids in pregnancy.
3. **Early detection** of fetal growth disturbances using international standards for fetal growth 7 and estimated fetal weight,8 based on ultrasound measurements, to replace the countless number of locally derived reference charts some of which are designed for specific ethnic groups.
4. **Newborn screening** to identify small-for-gestational-age (SGA) and preterm babies at high risk of adverse outcomes for appropriate referral to specialised care using international standards for newborn size for gestational age and sex,9,10 and a new phenotypic classification system for the SGA and preterm birth syndromes.11,12
5. Accurate **monitoring of postnatal growth** **for preterm babies**, based on international standards and feeding recommendations promoting the use of human milk.13
6. A multi-dimensional set of **neurodevelopment assessment tools** that non-specialist staff across the world can use to assess vision, cortical auditory processing, cognition, language skills, behaviour, motor skills, attention, and sleep-wake patterns at age 2.

The data resulting from the INTERGROWTH-21st Project provide unique biological insights into human growth and development, as well as the practical clinical tools and supporting resources needed to improve the quality of pregnancy and postnatal care, which will enhance the impact of existing, evidence-based interventions by targeting infants at high risk because of preterm birth or growth disturbances (stunting, wasting or excess weight).

The members of the INTERGROWTH-21st Consortium are now actively disseminating their findings and tools, with the help of WHO regional offices, to ensure their widespread adoption into clinical practice and research projects across the world. Examples of implementation to date include:

* The international standards for newborn size at birth for gestational age and sex, and postnatal growth of preterm infants, have been recommended by WHO and CDC (Centers for Disease Control and Prevention).14,15
* The Brazilian Ministry of Health has adopted the international standards for newborn size at birth for gestational age and sex and the preterm postnatal growth standards to assess all 3 million births per year in the country.
* The international standards for the postnatal growth of preterm infants have been recommended by the Scientific Department of Neonatology of the Brazilian Society of Pediatrics.
* Sri Lanka has become the first country in the world to adopt the international standards for the postnatal growth of preterm infants.
* Over 26,000 users have downloaded INTERGROWTH-21st tools to date from 180 countries

In summary, the findings of the INTERGROWTH-21st Project represent a major paradigm shift in our understanding of human growth and development demonstrating that a universal pattern of healthy growth exists from conception to 5 years of age. The colour of a woman’s skin plays no role in determining the variation in growth currently seen worldwide, especially in low-middle income countries, compared to the social conditions, health and nutritional state of the population. The failure to recognise this truth is a human rights issue.

As a result of the INTERGROWTH-21st Project, growth and development can now be monitored from womb to classroom using a unified set of high-quality clinical tools. Integrated monitoring of growth and neurodevelopment is desirable, scientifically supported, and likely both to standardise and improve health care and referral patterns. Such integration is only achievable through the use of international standards, especially in increasingly diverse mixed ancestry populations. The standards also allow, for the first time, comparisons to be made across populations from early pregnancy onwards, which will be vitally important for achieving the Sustainable Development Goals as newborn status is a very reliable biomarker of a population’s general health.

**Action is needed now**. The introduction of the international standards will immediately benefit approximately 20 million of the most vulnerable infants worldwide every year who are currently not being diagnosed as malnourished at birth because they are being assessed using inappropriate charts.\* Hence, they are being deprived of the necessary evidence-based interventions.

\* This estimate is based on a 2015 study from Johns Hopkins, which concluded that 24% of all newborns in developing countries, assessed using the INTERGROWTH-21st standards, are malnourished at birth.

**Quotes**

“In low-resource settings around the world, the availability of ultrasound for fetal growth monitoring is rare: when it does exist, guidelines are lacking and both underuse and overuse of ultrasound abound. Therefore, clinical measurement tools are essential complements of the ultrasound based ones, and will particularly benefit the most vulnerable women and babies. Clinicians in low resource settings can easily be trained to use the new INTERGROWTH-21st standards for symphysis-fundal height; efforts to introduce them should be scaled. The Maternal Health Task Force will support the translation of this sound research into clinical practice among our constituents”. *Professor Ana Langer, Director Maternal Health Task Force, Harvard T.H. Chan School of Public Health.*

“The publication of standardised methodology for measuring symphysis-fundal height and of international standards is a major step forward, because these standards will contribute to harmonizing care across the world.  The use of these simple, inexpensive screening tools will improve the clinical management of pregnancies, especially in resource-poor settings.  Although application of these standards is not expensive, it does require funds for implementation. I hope that such support from the international agencies will be forthcoming, and soon”. *Professor Michael Katz, Senior Advisor, Transdisciplinary Research, March of Dimes Foundation*

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16. **Objectives, Design and Implementation of the Project**

***Activity 1: Establish an online community of health professionals who are able to apply the feeding protocol and Preterm Postnatal Growth Standards (PPGS) growth monitoring***

In collaboration with our partner, the Geneva Foundation for Medical Education and Research (GFMER) we are developing an online, high quality, interactive, e-learning course targeted at health professionals caring for preterm infants that promotes the INTERGROWTH-21st feeding protocol and the new standards. Large-scale dissemination of the course will be implemented with the support of the INTERGROWTH-21st Consortium Network, the Global Health Network (TGHN), George Institute for Global Health (GIGH), Save the Children, and Maternal Health Taskforce (MHTF) to reach a global population of doctors, nurses and other health professionals caring for preterm infants, plus policymakers.

*Target 1: At least 2,000 health professionals directly involved in the care of preterm infants will have passed the online course within 3 years*

***Activity 2: Implementation of feeding protocol and PPGS growth monitoring in to selected, influential neonatal units around the world***

We plan to implement the feeding protocol and PPGS growth monitoring in 6-8 selected, progressive and opinion-leading neonatal units around the world. It is expected that these leading institutions will act as regional centres for dissemination. Several institutions and individuals have already expressed interest in participating in this activity from our pool of collaborating and associated institutions. Additional sites will be identified through the community participating in activity 1, the INTERGROWTH-21st Consortium Network of neonatal care units and our partner organisations (GFMER, TGHN, GIGH and MHTF).

Technical guidance and implementation support will be provided through regional offices and the central Coordinating Unit in Oxford (see Activity 3). No fee will be required to participate; however, neonatal units will need to nominate a local contact person and, if possible, provide anonymised summary data on programme uptake and relevant clinical outcomes until hospital discharge of all preterm infants cared for at the institution as part of the monitoring and evaluation of this activity. At the regional level, the Coordination Unit will guarantee the standardisation of the procedures and monitor the implementation process.

*Target 2: The leading units will influence a total of approximately 300 clinical neonatal units that will adopt the feeding protocol and PPGS growth monitoring worldwide within 3 years. A register of collaborating units will be maintained at the Coordinating Unit.*

***Activity 3: Gaining high-level health policy support for implementing the feeding protocol and PPGS growth monitoring***

We willestablish a global expert advisory group to guide the planning, roll-out and evaluation of the programme. The group, which will meet annually, will consist of key opinion leaders identified through the INTERGROWTH-21st Consortium Network, International Pediatrics Association and UN specialised agencies (WHO, UNFPA, UNICEF), as well as international experts in nutrition, breastfeeding and implementation science.

The central Coordinating Unit (Oxford) will facilitate the implementation of the feeding protocol and PPGS growth monitoring, and lobby for high-level adoption. We will also utilise our existing networks to establish regional offices in Sub-Saharan Africa (Nairobi, Kenya - also covering part of the Middle East), South Asia (Hyderabad, India), Latin America and the Caribbean. Regional coordinators will have experience in project management and national level implementation of maternal and child health programmes. They will be responsible for establishing links with all the relevant regional and country level representatives and organising regional training workshops to obtain policy support, and provide the neonatal units selected in activity 2 with the required technical advice and assistance during the implementation process.

The central Coordinating Unit and the three regional offices will each consist of a committed senior neonatologist (part-time), neonatal nurse and secretary (full-time). These staff will promote and provide support for adoption of the feeding protocol and PPFS growth monitoring at each neonatal unit and country or region targeted.

*Target 3: Country or regional level adoption where most of the neonatal units implementing the standards are located within 3 years*

**1) To join the Project what do I have to do?**

1. Complete a simple, descriptive online registration form

<https://docs.google.com/forms/d/1xm8neJOdEKyG-u_A1PtYOM2mdjZeRlkM67DVy7YOROY/edit?usp=sharing>

**2) To participate actively in the Project what do I have to do?**

1. Promote the free e-learning course to be taken by all health professionals providing care to preterm infants in your network or related institutions. All participants will receive a certificate from the University of Oxford/Geneva Foundation for Medical Education and Research on successful completion of the course.
2. Implement the INTERGROWTH-21st Preterm Postnatal Growth Standards in your healthcare institution. The standards are suitable for monitoring the growth of preterm infants during hospital stay and after discharge up to 64 weeks’ postmenstrual age.
3. Promote the INTERGROWTH-21st evidence-based Feeding Recommendations that are conceptually linked to the standards.
4. Collect data on the status at hospital discharge and feeding practices of all preterm babies cared for at the participating institution. The methods of data collection are as follows:
5. Collect data using a summary Pregnancy and Delivery form. Enter the data into the Project database using the online data management system. Data will be the property of each individual institution. Aggregated data analysis will be conducted using only the variables that are agreed among the investigators.
6. Institutions are asked that, after hospital discharge, growth of the preterm infant is monitored using the Preterm Postnatal Standards (copies can be downloaded from the website; alternatively, measures can be plotted directly on the chart online).

Neonatal units will need to nominate a local contact person to provide information on programme uptake. Technical guidance and implementation support will be provided through regional offices and the central Coordinating Unit in Oxford.

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1. **Supporting documents for the implementation of the Preterm Postnatal Growth Standards**
2. **Feeding recommendations for the routine care of preterm infants**

Exclusive breastfeeding for preterm infants, by the time of hospital discharge and during the first months of life, is the goal of these feeding recommendations. Although the focus is on moderate and late preterm newborns, who represent close to 90% of all preterms, the recommendations are also relevant to very preterm newborns who are moving to enteral feeding. The use of human milk should be considered an institutional priority and personal attitudes or experiences of individual staff members should not interfere with this evidence-based practice.

The recommendations presented here are based on: 1) the feeding practices used during the implementation of the Preterm Postnatal Follow-up study (PPFS) of the INTERGROWTH-21st Project;12) a review of the literature up to December 2016, and 3) extensive consultation with clinicians worldwide and the INTERGROWTH-21st Neonatal Advisory Committee2and the INTERPRACTICE-21st Steering Committee.

Using a mother’s own breast or expressed milk should be the first option, followed by pasteurised donor human milk (during hospital stay only). As a last resort, formula (preterm formula if <32 weeks’ gestation) should be used;3-7 however, proportional growth (length and weight) should be carefully monitored to avoid overfeeding.8For uncomplicated preterm infants, nutrient enriched formulas are not recommended. Breastfeeding should be encouraged and the benefits of human milk feeding clearly explained; other feeding options should not be presented as if they were equally safe and efficacious choices.9 In addition, adequate support for breastfeeding from caregivers and continuous education of healthcare providers with regard to breastfeeding promotion and counselling are required. Evidence-based methods that promote human milk feeding of preterm infants and internal policies to support breastfeeding and increase milk production (e.g. Kangaroo Mother Care promotion) should exist.10-13

For clinically stable infants <32 weeks’ gestation, small amounts of trophic feeds (10 - 24 ml/kg/day) may be introduced on the first day of life.14 For infants >32 weeks’ gestation fed with expressed human milk, a starting volume of ~60 - 80 ml/kg/day is indicated, to a maximum of ~160 - 180 ml/kg/day by the end of the first week of life. Daily increases of 10 - 20 ml/kg are indicated but there are suggestions that the increases may be as high as 30 ml/kg/day, which in Very Low Birth Weight (VLBW) infants is associated with a reduction in the time needed to establish full enteral feeding without increasing rates of necrotising enterocolitis (NEC) or death in stable very preterm newborns.6,12,13

Clinical conditions in very preterm infants which may warrant delayed initiation of enteral feeding include severe persistent neonatal asphyxia, severe sepsis, shock, bowel obstruction, peritonitis, gastrointestinal bleeding and NEC. Growth-restricted preterm infants with abnormal antenatal Doppler studies are at increased risk of developing NEC and initiation of enteral feeding is frequently delayed. However, a recent study shows that early introduction of enteral feeds in growth-restricted preterm infants results in earlier achievement of full enteral feeding and does not appear to increase the risk of NEC.15 If breastfeeding is not possible, human milk may be given via an oro-gastric or naso-gastric tube either intermittently or continuously. Given the lack of high-quality evidence comparing the two methods,16 local practice should dictate which method is used. Babies should be encouraged to suck at the breast once sucking behaviour is observed and the practice of non-nutritive sucking is advised during the transition from gavage to full oral feeding.17Mothers and clinical staff should be encouraged to observe and implement cue-based feeding practices that are associated with a reduction in the time needed to establish full feeds and hospital discharge.18

The indicated duration of exclusive breastfeeding is 6 months supplemented with 1 mg vitamin K given intramuscularly at birth,3,19 400 IU vitamin D per day started in the first days of life,3,20 and 2 - 3 mg/kg iron per day starting between 2 and 8 weeks after birth.6 WHO recommends that infants start receiving complementary foods at 6 months of age in addition to breast milk.21 Recent research confirms the recommendation to initiate complementary feeding at 6 months, rather than 4 months, of corrected age in infants less than 34 weeks of gestation.22

In the event that the infant is unable to suck at the breast, expressed breast milk or donor human milk should be fortified in order to reach the recommended nutrient intakes3,6 as summarised in Table 1. Milk fortification may be introduced once enteral feeds of 100 ml/kg/day are achieved. Human milk fortifiers containing 0⋅8 - 1⋅1 g proteins, 1⋅1 - 3⋅6 g carbohydrates, and minerals (e.g. calcium 51 - 117 mg and phosphorus 34 - 67 mg) may be added to expressed human milk until the infant’s weight has reached 1800 - 2000 g.3

It has been suggested 23,24 that for very preterm infants the use of individualised human milk fortification may be effective in maintaining adequate growth, with no detrimental effects.25,26 Such individualised fortification is not recommended for preterm infants >32 weeks’ gestation or infants with birthweight >1.5 kg and requires analysis of neonatal blood urea and mother’s milk protein content. Any fully breastfed infant receiving only “fortification” may be considered to be exclusively breastfed. 27

The preterm infants in the INTERGROWTH-21st Project were fed based upon the above recommendations although local practice sometimes varied if the infants were clinically unstable. The recommendations are summarised in Table 2.28 They include those items that were updated in December 2016 which represent minor changes to clinical practice.

**Table 1. Recommended daily enteral macronutrients for preterm infants >1000g at birth 3,6**

|  |  |  |  |
| --- | --- | --- | --- |
| Nutrient | Birth to 7 days | Stable - growing up to term | Term to 1 year of age |
| Energy, kcal/kg | 70 -– 80 | 105 - 135 | 100 - 120 |
| Protein, g/kg | 1.0 - 3.0 | 3.0 - 4.0 | 2.2 |
| Fat, g/kg | 0.5 - 3.6 | 4.5 - 6.8 | 4.4 - 7.3 |
| Carbohydrate, g/kg | 5.0 - 20.0 | 7.5 - 15.5 | 7.5 - 15.5 |

**Table 2. Evidence-based recommendations used in the Preterm Postnatal Follow-up Study of the INTERGROWTH-21st Project, updated to December 2016**

|  |  |
| --- | --- |
| The overall goal is to promote exclusive breastfeeding for preterm infants at hospital discharge | |
| What to feed? Order according to evidence | 1. Mother’s own milk from the breast.  2. Mother’s expressed breast milk.  3. Donor human milk, fortified for preterms <32 weeks’ gestation.  4. Preterm formula (≤32weeks’ gestation) according to recommended intakes. |
| Feed volume for expressed or donor human milk | Start with 60 - 80 ml/kg per day for infants >1500g or >32 weeks’ gestation.  Increase by 10 - 20 ml/kg per day (to 30 ml/kg per day) to a maximum of 160 - 180 ml/kg per day by the end of the first week of life. |
| Feed progression | Most infants >32 weeks’ gestation will tolerate maintenance enteral feeds from the first day of life.  Infants <32 weeks’ gestation should be introduced to small amounts of trophic feeds (10 - 24 ml/kg per day) on first day of life. Infants >32 weeks’ gestation are likely to tolerate faster increases in volume (up to 30 ml/kg per day). |
| How to feed | Oro-gastric feeding is preferred to a naso-gastric tube, especially if the infant has increased work of breathing.  Either continuous feeds or bolus.  Infants should be encouraged to suck at the breast once sucking behaviour is observed. |
| Human milk supplementation | Vitamin D: 400 IU per day.  Phosphorus and calcium: Some evidence for reducing metabolic bone disease in infants weighing <1,500 g.  Iron: 2 - 3 mg/kg per day, start by 8 weeks of age.  Multi or single-component fortifiers: Associated with short-term increases in weight gain, linear growth and head growth. |
| Duration of exclusive  Breastfeeding | 6 months. |

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2. **Breastfeeding Resources**

Many websites providing useful information on breastfeeding are available. An example is given in the link below.

[http://med.stanford.edu/newborns/professional-educ...](http://med.stanford.edu/newborns/professional-education/breastfeeding.html)

[**Breastfeeding in the First Hour**](http://med.stanford.edu/newborns/professional-education/breastfeeding/breastfeeding-in-the-first-hour.html)

[**Early Initiation of Breastfeeding**](http://med.stanford.edu/newborns/professional-education/breastfeeding/early-initiation-of-breastfeeding.html)

[**Maximizing Milk Production**](http://med.stanford.edu/newborns/professional-education/breastfeeding/maximizing-milk-production.html)

[**ABC's of Breastfeeding**](http://med.stanford.edu/newborns/professional-education/breastfeeding/abcs-of-breastfeeding.html)

[**The Well Fed Baby Checklist**](http://med.stanford.edu/newborns/professional-education/breastfeeding/well-fed-baby-checklist.html)

[**Breastmilk and Medications**](http://med.stanford.edu/newborns/professional-education/breastfeeding/milk-and-meds.html)

[**A Perfect Latch**](http://med.stanford.edu/newborns/professional-education/breastfeeding/a-perfect-latch.html)

[**Hand Expressing Milk**](http://med.stanford.edu/newborns/professional-education/breastfeeding/hand-expressing-milk.html)

**Babies at Risk**

1. **International Postnatal Growth Standards for Preterm Infants**

The INTERGROWTH-21st Project assessed fetal, newborn and postnatal growth in eight geographically defined populations, in which maternal educational, healthcare and nutritional needs were met. From these populations, the *Fetal Growth Longitudinal Study* selected low-risk women starting antenatal care <14 weeks’ gestation and monitored fetal growth by ultrasound. All preterm births from this cohort were eligible for the *Preterm Postnatal Follow-up Study*, which included standardised anthropometric measurements, feeding practices based on breastfeeding and data on morbidity, treatments and development.

To construct the Preterm Postnatal Growth Standards, we selected all live singletons, born between 26 and <37 weeks’ gestation, without congenital malformations, fetal growth restriction or severe postnatal morbidity. We used second-degree fractional polynomial regression models in a multi-level framework accounting for repeated measures.

We enrolled 4607 women, resulting in 224 (4.9%) preterm births, of which 201 fulfilled the selection criteria. Variance component analysis demonstrated that only 0.24% and 4.0% of the total variability in postnatal length and head circumference could be attributed to between-site differences, justifying pooling the data from all study sites. We present here standards according to postmenstrual age and sex for postnatal weight, length and head circumference. The standards clearly exhibit different growth patterns compared to the published INTERGROWTH-21st Newborn Size Standards. They overlap with the WHO Child Growth Standards by 64 weeks of postmenstrual age.

The Preterm Postnatal Growth Standards (shown in **APPENDIX 2**) should be used to evaluate preterm infants until 64 weeks’ postmenstrual age, after which the WHO Child Growth Standards are appropriate. Size-at-birth charts are not appropriate for monitoring the postnatal growth of preterm infants.

1. **How to use the INTERGROWTH-21st Preterm Postnatal Growth Standards: Frequently Asked Questions (FAQs)**

**Why is the postnatal growth of preterm infants important?**

Fetal and newborn growth is an important predictor of an individual’s health, both in the short-term and across the whole life course. Preterm birth is a leading public health problem worldwide; it is responsible for up to 30% of neonatal deaths, and indirectly responsible for a further 20%.1,2 Standards are essential tools for monitoring growth; they are used at the individual and community level to ensure timely and adequate nutritional intervention, referral, and treatment of individuals and populations.

**What tools are currently used to measure preterm infant growth and what are their limitations?**

Five strategies exist for monitoring the postnatal growth of preterm infants; each has considerable limitations:

1. **Estimation of fetal weight by ultrasound:** This is not appropriate because estimated fetal weight is, by definition, an *estimation* with large measurement errors.3,4 These ‘intrauterine’ growth charts do not consider the physiological weight loss that occurs during the neonatal period. Furthermore, striving to match the growth of ‘healthy’ fetuses (an aim not substantiated by any data) may be a challenge especially for very preterm infants. Even if achievable, such a goal may be associated with adverse short- and long-term consequences.5
2. **Birthweight for gestational age charts:** Data to construct them are cross-sectional and obtained from a single measure taken immediately after birth (which is a summary measure of fetal growth). ‘Size-at-birth charts’ should not be used to monitor postnatal growth.
3. **Postnatal longitudinal growth charts for preterm infants:** Considerable efforts have been made to document the actual postnatal growth of very low birthweight babies. Many of these charts are not suitable for clinical use.6 Most lack rigorous participant inclusion/exclusion criteria; adequate quality control measures; reliable ultrasound based estimation of gestational age; adequate duration of follow-up and description of feeding practices.
4. **Prescriptive growth standards for infants born at term**: The WHO prescriptive standards are used globally for term infants. 7 However, when these charts are used for preterm infants, the growth measures often fall far below the lowest centiles because the postnatal growth of preterms is different from that of term infants.
5. **A combination of birthweight for gestational age charts and prescriptive growth standards for term babies:** This combination has the same fundamental problems listed above for each of its components.

**What is the difference between a reference and a standard for growth monitoring?**

**References**, often based on data routinely collected with limited or no standardisation and quality control, describe how subjects *have* grown at a particular place and time. In contrast, **Prescriptive Standards** describe how subjects should grow under optimal conditions - in the case of preterm newborns, according to their clinical status and degree of maturation.8,9 This prescriptive strategy for monitoring the growth of humans has been recommended by WHO since 1995.10 Standards are universal and may be used across time; they are ideal tools for standardisation of research protocols, systematic reviews and meta-analyses and international comparisons of nutritional status. These characteristics are crucial in the 21st century given the extent of ancestral admixture, migration, global economic growth and refugee crises.11

**Is a standard suitable to monitor the growth of a preterm infant?**

YES. It has been reported that standards cannot be produced for preterm infants because babies born preterm are neither “normal” nor “healthy”. We believe that preterms are in an “immature” rather than pathological state, i.e. the pathological component, which is organ specific, is related to gestational age and complications of immaturity. The **INTERGROWTH-21st Preterm Postnatal Standards**12 may be used for monitoring postnatal growth in preterm babies and complement the international standards for Crown-Rump Length in the first trimester of pregnancy,13 Fetal Growth,14 Newborn Size at Birth,15 Very Preterm Size at Birth16 and Child Growth for term infants.7 Thus, growth and development may be monitored from the first trimester of pregnancy until 5 years of age, irrespective of location, ancestral origin, or timing of birth.

**Are the INTERGROWTH-21st Preterm Postnatal Growth Standards applicable to all preterm infants?**

YES. **The INTERGROWTH-21st Preterm Postnatal Growth Standards** 12 are suitable for all preterm babies. Theywere constructed using data from singleton preterm babies born at 26 to less than 37 weeks’ gestation. They are particularly suitable formonitoring postnatal growth in preterm babies after 32 weeks’ postmenstrual age and may be used for the assessment of preterm infants until 64 weeks’ postmenstrual age (6 months “corrected” age), the time at which they overlap, without the need for any curve adjustment, with the WHO Child Growth Standards for term newborns.

The construction of charts for very preterm infants <32 weeks’ gestation is problematic because there is no definitive information on the nutritional needs of these tiny babies; it may be argued that, during these early postnatal weeks, monitoring of growth should be carried out only to track a growth trajectory rather than used as a screening tool for detecting growth restriction.

The INTERGROWTH-21st standards allow all preterms to benefit from a postnatal growth monitoring strategy that matches the WHO Child Growth Standards, and provides continuity of care from the special neonatal care unit to the outpatient clinic.

**How did the INTERGROWTH-21st Project select preterm infants for the standards?**

INTERGROWTH-21st has produced prospective, longitudinal, prescriptive, postnatal growth standards specifically constructed for preterm infants from 27 weeks’ gestation, born to healthy mothers with well-dated pregnancies and no evidence of intrauterine growth impairment assessed by serial ultrasound from <14 weeks’ gestation.12 This unique cohort of infants was followed up using rigorous, standardised methodology for the assessment of anthropometric measures, health, nutrition, motor- and neuro-development until 2 years of age.

**How were the preterm infants enrolled in the INTERGROWTH-21st Project fed?**

An evidence-based, nutritional protocol derived from currently recommended guidelines (mostly for stable infants who were able to have enteral feeding) was implemented across the participating study sites (please see section on feeding recommendations). It was based on exclusive breastfeeding at the time of hospital discharge, ideally continued exclusively until 6 months of age. It proved to be feasible and well accepted by clinical staff and mothers.17

**What statistical methodology was used to generate the Preterm Postnatal Growth Standards?**

The statistical methods were based on those used to construct the INTERGROWTH-21st Fetal Growth Standards 14,18 and are described in detail elsewhere.12

**Is a sample size of 201 preterm infants enough to create reliable standards?**

YES. In this study of a low- to medium-risk population in which women were recruited in the first trimester of pregnancy and received frequent antenatal care, few preterm infants were born despite the large sample size (4607 pregnant women) from which they were derived.12

There are additional issues to consider when judging the “small” sample size of this study: a) WHO recommends, as a general rule, a total sample of 200 subjects of each sex for studies of human growth from a longitudinal design;19 b) longitudinal studies are more precise than cross-sectional ones. It has been calculated, in studies on fetal growth, that a longitudinal design requires half the sample size of a cross-sectional study in order to estimate a given centile with the same precision,20 i.e. our 201 newborns, who contributed 1750 measures during the follow-up, have power equivalent to a sample of 3500 in a cross-sectional study; c) the strict standardised protocols, training of staff, equipment and quality control procedures reduced measurement error and the likelihood of biased estimates; d) the resulting curves do not have any unexpected behaviour at any gestational age that can be related to the small amount of data available. Although it is likely that a larger sample would increase variability, the centiles close to the median are not expected to change markedly; and e) plots of individual measurements with overlapping centile curves and comparisons of empirical and fitted centiles showed good agreement.

Hence, the INTERGROWTH-21st standards are robust for more than 90% of the preterm population and, for those born <32 weeks’ gestation, are also robust after a few weeks of postnatal life when the babies are in a more clinically stable condition and able to start some enteral feeding.

**Can the preterm longitudinal standards be used from birth?**

The **first** evaluation of a **preterm** birth <37 weeks’ gestation should be done using the cross-sectional size Very Preterm Size at Birth Reference Charts 15,16  **(intergrowth21.tghn.org)** because this value is a cross-sectional summary measure of the fetus’ attained size. In other words, the Very Preterm Size at Birth Reference Charts should be used at one time point only i.e. at the time of preterm birth. The INTERGROWTH-21st Preterm Postnatal Longitudinal Growth Standards should be used for monitoring growth after birth. The postnatal weight loss experienced by neonates during the first days of life, due mainly to water loss, is better assessed as the percentage of weight lost from birth. After that, the Preterm Postnatal Longitudinal Growth Standards should be used during hospital stay and after discharge up to 6 months’ post-term.

**How to monitor postnatal growth of preterms born between 24 and 27 weeks’ gestation?**

There is a small yet very high-risk group of preterms born between 24 and 27 weeks’ gestation. For this subgroup, the Very Preterm Size at Birth Reference Charts should be used at birth. Monitoring their growth during the period until they reach 27 weeks’ postmenstrual age is recognised as a useful instrument to evaluate their health and nutritional status, but there are no specific longitudinal growth charts. It is advisable to take into account the percentage loss of postnatal weight as an indicator of weight trajectory until recovery of the birthweight. Estimation of the water balance during parenteral nutrition is an additional tool in monitoring the clinical course during the first two or three weeks of life, a very critical time period, until the Preterm Postnatal Growth Standards can be used.

**Which standards should be used for the assessment of preterm infants older than 6 months?**

The WHO Child Growth Standards for term infants 7 are the natural continuation of the INTERGROWTH-21st Postnatal Growth Standards and should be used to monitor the growth of preterm infants older than 6 months.

**How different are the INTERGROWTH-21st standards from the old reference charts?**

The results of our systematic review of the literature showed that the methodological quality of the previous longitudinal charts was fair to low, with most charts being affected by methodological weaknesses.6 The INTERGROWTH-21st Preterm Postnatal Growth Standards are the only available standards that have all the following characteristics:

1) Gestational age was accurately assessed by combining a reliable LMP with early fetal ultrasound.

2) Anthropometric measurements were taken by trained staff using identical, standardised instruments and techniques.

4) Fetal growth was monitored by serial ultrasound to exclude preterm cases with evidence of fetal growth restriction.

5) The follow-up period was extended to 8 months to avoid the so-called right-edge effect in constructing the growth standards.

6) We avoided using birthweight as a proxy for prematurity.

7) Well-described analytical, statistical, and reporting methods were used.

# Do the INTERGROWTH-21st Preterm Postnatal Growth Standards change the current definition of “extra-uterine growth restriction”?

YES. The new Preterm Postnatal Growth Standards 12 completely change the perspective. They are no longer based on the assumption that the postnatal growth of preterm infants should mimic the intrauterine growth of fetuses of the same gestational age, but rather describe the actual growth of preterm infants monitored longitudinally after birth. The new centiles are different from the fetal 14 and the cross-sectional size at birth neonatal centiles 15 and suggest to us that preterm infants should not be forced to grow rapidly to mimic fetal growth. The concept of iatrogenic “extrauterine growth restriction” will also no longer apply; the truly complicated infants will be detected by their slow growth compared to their preterm, but healthy, peers.

# What should be done to ensure that all infants grow well according to these standards?

Breastfeeding should be supported, protected, and promoted. As recommended for term infants by WHO, and also for preterms for the first 6 months, mothers need to be informed and empowered to practise exclusive breastfeeding. Good health care and nutritional practices 21 **(please see section on the feeding protocol)** should be available and accessible to all infants.

**How do I obtain copies of the new growth charts and/or calculate centiles and z scores?**

Centiles for weight, length and head circumference, with corresponding z scores, are presented in paper, electronic and phone-friendly formats for the follow-up of preterm infants from hospital care to outpatient clinics and family care. (<https://intergrowth21.tghn.org>).

**How can I be sure I am using the charts correctly?**

Educational materials and e-learning modules for use of the charts and anthropometry are available at <https://intergrowth21.tghn.org>

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22. **Anthropometric Manual for the Measurement of Preterm Babies**

**Training Video**

An anthropometry training video showing how to measure infant weight, length and head circumference (HC) is now available at

<https://intergrowth21.tghn.org/>

**Recumbent length**

Infant length may be measured using the Harpenden Infantometer (range 300–1100 mm; Chasmors Ltd, London, UK), which has a fixed headboard, moveable footboard and digital counter accurate to 0.1 cm. To measure recumbent length, the infantometer is placed on a raised, flat surface that is level and stable. The infant is undressed and positioned on the horizontal board, which is covered with a thin cloth or soft paper. The anthropometrist stands by the side of the infantometer with the digital counter so as to be able to read the measurement. With the left hand, the anthropometrist holds the infant’s legs, leaving the right hand free to manoeuvre the footboard. The second anthropometrist stands at the headboard and positions the infant’s head in the Frankfort Vertical Plane, ensuring that the infant’s spine is not arched when the reading is taken.

The footboard is pressed against the feet to compress the soles slightly before the measurement is taken. Both length and HC are recorded in cm to the last completed (not the nearest) mm. For example, if the value for length lay between 50.2 cm and 50.3 cm, the value is recorded as 50.2 cm.

**Head circumference**

Head circumference may be measured using a self-retracting, flat metal tape measure (Chasmors Ltd, London, UK), 0.7 cm wide, range 0–2 m, precise to 1 mm with an 8 cm blank lead-in. This tape was chosen because it is non-extendable, durable and stays in a single plane around the head.

To measure HC, one anthropometrist positions the infant on his/her lap while supporting the head. The other anthropometrist loops the tape (with the cm markings on the outside), with the zero end in the inferior position, before slipping it over the infant’s head. The tape is anchored just above the eyebrows, with the zero point on the side of the infant’s head closest to the anthropometrist taking the measurement. The forehead anchor point is important for standardised measurement within and across study sites. At the back of the head, the tape is positioned over the fullest protuberance of the skull. The second anthropometrist assists by positioning the tape correctly, i.e. level, on the other side of the infant’s head. Once the tape is positioned correctly, the anthropometrist pulls the tape tight to compress the hair and skin being careful not to pull the tape too tight and cause discomfort, especially to newborns.

**Weight**

Infant weight may be measured using a portable, electronic weighing scale (Seca model 376; Seca, Hangzhou, China or equivalent). The Seca scale has a tare facility and weighs in kilograms to the nearest 5 g up to 7.5 kg, and to the nearest 10 g up to 20 kg. These scales are easy to use, and the tare function allows the baby to be covered in a blanket in cold climates and in cultures where it is unacceptable to undress the baby. Infant weight is measured last because of the need to remove all the infant’s clothes. If a blanket or cloth is required to wrap the infant, the scale is first tared with the item to give a zero reading. The infant is then placed carefully on the scale and once he/she stops moving the anthropometrist presses the ‘Hold’ button on the scale to obtain a stable weight and freeze the reading on the display.

The value is then recoded on the data collection form.

In the case of an extremely sick infant in a neonatal intensive care unit, the incubator’s electronic scale (if available) is used, having been calibrated in the same way as the baby scales. For most babies in an incubator, HC is measured as described above. For those reliant on nasal continuous positive airflow pressure, the HC measurement is delayed until the nasal tubes are removed. Length is measured within the first 7 days of life, where possible, once the baby has been removed from the incubator. The date and time of all measurements, as well as the infant’s

date and time of birth, are recorded on the data collection forms.

1. **Pregnancy and Delivery Form (Appendix 1)**

The Pregnancy and Delivery form is a standardised data collection form and should be completed at hospital discharge of the preterm babies.

<http://www.medscinet.net/Interbio/Uploads/ProtocolDocs/FSNS%20INTERBIO%20Pregnancy%20&%20Delivery%20%28Apr%2023,%20UK%29.pdf>

The form includes sections on the newborn outcome and anthropometric measures. Instructions for its completion are available on the Project website.

<http://www.medscinet.net/Interbio/Uploads/ProtocolDocs/INTERBIO%20PREG-DEL%20Instructions%20v1.4%2002-2013.pdf>

1. **Ultrasound Form (Appendix 1)**

The ultrasound form should be completed for each ultrasound examination available in the woman’s medical records. (Completion of this form is optional).

1. **Neonatal Follow-up (2-8 weeks, Appendix 1)**

This form should be completed for neonates aged between 2 and 8 weeks. (Completion of this form is optional).

1. **Infant Follow-up (3-6 months, Appendix 1)**

This form should be completed for neonates aged between 3 and 6 months. (Completion of this form is optional).

**5. e-Learning Course**

**5. e-Learning Course**

An e-learning course on the use of the INTERGROWTH-21st Preterm Postnatal Growth Standards, evidence-based neonatal preterm newborn care and feeding recommendations is freely available on our website.

<http://www.gfmer.ch>

The Project Coordinator in each participating neonatal unit should ensure that all clinical staff, medical students and trainees in their hospital complete the free e-learning course during the preparatory phase. They should also promote the course in other hospitals in their area. Participants will receive a certificate from the University of Oxford and GFMER on successful completion.

**6.Governance**

**Preliminary Project Structure**

**Steering Committee**

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1. **APPENDIX 1**
2. **APPENDIX 2**