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Prematurity detection evaluating interaction between newborn skin and light: The Premie-Test Multicenter Clinical Trial to validate a new medical device

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Keywords:	Gestational Age, Infant, Premature, Skin Physiological Phenomena, Photomedicine, Equipment and Supplies

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Manuscripts

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4 **Prematurity detection evaluating interaction between newborn skin and light:**
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6 **The Premie-Test Multicenter Clinical Trial to validate a new medical device**
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Abstract

Introduction: Recognizing prematurity is critical in order to attend to immediate needs in childbirth settings, guiding the extent of medical care provided for newborns. A new medical device has been developed to carry out the Premie-Test, an innovative approach to estimate gestational age (GA), based on the photobiological properties of the newborn's skin. This study will validate the Premie-Test for GA estimation at birth and its accuracy to detect prematurity. Secondly, the study intends to associate the infant's skin reflectance with lung maturity, as well as evaluate safety, precision, and usability of a new medical device to offer a suitable product for health professionals during childbirth and in neonatal care settings.

Methods and analysis: Research protocol for diagnosis, single-group, single-blinding, and single-arm multicenter clinical trials with a reference standard. Alive newborns, with 24 weeks or more of pregnancy age, will be enrolled during the first 24 hours of life. Sample size is 787 subjects. The primary outcome is the difference between the GA calculated by the photobiological neonatal skin assessment methodology and the GA calculated by the comparator antenatal ultrasound or reliable last menstrual period. Immediate complications caused by pulmonary immaturity during the first 72 hours of life will be associated with skin reflectance in a nested case-control study.

Ethics and dissemination: Each local independent ethics review board approved the trial protocol. The authors intend to share the minimal anonymized data set necessary to replicate study findings.

Trial registration number: U1111-1205-0539; WHO Clinical Trial
<http://apps.who.int/trialsearch/Trial2.aspx?TrialID=RBR-3f5bm5>.

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6 **Key-words:** Gestational Age, Infant, Premature; Skin Physiological Phenomena;
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8 Photomedicine; Equipment and Supplies.
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10 11 12 13 14 **Article Summary**

15 16 17 **Strengths and limitations of this study:**

- 18 • The study has the potential to validate a new approach for pregnancy dating.
- 19 • The device will be subjected to high-quality clinical study to demonstrate benefits.
- 20 • The gold standard comparator for pregnancy dating does not exist, instead a reference
21 standard will be used with blinded primary outcome.
- 22 • The agreement endpoint between methods for gestational age determination
23 precluded randomization of the intervention.
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Introduction

In childbirth settings, health professionals continuously need to make timely decisions to provide proper neonatal care. The day of birth is the riskiest for newborns and mothers almost everywhere¹. Perinatal causes related to prematurity and complications during childbirth, which are generally preventable through qualified health care, are the primary causes of death among newborns^{1,2}. Most of these deaths took place in countries with low resources and a scarcity of health facilities³. The opportune recognition of prematurity is critical in order to judge the viability of the newborn and to attend to his/her immediate needs, guiding the complexity of the medical care provided for the newborn. Without reliable information on the age of the unborn phase, actions to preserve the potential for survival of the newborn can be neglected⁴. Indeed, the attempted management of the risk of mortality and severe complications are sensitive issues to the gestational age (GA), which involves temperature maintenance, ventilatory support, transport to a neonatal intensive care unit (NICU), and the early treatment of respiratory distress syndrome (RDS), the most severe complication of premature birth⁵. In addition to the GA information or birthweight, the prediction of neonatal respiratory morbidity may be critical in planning immediate medical care⁶, since the respiratory system is among the last of the fetal organ systems to mature, which is associated with enhanced morbidity and mortality⁶.

Current methods of dating pregnancy remain a worldwide challenge. Early obstetric ultrasound currently offers the best due date⁷. However, access to this type of exam is limited because of high equipment costs, poor training and skills of health professionals, or late prenatal care⁸. Despite a 10-days or more margin of error during the second and third trimester of gestation, ultrasound is still a reasonable methodology for GA determination, when the best opportunity was lost⁷. The calculation, based on the historical information of

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4 the last menstrual period (LMP), is impacted by the uncertainty of both the fertility days and
5 date of conception⁹, due to the bias of memory, the use of hormonal contraception, and
6 breastfeeding¹⁰. After birth, neurological scores, such as the New Ballard¹¹, show a tendency
7 to overestimate GA in preterm infants and underestimate GA in growth-restricted infants¹².
8 Efforts to enhance the reliability of pregnancy dating, through more accurate and accessible
9 technologies, seek to improve pregnancy outcomes and neonatal survival¹³.

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17 A new medical device has been developed to carry out the Premie-Test, an innovative
18 approach used to estimate GA, based on the photobiological properties of the newborn's
19 skin. This reflective test is noninvasive, and the device automatically processes the light,
20 scattered by the constituents of the skin layers, when a small optoelectronic light
21 emitter/receiver sensor touches the newborn's skin¹⁴. the device under test is easy to use
22 and every effort is being made to ensure that it has excellent accuracy, be it safe and low
23 cost. The feasibility study provides a mathematical model to predict GA based on the skin
24 reflectance adjusted to clinical variables ($R^2 = 0.828$, $P < 0.001$)¹⁵. However, before the
25 adoption or use of an innovation, an effectiveness trial of intervention is a critical step in the
26 research chain regarding its the social utility when completing the translation from the proof
27 of concept to clinical science ¹⁶. The rationale for the main hypothesis in this study is that
28 the skin maturity of a newborn, obtained by the analysis of its optical properties, is useful in
29 pregnancy dating for clinical use and respiratory prognosis, especially in a scenario with no
30 reliable GA based on current methods. This study aims to validate the photobiological model
31 of the skin, called the "Premie-test", in order to estimate GA at birth and determine its
32 accuracy in detecting prematurity. Secondly, it also seeks to associate the infant's skin
33 reflectance with lung maturity. Moreover, this study intends to evaluate the safety, precision,
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4 and the usability of a new medical device to offer a suitable product to support health
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6 professionals during childbirth and in neonatal care settings.
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8 9 **Methods**

10 11 ***Study design***

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14 This study will use a protocol for diagnosis, single-group, single-blinding, and single-arm
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16 multicenter clinical trials with a reference standard. This new photobiological approach to
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18 the skin, gathered in a medical device, is currently in the pivotal phase of innovation
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20 development from the prototype to regulatory approval¹⁷. This step aims to provide the
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22 translation¹⁶ of the scientific model for GA detection based on skin maturity. This Protocol
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24 version is 1, July/10th/2018. Faculty of Medicine, Universidade Federal de Minas Gerais is
25
26 the Coordinator Center.
27

28 29 ***Study Settings, Ethics and Dissemination***

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32 Selected Brazilian referral centers for high-risk pregnancy and neonatal care will participate
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34 in the study, according to this protocol: Hospital das Clínicas, Universidade Federal de
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36 Minas Gerais, as the Center for Coordination; Hospital Sofia Feldman, Minas Gerais State;
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38 Hospital da Universidade Luterana do Brasil, Rio Grande do Sul State; Hospital Materno-
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40 infantil de Brasília, Distrito Federal; and Hospital Universitário da Universidade Federal do
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42 Maranhão, Maranhão State. Each local independent ethics review board approved the trial
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44 protocol, and the Brazilian National Research Council (CONEP) approved all study activities
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46 and protocol prior to the commencement of study activities, in accordance with the
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48 Declaration of Helsinki (2008), good clinical practice as set forth by the International
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50 Organization for Standardization (ISO) 14155:2011, and the Brazilian regulatory health
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52 agency's recommendations¹⁸. This study was logged under both protocol number CAAE
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4 81347817.6.1001.5149 and the International Clinical Trials Registry Platform under
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6 Universal Trial Number U1111-1205-0539 is accessible by
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8 <http://apps.who.int/trialsearch/Trial2.aspx?TrialID=RBR-3f5bm5>. Parents will sign an
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10 informed consent form on behalf of the newborn before participating in the clinical trial
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12 (supplementary file).
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14 15 ***Data Sharing Statement***

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18 The authors intend to share the minimal anonymized data set necessary to replicate study
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20 findings. Data sharing will include: the reference and comparators GA, GA estimated by the
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22 Premie-test, birth weight, RDS or transient tachypnea of the newborn (TTN) diagnosis,
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24 ventilatory support due to pulmonary immaturity, neonatal intensive care unit (NICU)
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26 admission due to RDS or TTN, and any adverse events regarding device's safety.
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28 Unidentified data and study-related documents as ethical approvals will be accessible by
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30 URLs for researchers, regulatory agencies, and sponsors.
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33 ***Patient and Public Involvement***

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36 Patients and the public were not involved in the design of this study. The results will be
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38 disseminated to study parents of participants through scientific publications, non-
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40 scientific publications, and on the website of the project: <http://skinage.medicina.ufmg.br>.
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43 ***Eligibility criteria and participant's timeline***

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46 A prospective sequential and concurrent enrollment process will select newborns in referral
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48 hospitals centers for neonatal care. Infants are eligible with the following inclusion criteria:
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50 (1) alive newborn; (2) enrollment during first 24 hours of life; (3) be 24 weeks or more of
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52 gestational age, at birth; (4) fetus underwent an obstetric ultrasound assessment before 14
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54 weeks of pregnancy; (5) fetus also had obstetric ultrasound assessment between 14 and 22
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4 gestational weeks. Exclusion criteria are: (1) malformation with structural skin alterations;
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6 (2) skin modifiers: anhydramnios, hydrops, congenital skin diseases or chorioamnionitis.
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8 Randomisation was not appropriate to assess the agreement between different methods to
9
10 assess pregnancy dating.
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13 In a nested case-control study, we will select newborns within the first 72 hours of life,
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15 discharge, or death, whichever occurs first, with the following inclusion criteria: (1) RDS or
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17 (2) TTN diagnosis. Ranges of gestational age will randomly pair controls. Exclusion criteria
18
19 include: (1) the existence of extra pulmonary conditions with tachypnea not due to
20
21 prematurity and (2) diagnosis of Clinical or Laboratory-Confirmed Bloodstream Infection.
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23 24 ***Intervention: The Premie-Test***

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27 The Premie-Test assessment occurs as soon as possible after birth, in the first 24 hours,
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29 inside incubators, open heating crib, common crib or in the mother's lap, in order to ensure
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31 minimum manipulation and stable clinical conditions. The acquisitions of all newborns will
32
33 be stored in a database for further statistical analysis.
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36 A noninvasive, handheld optoelectronic prototype has been developed to measure the
37
38 backscattered light signal from the skin¹⁵. The equipment regulates the emitted light and
39
40 processes the received light signal in the sensor, resulting in the prediction of GA by a
41
42 mathematical model, associated or not with clinical variables. According to the Brazilian
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44 regulatory health agency (ANVISA), this medical device is categorized as a Class II safety:
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46 noninvasive and medium risk. The prototype unit of measurement and the process of GA
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48 estimation were patented under number BR1020170235688 (CTIT-PN862)¹⁴. An updated
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50 version of the invention received improvements in order to safeguard reliability and to
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52 minimize examiner interferences on the skin's backscattering acquisition. The light emitting-
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54 sensor touches the skin over the sole of the foot for a few seconds. The skin reflectance will
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4 be sensed once the light has been emitted by a light emitting diode (LED) at wavelengths
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6 from 400 nm to 1200 nm. Data acquisitions occur automatically, without operator influence,
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8 and are obtained three times per newborn, in the same site and sequentially. Digital
9
10 recordings will be uploaded to a server for further analysis. The prototype will blind the
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12 examiner to the predicted GA value.
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17 The criterium for discontinuing the interventions for a given trial participant will be in case of
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19 parents of the newborns' request.
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22 ***Training and monitoring***

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24 Systematic monitoring of data collection, through an electronic information system, would
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26 trigger any adverse event. This medical team is still responsible for the training of healthcare
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28 professionals to recruit participants, data collection, a safely performed Premie-Test during
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30 the newborn's assessment, and the monitoring of data quality. The certification of co-
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32 participant centers involved the accomplishment of at least 30 simulated examinations by
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34 the participant health professionals in the study.
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38 ***Gestational age methods of calculation and comparators***

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40 Reference-GA (R) is calculated upon enrollment, using the embryo measurement assessed
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42 by ultrasound exam at <14 weeks of gestation as a reference. Crown-rump-length (CRL)
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44 data, recorded from the ultrasound report or prenatal care book-document, will be
45
46 considered the crude data, when available. Intergrowth's 21st standard curve for ultrasound
47
48 measurements from 7 weeks and 3 days up to 13 weeks and 6 days will be adjusted to all
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50 GA data, according to CRL¹⁹.
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54 GA methods to calculate GA in the childbirth setting, and their comparators are as follows:
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- Premie-Test-GA (T): data statistically determined by analyzing the acquired information stored in the device's processor.
- Comparators-GA (C): calculated using the first ultrasound exam after 13 weeks and 6 days of gestation and before 22 weeks (C1). When available, a second comparator is GA based on a reliable LMP (C2)¹³.

We will take a scanning copy of the prenatal care book or the ultrasound report. After evaluating the data quality, the images will be discarded. To achieve a reliable LMP, we will interview the woman, as suggested by Nguyen et al. (2000)¹³.

Primary outcome measures

The primary target is the agreement between the GA offered by the Premie-Test (T) and the GA calculated by the comparators (C1 and C2), so as to perform the new test in scenarios without the Reference-GA (R). The outcome is the difference between the GA calculated by the photobiological neonatal skin assessment methodology in relation to the age calculated by the comparators.

Another measure for the primary target is the detection of preterm newborns, considering the age before 37 weeks of pregnancy as the threshold between term and preterm births, and analyzing sub-categories of preterm birth, based on GA⁴:

- extremely preterm (less than 28 weeks)
- very preterm (28 to 32 weeks)
- moderate to late preterm (more than 32 to less than 37 weeks).

In this case, the outcome is the proportion of the preterm newborn correctly detected at birth, based on the photobiological test of the skin, within a one-week error.

Secondary outcome measures

1. In a simulated scenario, in which the Reference-GA (R) is unknown, two groups will be randomly assigned from the complete database in order to compare differences among the Reference-GA (R), the GA obtained through the Premie-Test (T), and the GA calculated by the comparators. Figure 1 presents such subgroups and measures for comparison.
2. To monitor the device's safety when in regular use by participants over a 72-hour period. Adverse events will be monitored, according to ISO 14155:2011 standards. This means any unexpected medical events, unintended disease or injury, or unfortunate clinical signs in subjects, users, or other people, whether related to the investigational medical device or not.
3. To establish the *ease of use* of the Premie-Test measurement as a potential method for preterm newborn diagnosis.

The secondary outcome measures in the case-control nested study

Immediate complications, occurring during the first 72 hours of life due to pulmonary immaturity, are the secondary target. The outcome measures are as follows:

- To describe the relationship of the measurement of the newborn's skin reflectance with RDS and with diagnoses based on clinical and radiological findings and respiratory outcomes^{6,20}.
- To describe the relationship of the measurement of the newborn's skin reflectance with the TTN and with diagnoses based on clinical findings and respiratory outcomes⁶.

- To describe the relationship of the measurement of the newborn's skin reflectance with ventilatory support due to pulmonary immaturity.
- To describe the relationship of the measurement of the newborn's skin reflectance with NICU admission due to RDS or TTN.

Time schedule of enrollment, intervention, and outcome measurements are presented in a schematic diagram (see Figure 2). The assessment occurs during the first 24 hours of life, but participants will be followed up for 72 hours or until discharge or death, whichever occurs first, for the monitoring of neonatal outcomes and adverse events.

Sampling and sample size

The sample size calculation is estimated based on the primary endpoint. To test the hypothesis of equivalence between the Premie-Test GA and the comparators GA, a sample of 787 subjects is necessary to detect an effect size of 10%. Using the G-Power 3.1 software²¹, we assumed an alpha error of 0.05, and a power of test of 0.80 to support a paired t-test.

Sampling intends to arrange three groups of GA enrollment to preserve enough premature newborns with 3:2:1 proportion, similar to Wilson et al. (2017)²²: 392 term newborns, 263 premature newborns from 32 to 36 weeks and six days of GA, and 132 extremely premature newborns from 24 to 31 weeks and six days of GA.

Usability

The usability assessment will be performed by applying a checklist to participants who use the prototype device to perform the Premie-Test. The 10 heuristics proposed by Nielsen and Marck [(1994)²³] will be adapted to build a checklist to evaluate the device, namely: (a) system visibility, (b) correspondence with the real world, (c) user control and freedom, (d)

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4 consistency of results and standardization, (e) error prevention, (f) visual recognition rather
5 than memorization, (g) flexibility and efficiency of use, (h) esthetic and minimalist design, (i)
6 help for the user to recognize, diagnose, and recover from errors, and (j) user documentation
7 and help.
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13 ***Data collection***

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15 Standard operational procedures set data entries in structured questionnaires. In this
16 concurrent clinical trial, an electronic information system was developed to collect data in
17 different hospitals, simultaneously. Entry forms validations were implemented with data
18 values ranges to ensure the quality of the information. An audit of the data will be
19 permanently performed and the data summary available on the project webpage. Double
20 system, paper-based and electronic will permit audit concerning reliability and validity.
21 Independent rater over-read all papers files and cross check with the electronic information
22 from all patients.
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33 ***Data analysis***

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35 Demographics and baseline characteristics of the study group, as well the intervention
36 measurements, will be summarized by the frequencies and the mean and standard deviation
37 (SD), the whereas median and interquartile range will be preferred for non-normally
38 distributed continuous variables.
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45 To model the GA prediction, computational randomization will select two subsamples in the
46 database. One of them to train the prediction model of GA based on skin reflectance and
47 clinical variables, such as sex, time in an incubator, phototherapy, birth weight, among
48 others. Another part will be for the analytical validation of the predictive model.
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4 Improvements in the existing prediction models for GA (Premie-Test), will be conducted
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6 with conventional statistical and data mining analyses.
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9 Regarding the primary endpoint, the agreement among three methods for GA will be
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11 calculated using the Intraclass coefficient correlation and Bland & Altman plots²⁴, and paired
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13 t-testing. The accuracy of the Premie-Test in identifying the premature newborn, within a
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15 one-week margin of error, will be the target of the accuracy analysis.
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18 The relationship between the measurement of the newborn's skin reflectance and
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20 complications due to pulmonary distress associated with immaturity will be evaluated by
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22 means of association tests and risk. The significance level for hypothesis tests will be 5%,
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24 together with 95% confidence intervals.
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26 27 28 29 **Results**

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32 The study begun with the training of health professionals in September 2018. It is anticipated
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34 that the recruitment will take place from January to December 2019. Data analysis will be
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36 finalized, the results of which are expected in May 2020.
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38 39 40 41 **Discussion**

42 43 44 ***Strengths and Limitations***

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46 Availability of trustworthy GA information is a prerequisite for preterm birth classification and
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48 healthcare decisions²⁵. In this light, the results of this clinical study have the potential to
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50 validate a new device for pregnancy dating. The Premie-Test was prepared to operate with
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4 minimum operator intervention and for use by healthcare professionals anywhere a birth
5 takes place without a reliable GA.
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9 The purpose of medical research involving neonates is intended to improve clinical
10 procedures²⁶. In this context, a clinical trial is a research study in which subjects are
11 prospectively assigned to intervention and the effects of those interventions on health-
12 related outcomes are thereby evaluated²⁷. However, clinical trials on medical devices face
13 barriers when an effective standard procedure does not exist, as is the case of the
14 comparator procedure²⁸. Our challenge in preparing the present protocol was the absence
15 of a gold standard for pregnancy dating, since the fetal age begins upon conception;
16 however, this information is difficult to be accurately determined⁷.
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Author statement:

ZSNR: designed the study, planned data collection, prepared the team for good clinical practices, wrote and revised the paper. RNG, RAPLA, MASR, RMCR and JSG made substantial contributions to study design, planned data collection, prepared the team for good clinical practices, wrote and revised the paper. GLNV, MAAR, GSN, PJHN, MDRM, and MVN made contributions to standard procedures in methods, drafted the manuscript, reviewed the paper, and approved the final manuscript. EAC: drafted the work and reviewed it critically for important intellectual content, as statistic consultant.

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4 training; Fotini Toscas from the Brazilian Ministry of Health for the active intermediation as
5
6 the trial sponsor contact.
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11 **Roles and responsibilities:** ZSNR is the Principal Investigator and coordinator of the
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13 Directive Committee. JSG is the coordinator of the Data Management Team and will
14
15 continuously receive report adverse events of trial interventions or trial conduct. RAPLA is
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17 the coordinator of the Clinical Trial Quality Committee, responsible for important protocol
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19 modifications, if necessary.
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24 **Conflict of interests statement**

25
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27 Authors declare a patent deposit on behalf of the Universidade Federal de Minas Gerais
28
29 and Fundação de Amparo a Pesquisa de Minas Gerais, Brazil, <http://www.fapemig.br/en/>.
30
31 The inventors were Reis, Zilma Silveira Nogueira and Guimaraes, Rodney Nascimento:
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33 BR1020170235688 (CTIT-PN862)¹⁴.
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39 Figure 1. Secondary outcome comparisons between the reference GA and the
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41 Premie-Test in a simulated scenario without best pregnancy dating
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46 Legends: *Gestational age from crown-rump-length data adjusted to Intergrowth's
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48 21st fetal standard¹⁹. R: reference. GA: gestational age. T: test. C1: comparator 1 is
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50 the gestational age calculated using the first ultrasound exam after 13 weeks and 6
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52 days and before 22 weeks of gestation. C2: comparator 2 is the gestational age
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54 based on a reliable last menstrual period.
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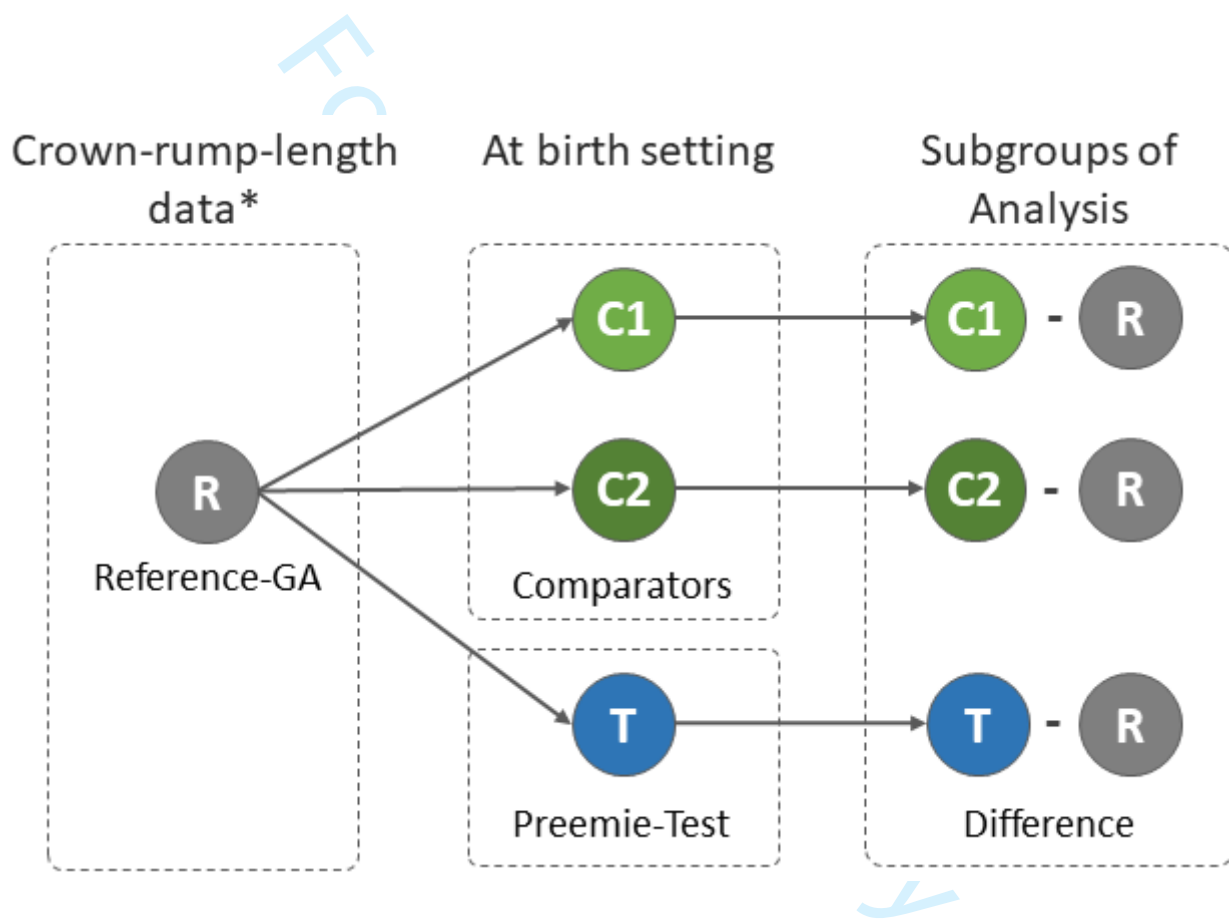
Figure 2. Participant timeline of the study

Legends: GA: gestational age. R: reference. LMP: last menstrual period.

Word Count: 3415 words

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		STUDY PERIOD			
		Enrollment	Assessment	Close-out	Allocation
TIMEPOINT		$-t_1$	0	72 hours	Analysis
ENROLLMENT:					
	Eligibility screen	X			
	Informed consent	X			
INTERVENTION:					
	Preemie-Test		X		
ASSESSMENTS AND ANALYSIS:					
	Preemie-Test: data acquisition		X		
	Reference GA: calculated by obstetric ultrasound at <14 weeks of gestation	X			X
	Comparator 1: GA calculated by obstetric ultrasound at ≥ 14 and <22 weeks	X			X
	Comparator 2: GA calculated by reliable LMP	X			X
	Case-control nested study: lung maturity		←————→		

Fig. 2. Participant timeline of the study

GA: gestational age. R: reference. LMP: last menstrual period.

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Detecção da prematuridade através da interação entre a luz e a pele neonatal: a validação do Premie-Teste

Sob responsabilidade da pesquisadora Profa Zilma Silveira Nogueira Reis

Cara senhora, você está sendo convidada a participar deste estudo porque acaba de ter um parto no hospital (nome do hospital do centro colaborador) _____.

Apresentação do estudo

O objetivo deste estudo é descobrir novas técnicas para estimar a idade de um bebê ao nascer e identificar aqueles que nasceram antes de nove meses, os prematuros. A idade gestacional desconhecida pode aumentar o risco dos bebês no momento de seu nascimento. As técnicas atuais para se estimar a idade do bebê possuem grande margem de erro.

Acreditamos que a pele possui características que, se bem estudadas, podem refletir a idade das pessoas, e também dos bebês. Por isso, estamos desenvolvendo um novo equipamento médico que se encontra em teste. Ele utiliza a luz para avaliar a composição da pele do bebê e detectar sua idade. Os resultados poderão beneficiar os bebês que nascem sem a informação confiável da idade gestacional.

Instituições envolvidas no estudo

O estudo é desenvolvido pela Faculdade de Medicina da Universidade Federal de Minas Gerais (UFMG), em cooperação com maternidades brasileiras, entre elas a que você se encontra internada. A previsão deste estudo é que 787 crianças recém-nascidas sejam examinadas.

A participação no estudo, riscos e cuidados

Convidamos você e seu bebê para participar deste estudo. Isso incluirá um exame na pele do bebê com a luz, uma breve entrevista com você e a consulta aos registros de saúde sobre a gravidez e os do seu bebê neste hospital. Na entrevista serão tomados todos os cuidados a fim de minimizar os constrangimentos para você. A consulta ao prontuário médico será realizada resguardando o direito de sigilo da informação. Pedimos sua permissão para fotografar a caderneta da gestante ou outro documento equivalente, para conferir a idade gestacional calculada pelos ciclos menstruais e pelos exames de ultrassom. As partes da fotografia que contenham sua identificação serão retiradas da imagem e a manteremos até o final do estudo, quando o arquivo será apagado dos registros da pesquisa.

Pedimos sua permissão para fazer um exame na pele de seu bebê, na região da sola do pé, usando um equipamento em teste. O exame é indolor e externo ao corpo, considerado não-invasivo. A parte que encosta no bebê é pequena e não apresenta pontas que possam ferir a sua pele. Outros equipamentos parecidos, que emitem luz, já são usados nos bebês de forma segura. Por exemplo o oxímetro que faz teste do coraçãozinho. Assim como esse, não se espera que ocorram efeitos imediatos ou futuros na saúde do bebê. Os riscos do teste que faremos incluem a exposição do pé do bebê com perda temporária de calor do corpo e estresse. Cuidados serão tomados a fim de minimizar estes desconfortos. Esclarecemos que o teste dura alguns segundos reduzindo ao mínimo chance de causar marcas ou irritação no local. Caso seu bebê apresente sinais de desconforto durante o exame, o mesmo será interrompido. Você ou familiares poderão permanecer junto ao seu filho durante o exame. Nas crianças que estiverem na Unidade Neonatal, o exame será realizado onde ela já está sendo cuidada, acompanhado pelo profissional de saúde que já está cuidando dela. Caso o seu bebê seja prematuro, todos os devidos cuidados serão tomados antes de cada exame para reduzir a chance de perda de calor, seguindo todas as recomendações de um bebê que fica em incubadora.

Esclarecemos que este estudo não trará benefícios diretos a você ou seu filho, entretanto auxiliará na validação de um novo teste que poderá no futuro identificar o bebê prematuro. Os resultados poderão

também gerar informações que ajudem a melhorar os cuidados com outros bebês, quando a idade gestacional é desconhecida. Informamos que os resultados da pesquisa serão publicados em revistas científicas e apresentados em congressos, sem contudo revelar sua identidade ou a do bebê. As informações obtidas durante a pesquisa serão confidenciais, guardadas em computadores, protegidos por senha e não serão usadas para outros fins. O roubo das informações que coletaremos no estudo é um risco remoto. Para isso, as melhores práticas em segurança de dados serão empregadas. Também poderão ter acesso aos dados da pesquisa o comitê que coordena o estudo, assim como a agência reguladora ANVISA, sem jamais violar a confidencialidade e privacidade dos dados, para que seja possível monitorar se os procedimentos de qualidade e segurança da pesquisa estão sendo seguidos.

Seus direitos como participante

Informamos que a sua participação deve ser voluntária, ou seja, não é obrigatória e caso não concorde ou resolva desistir a qualquer momento isto não trará nenhum constrangimento para você ou para a forma como você será tratada neste hospital. Também não está previsto nenhum tipo de pagamento por sua participação na pesquisa. Este estudo não implica em gastos para você, pois não terá que se deslocar para outro local, permanecer mais tempo no hospital, uma vez que o exame é feito durante sua internação e de seu bebê na maternidade. Caso seja de seu interesse, os resultados do exame que estarão guardados com o pesquisador e lhe serão entregues assim que você solicitar.

Os pesquisadores garantem que acompanharão gratuitamente seu bebê durante a realização do exame e a qualquer momento que se fizer necessário, em qualquer problema que por ventura esteja associado ao estudo ou efeito do teste com a luz.

Este Termo de Consentimento está elaborado em duas vias iguais. Ambas devem ser assinadas por você, pelo pai da criança e pelo pesquisador. Uma via ficará com o participante e a outra com o pesquisador.

O Comitê de Ética em Pesquisa da UFMG pode ser contatado em caso de haver dúvidas quanto aos aspectos éticos da pesquisa, através do telefone (31) 3409-4592 ou endereço completo apresentado a seguir.

Meu nome	
Documento de identidade	
Data de hoje	

Eu declaro que estou em condições de tomar esta decisão e ciente do que foi exposto acima. Autorizo o uso de minhas informações de saúde e as do meu bebê para este projeto de pesquisa, assim como a realização do novo teste. Participo voluntariamente deste estudo e estou ciente que o exame na pele do meu bebê com a luz não traz prejuízo à sua saúde

Assinatura da puérpera:
Assinatura do pai da criança:
Assinatura do pesquisador:

Telefones de contato:

Maternidade Hospital das Clínicas da UFMG – (31) 34099422

1
2 Hospital (nome e telefone do hospital colaborador)

3 Zilma Reis – (31) 985177473 e-mail: skinage.ufmg@gmail.com

4 Comitê de Ética em Pesquisa da UFMG – Av. Prof. Antônio Carlos, 6627, Unidade Administrativa II, 2º andar, sala 2005,
5 Campus Pampulha, CEP: 31270-901. E-mail:coep@prpq.ufmg.br. Fone (31) 34094592.

6 Comitê de Ética em Pesquisa do centro colaborador e endereço completo, com e-mail.
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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. *Ann Intern Med.* 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	6
Funding	#4	Sources and types of financial, material, and other support	18
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	19
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	19

1	sponsor contact			
2	information			
3				
4	Roles and	#5c	Role of study sponsor and funders, if any, in study design;	18
5	responsibilities:		collection, management, analysis, and interpretation of data;	
6	sponsor and funder		writing of the report; and the decision to submit the report for	
7			publication, including whether they will have ultimate	
8			authority over any of these activities	
9				
10				
11				
12	Roles and	#5d	Composition, roles, and responsibilities of the coordinating	18
13	responsibilities:		centre, steering committee, endpoint adjudication committee,	
14	committees		data management team, and other individuals or groups	
15			overseeing the trial, if applicable (see Item 21a for data	
16			monitoring committee)	
17				
18				
19				
20	Background and	#6a	Description of research question and justification for	4
21	rationale		undertaking the trial, including summary of relevant studies	
22			(published and unpublished) examining benefits and harms for	
23			each intervention	
24				
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26				
27	Background and	#6b	Explanation for choice of comparators	4
28	rationale: choice of			
29	comparators			
30				
31				
32	Objectives	#7	Specific objectives or hypotheses	5
33				
34				
35	Trial design	#8	Description of trial design including type of trial (eg, parallel	6
36			group, crossover, factorial, single group), allocation ratio, and	
37			framework (eg, superiority, equivalence, non-inferiority,	
38			exploratory)	
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42	Study setting	#9	Description of study settings (eg, community clinic, academic	6
43			hospital) and list of countries where data will be collected.	
44			Reference to where list of study sites can be obtained	
45				
46				
47	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable,	7
48			eligibility criteria for study centres and individuals who will	
49			perform the interventions (eg, surgeons, psychotherapists)	
50				
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52	Interventions:	#11a	Interventions for each group with sufficient detail to allow	7-8
53	description		replication, including how and when they will be administered	
54				
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56	Interventions:	#11b	Criteria for discontinuing or modifying allocated interventions	9
57	modifications		for a given trial participant (eg, drug dose change in response	
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to harms, participant request, or improving / worsening disease)

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4	Interventions:	#11c	Strategies to improve adherence to intervention protocols, and NA
5	adherence		any procedures for monitoring adherence (eg, drug tablet
6			return; laboratory tests)
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9	Interventions:	#11d	Relevant concomitant care and interventions that are permitted 9
10	concomitant care		or prohibited during the trial
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12			
13	Outcomes	#12	Primary, secondary, and other outcomes, including the specific 9-10
14			measurement variable (eg, systolic blood pressure), analysis
15			metric (eg, change from baseline, final value, time to event),
16			method of aggregation (eg, median, proportion), and time point
17			for each outcome. Explanation of the clinical relevance of
18			chosen efficacy and harm outcomes is strongly recommended
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23	Participant timeline	#13	Time schedule of enrolment, interventions (including any run- 11
24			ins and washouts), assessments, and visits for participants. A
25			schematic diagram is highly recommended (see Figure)
26			
27			
28	Sample size	#14	Estimated number of participants needed to achieve study 11-12
29			objectives and how it was determined, including clinical and
30			statistical assumptions supporting any sample size calculations
31			
32			
33	Recruitment	#15	Strategies for achieving adequate participant enrolment to 7
34			reach target sample size
35			
36			
37	Allocation: sequence	#16a	Method of generating the allocation sequence (eg, computer- NA
38	generation		generated random numbers), and list of any factors for
39			stratification. To reduce predictability of a random sequence,
40			details of any planned restriction (eg, blocking) should be
41			provided in a separate document that is unavailable to those
42			who enrol participants or assign interventions
43			
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47	Allocation	#16b	Mechanism of implementing the allocation sequence (eg, NA
48	concealment		central telephone; sequentially numbered, opaque, sealed
49	mechanism		envelopes), describing any steps to conceal the sequence until
50			interventions are assigned
51			
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54	Allocation:	#16c	Who will generate the allocation sequence, who will enrol NA
55	implementation		participants, and who will assign participants to interventions
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1	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
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6	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is	NA
7	emergency unblinding		permissible, and procedure for revealing a participant's allocated intervention during the trial	
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11	Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12
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23	Data collection plan:	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12
24	retention			
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30	Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
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38	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12
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43	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12
44	analyses			
45				
46				
47	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	NA
48	population and missing			
49	data			
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51				
52	Data monitoring:	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be	18
53	formal committee			
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found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

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4	Data monitoring:	#21b	Description of any interim analyses and stopping guidelines, NA
5	interim analysis		including who will have access to these interim results and
6			make the final decision to terminate the trial
7			
8			
9	Harms	#22	Plans for collecting, assessing, reporting, and managing 19
10			solicited and spontaneously reported adverse events and other
11			unintended effects of trial interventions or trial conduct
12			
13			
14	Auditing	#23	Frequency and procedures for auditing trial conduct, if any, 12
15			and whether the process will be independent from investigators
16			and the sponsor
17			
18			
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20	Research ethics	#24	Plans for seeking research ethics committee / institutional 6
21	approval		review board (REC / IRB) approval
22			
23			
24	Protocol amendments	#25	Plans for communicating important protocol modifications (eg, 19
25			changes to eligibility criteria, outcomes, analyses) to relevant
26			parties (eg, investigators, REC / IRBs, trial participants, trial
27			registries, journals, regulators)
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30	Consent or assent	#26a	Who will obtain informed consent or assent from potential trial 6
31			participants or authorised surrogates, and how (see Item 32)
32			
33			
34	Consent or assent:	#26b	Additional consent provisions for collection and use of NA
35	ancillary studies		participant data and biological specimens in ancillary studies, if
36			applicable
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40	Confidentiality	#27	How personal information about potential and enrolled 6
41			participants will be collected, shared, and maintained in order
42			to protect confidentiality before, during, and after the trial
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44			
45	Declaration of interests	#28	Financial and other competing interests for principal 18
46			investigators for the overall trial and each study site
47			
48			
49	Data access	#29	Statement of who will have access to the final trial dataset, and 7
50			disclosure of contractual agreements that limit such access for
51			investigators
52			
53			
54	Ancillary and post trial	#30	Provisions, if any, for ancillary and post-trial care, and for NA
55	care		compensation to those who suffer harm from trial participation
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1	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate trial results	7
2	trial results		to participants, healthcare professionals, the public, and other	
3			relevant groups (eg, via publication, reporting in results	
4			databases, or other data sharing arrangements), including any	
5			publication restrictions	
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9	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of	NA
10	authorship		professional writers	
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13	Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol,	7
14	reproducible research		participant-level dataset, and statistical code	
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17	Informed consent	#32	Model consent form and other related documentation given to	6
18	materials		participants and authorised surrogates	
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21	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of	NA
22			biological specimens for genetic or molecular analysis in the	
23			current trial and for future use in ancillary studies, if applicable	
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BMJ Open

Prematurity detection evaluating the interaction between newborn skin and light: The Premie-Test Multicenter Clinical Trial in Brazilians' hospitals to validate a new medical device

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Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Global health, Diagnostics, Paediatrics
Keywords:	Gestational Age, Infant, Premature, Skin Physiological Phenomena, Photomedicine, Equipment and Supplies

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4 **Prematurity detection evaluating the interaction between newborn skin**
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6 **and light: The Premie-Test Multicenter Clinical Trial in Brazilians'**
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8 **hospitals to validate a new medical device**
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57 **Abstract**
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6 **Introduction:** Recognizing prematurity is critical in order to attend to immediate needs
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8 in childbirth settings, guiding the extent of medical care provided for newborns. A new
9
10 medical device has been developed to carry out the Preemie-Test, an innovative
11
12 approach to estimate gestational age (GA), based on the photobiological properties of
13
14 the newborn's skin. This study will validate the Preemie-Test for GA estimation at birth
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16 and its accuracy to detect prematurity. Secondly, the study intends to associate the
17
18 infant's skin reflectance with lung maturity, as well as evaluate safety, precision, and
19
20 usability of a new medical device to offer a suitable product for health professionals
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22 during childbirth and in neonatal care settings.
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25 **Methods and analysis:** Research protocol for diagnosis, single-group, single-blinding,
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27 and single-arm multicenter clinical trials with a reference standard. Alive newborns, with
28
29 24 weeks or more of pregnancy age, will be enrolled during the first 24 hours of life.
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31 Sample size is 787 subjects. The primary outcome is the difference between the GA
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33 calculated by the photobiological neonatal skin assessment methodology and the GA
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35 calculated by the comparator antenatal ultrasound or reliable last menstrual period.
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37 Immediate complications caused by pulmonary immaturity during the first 72 hours of life
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39 will be associated with skin reflectance in a nested case-control study.
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42 **Ethics and dissemination:** Each local independent ethics review board approved the
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44 trial protocol. The authors intend to share the minimal anonymized data set necessary
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46 to replicate study findings.
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48 **Trial registration number:** WHO Clinical Trial
49
50 <http://apps.who.int/trialsearch/Trial2.aspx?TrialID=RBR-3f5bm5>.
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55 **Key-words:** Gestational Age, Infant, Premature; Skin Physiological Phenomena;
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57 Photomedicine; Equipment and Supplies.
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Article Summary

Strengths and limitations of this study:

- The study has the potential to validate a new approach for pregnancy dating.
- The device will be subjected to high-quality clinical study to demonstrate benefits.
- The gold standard comparator for pregnancy dating does not exist, instead a reference standard will be used with blinded primary outcome.
- The agreement endpoint between methods for gestational age determination precluded randomization of the intervention.

Introduction

In childbirth settings, health professionals continuously need to make timely decisions to provide proper neonatal care. The day of birth is the riskiest for newborns and mothers almost everywhere¹. Perinatal causes related to prematurity and complications during childbirth, which are generally preventable through qualified health care, are the primary causes of death among newborns^{1,2}. Most of these deaths took place in countries with low resources and a scarcity of health facilities³. The opportune recognition of prematurity is critical in order to judge the viability of the newborn and to attend to his/her immediate needs, guiding the complexity of the medical care provided for the newborn. Without reliable information on the age of the unborn phase, actions to preserve the potential for survival of the newborn can be neglected⁴. Indeed, the attempted management of the risk of mortality and severe complications are sensitive issues to the gestational age (GA), which involves temperature maintenance, ventilatory support, transport to a neonatal intensive care unit (NICU), and the early treatment of respiratory distress syndrome (RDS), the most severe complication of premature birth⁵. In addition to the GA information or birthweight, the prediction of neonatal respiratory morbidity may be critical in planning immediate medical care⁶, since the respiratory system is among the last of the fetal organ systems to mature, which is associated with enhanced morbidity and mortality⁶.

Current methods of dating pregnancy remain a worldwide challenge. Early obstetric ultrasound currently offers the best due date⁷. However, access to this type of exam is limited because of high equipment costs, poor training and skills of health professionals, or late prenatal care⁸. Despite a 10-days or more margin of error during the second and third trimester of gestation, ultrasound is still a reasonable methodology for GA determination, when the best opportunity was lost⁷. The calculation, based on the historical information of the last menstrual period (LMP), is impacted by the uncertainty

Methods

Study design

This study will use a protocol for diagnosis, single-group, single-blinding, and single-arm multicenter clinical trials with a reference standard. This new photobiological approach to the skin, gathered in a medical device, is currently in the pivotal phase of innovation development from the prototype to regulatory approval¹⁷. This step aims to provide the translation¹⁶ of the scientific model for GA detection based on skin maturity. This Protocol version is 1, July/10th/2018. Faculty of Medicine, Universidade Federal de Minas Gerais is the Coordinator Center.

Study Settings, Ethics and Dissemination

Selected Brazilian referral centers for high-risk pregnancy and neonatal care will participate in the study, according to this protocol: Hospital das Clínicas, Universidade Federal de Minas Gerais, as the Center for Coordination; Hospital Sofia Feldman, Minas Gerais State; Hospital da Universidade Luterana do Brasil, Rio Grande do Sul State; Hospital Materno-infantil de Brasília, Distrito Federal; and Hospital Universitário da Universidade Federal do Maranhão, Maranhão State. Each local independent ethics review board approved the trial protocol, and the Brazilian National Research Council (CONEP) approved all study activities and protocol prior to the commencement of study activities, in accordance with the Declaration of Helsinki (2008), good clinical practice as set forth by the International Organization for Standardization (ISO) 14155:2011, and the Brazilian regulatory health agency's recommendations¹⁸. This study was logged under both protocol number CAAE 81347817.6.1001.5149 and the International Clinical Trials Registry Platform under Universal Trial Number U1111-1205-0539 is accessible by <http://apps.who.int/trialsearch/Trial2.aspx?TrialID=RBR-3f5bm5>. Parents will sign an informed consent form on behalf of the newborn before participating in the clinical trial (supplementary file).

Data Sharing Statement

The authors intend to share the minimal anonymized data set necessary to replicate study findings. Data sharing will include: the reference and comparators GA, GA estimated by the Premie-test, birth weight, RDS or transient tachypnea of the newborn (TTN) diagnosis, ventilatory support due to pulmonary immaturity, neonatal intensive care unit (NICU) admission due to RDS or TTN, and any adverse events regarding device's safety. Unidentified data and study-related documents as ethical approvals will be accessible by URLs for researchers, regulatory agencies, and sponsors.

Patient and Public Involvement

Patients and the public were not involved in the design of this study. The results will be disseminated to study parents of participants through scientific publications, non-scientific publications, and on the website of the project:

<http://skinage.medicina.ufmg.br>.

Eligibility criteria and participant's timeline

A prospective sequential and concurrent enrollment process will select newborns in referral hospitals centers for neonatal care. Infants are eligible with the following inclusion criteria: (1) alive newborn; (2) enrollment during first 24 hours of life; (3) be 24 weeks or more of gestational age, at birth; (4) fetus underwent an obstetric ultrasound assessment before 14 weeks of pregnancy; (5) fetus also had obstetric ultrasound assessment between 14 and 22 gestational weeks. Exclusion criteria are: (1) malformation with structural skin alterations; (2) skin modifiers: anhydramnios, hydrops, congenital skin diseases or chorioamnionitis. Randomisation was not appropriate to assess the agreement between different methods to assess pregnancy dating.

In a nested case-control study, we will select newborns within the first 72 hours of life, discharge, or death, whichever occurs first, with the following inclusion criteria: (1) RDS

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4 or (2) TTN diagnosis. Ranges of gestational age will randomly pair controls. Exclusion
5
6 criteria include: (1) the existence of extra pulmonary conditions with tachypnea not due
7
8 to prematurity and (2) diagnosis of Clinical or Laboratory-Confirmed Bloodstream
9
10 Infection.
11

12 13 ***Intervention: The Preemie-Test*** 14

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16 The Preemie-Test assessment occurs as soon as possible after birth, in the first 24
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18 hours, inside incubators, open heating crib, common crib or in the mother's lap, in order
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20 to ensure minimum manipulation and stable clinical conditions. The acquisitions of all
21
22 newborns will be stored in a database for further statistical analysis.
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25 A noninvasive, handheld optoelectronic prototype has been developed to measure the
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27 backscattered light signal from the skin¹⁵. The equipment regulates the emitted light and
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29 processes the received light signal in the sensor, resulting in the prediction of GA by a
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31 mathematical model, associated or not with clinical variables. According to the Brazilian
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33 regulatory health agency (ANVISA), this medical device is categorized as a Class II
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35 safety: noninvasive and medium risk. The prototype unit of measurement and the
36
37 process of GA estimation were patented under number BR1020170235688 (CTIT-
38
39 PN862)¹⁴. An updated version of the invention received improvements in order to
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41 safeguard reliability and to minimize examiner interferences on the skin's backscattering
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43 acquisition. The light emitting-sensor touches the skin over the sole of the foot for a few
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45 seconds. The skin reflectance will be sensed once the light has been emitted by a light
46
47 emitting diode (LED) at wavelengths from 400 nm to 1200 nm. Data acquisitions occur
48
49 automatically, without operator influence, and are obtained three times per newborn, in
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51 the same site and sequentially. Digital recordings will be uploaded to a server for further
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53 analysis. The prototype will blind the examiner to the predicted GA value.
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4 The criterium for discontinuing the interventions for a given trial participant will be in case
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6 of parents of the newborns' request.
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8 9 ***Training and monitoring***

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11 Systematic monitoring of data collection, through an electronic information system,
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13 would trigger any adverse event. This medical team is still responsible for the training of
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15 healthcare professionals to recruit participants, data collection, a safely performed
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17 Premie-Test during the newborn's assessment, and the monitoring of data quality. The
18
19 certification of co-participant centers involved the accomplishment of at least 30
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21 simulated examinations by the participant health professionals in the study.
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24 25 ***Gestational age methods of calculation and comparators***

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27 Reference-GA (R) is calculated upon enrollment, using the embryo measurement
28
29 assessed by ultrasound exam at <14 weeks of gestation as a reference. Crown-rump-
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31 length (CRL) data, recorded from the ultrasound report or prenatal care book-document,
32
33 will be considered the crude data, when available. Intergrowth's 21st standard curve for
34
35 ultrasound measurements from 7 weeks and 3 days up to 13 weeks and 6 days will be
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37 adjusted to all GA data, according to CRL¹⁹.
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41 GA methods to calculate GA in the childbirth setting, and their comparators are as
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43 follows:
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- 45 • Premie-Test-GA (T): data statistically determined by analyzing the acquired
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47 information stored in the device's processor.
- 48
49 • Comparators-GA (C): calculated using the first ultrasound exam after 13 weeks
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51 and 6 days of gestation and before 22 weeks (C1). When available, a second
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53 comparator is GA based on a reliable LMP (C2)¹³.
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4 We will take a scanning copy of the prenatal care book or the ultrasound report. After
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6 evaluating the data quality, the images will be discarded. To achieve a reliable LMP, we
7
8 will interview the woman, as suggested by Nguyen et al. (2000)¹³.
9

10 **Primary outcome measures**

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13 The primary target is the agreement between the GA offered by the Premie-Test (T)
14
15 and the GA calculated by the comparators (C1 and C2), so as to perform the new test in
16
17 scenarios without the Reference-GA (R). The outcome is the difference between the GA
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19 calculated by the photobiological neonatal skin assessment methodology in relation to
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21 the age calculated by the comparators.
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25 Another measure for the primary target is the detection of preterm newborns, considering
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27 the age before 37 weeks of pregnancy as the threshold between term and preterm births,
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29 and analyzing sub-categories of preterm birth, based on GA⁴:
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- 31 • extremely preterm (less than 28 weeks)
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- 33 • very preterm (28 to 32 weeks)
- 34
- 35 • moderate to late preterm (more than 32 to less than 37 weeks).
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39 In this case, the outcome is the proportion of the preterm newborn correctly detected at
40
41 birth, based on the photobiological test of the skin, within a one-week error.
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44 **Secondary outcome measures**

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46 1. In a simulated scenario, in which the Reference-GA (R) is unknown, two groups
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48 will be randomly assigned from the complete database in order to compare
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50 differences among the Reference-GA (R), the GA obtained through the Premie-
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52 Test (T), and the GA calculated by the comparators. Figure 1 presents such
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54 subgroups and measures for comparison.
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2. To monitor the device's safety when in regular use by participants over a 72-hour period. Adverse events will be monitored, according to ISO 14155:2011 standards. This means any unexpected medical events, unintended disease or injury, or unfortunate clinical signs in subjects, users, or other people, whether related to the investigational medical device or not.
3. To establish the *ease of use* of the Preemie-Test measurement as a potential method for preterm newborn diagnosis.

The secondary outcome measures in the case-control nested study

Immediate complications, occurring during the first 72 hours of life due to pulmonary immaturity, are the secondary target. The outcome measures are as follows:

- To describe the relationship of the measurement of the newborn's skin reflectance with RDS and with diagnoses based on clinical and radiological findings and respiratory outcomes^{6,20}.
- To describe the relationship of the measurement of the newborn's skin reflectance with the TTN and with diagnoses based on clinical findings and respiratory outcomes⁶.
- To describe the relationship of the measurement of the newborn's skin reflectance with ventilatory support due to pulmonary immaturity.
- To describe the relationship of the measurement of the newborn's skin reflectance with NICU admission due to RDS or TTN.

Time schedule of enrollment, intervention, and outcome measurements are presented in a schematic diagram (see Figure 2). The assessment occurs during the first 24 hours of life, but participants will be followed up for 72 hours or until discharge or death, whichever occurs first, for the monitoring of neonatal outcomes and adverse events.

Sampling and sample size

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4 The sample size calculation is estimated based on the primary endpoint. To test the
5 hypothesis of equivalence between the Premie-Test GA and the comparators GA, a
6 sample of 787 subjects is necessary to detect an effect size of 10%. Using the G-Power
7 3.1 software²¹, we assumed an alpha error of 0.05, and a power of test of 0.80 to support
8 a paired t-test.
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15 Sampling intends to arrange three groups of GA enrollment to preserve enough
16 premature newborns with 3:2:1 proportion, similar to Wilson et al. (2017)²²: 392 term
17 newborns, 263 premature newborns from 32 to 36 weeks and six days of GA, and 132
18 extremely premature newborns from 24 to 31 weeks and six days of GA.
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23 **Usability**

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27 The usability assessment will be performed by applying a checklist to participants who
28 use the prototype device to perform the Premie-Test. The 10 heuristics proposed by
29 Nielsen and Marck |(1994)²³ will be adapted to build a checklist to evaluate the device,
30 namely: (a) system visibility, (b) correspondence with the real world, (c) user control and
31 freedom, (d) consistency of results and standardization, (e) error prevention, (f) visual
32 recognition rather than memorization, (g) flexibility and efficiency of use, (h) esthetic and
33 minimalist design, (i) help for the user to recognize, diagnose, and recover from errors,
34 and (j) user documentation and help.
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44 **Data collection**

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47 Standard operational procedures set data entries in structured questionnaires. In this
48 concurrent clinical trial, an electronic information system was developed to collect data
49 in different hospitals, simultaneously. Entry forms validations were implemented with
50 data values ranges to ensure the quality of the information. An audit of the data will be
51 permanently performed and the data summary available on the project webpage. Double
52 system, paper-based and electronic will permit audit concerning reliability and validity.
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4 Independent rater over-read all papers files and cross check with the electronic
5 information from all patients.
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8 **Data analysis**

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10 Demographics and baseline characteristics of the study group, as well the intervention
11 measurements, will be summarized by the frequencies and the mean and standard
12 deviation (SD), the whereas median and interquartile range will be preferred for non-
13 normally distributed continuous variables.
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20 To model the GA prediction, computational randomization will select two subsamples in
21 the database. One of them to train the prediction model of GA based on skin reflectance
22 and clinical variables, such as sex, time in an incubator, phototherapy, birth weight,
23 among others. Another part will be for the analytical validation of the predictive model.
24 Improvements in the existing prediction models for GA (Premie-Test), will be conducted
25 with conventional statistical and data mining analyses.
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33 Regarding the primary endpoint, the agreement among three methods for GA will be
34 calculated using the Intraclass coefficient correlation and Bland & Altman plots²⁴, and
35 paired t-testing. The accuracy of the Premie-Test in identifying the premature newborn,
36 within a one-week margin of error, will be the target of the accuracy analysis.
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42 The relationship between the measurement of the newborn's skin reflectance and
43 complications due to pulmonary distress associated with immaturity will be evaluated by
44 means of association tests and risk. The significance level for hypothesis tests will be
45 5%, together with 95% confidence intervals.
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51 **Results**

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4 The study begun with the training of health professionals in September 2018. It is
5 anticipated that the recruitment will take place from January to December 2019. Data
6 analysis will be finalized, the results of which are expected in May 2020.
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10 11 12 13 **Discussion**

14 15 16 **Strengths and Limitations**

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18 Availability of trustworthy GA information is a prerequisite for preterm birth classification
19 and healthcare decisions²⁵. In this light, the results of this clinical study have the potential
20 to validate a new device for pregnancy dating. The Premie-Test was prepared to
21 operate with minimum operator intervention and for use by healthcare professionals
22 anywhere a birth takes place without a reliable GA.
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30 The purpose of medical research involving neonates is intended to improve clinical
31 procedures²⁶. In this context, a clinical trial is a research study in which subjects are
32 prospectively assigned to intervention and the effects of those interventions on health-
33 related outcomes are thereby evaluated²⁷. However, clinical trials on medical devices
34 face barriers when an effective standard procedure does not exist, as is the case of the
35 comparator procedure²⁸. Our challenge in preparing the present protocol was the
36 absence of a gold standard for pregnancy dating, since the fetal age begins upon
37 conception; however, this information is difficult to be accurately determined⁷.
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49 randomised clinical trials on medical devices. *Trials.* 2017;18(1):427.
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Author statement:

ZSNR: designed the study, planned data collection, prepared the team for good clinical practices, wrote and revised the paper. RNG, RAPLA, MASR, RMCR and JSG made substantial contributions to study design, planned data collection, prepared the team for good clinical practices, wrote and revised the paper. GLNV, MAAR, GSN, PJN, MDRM, and MSV made contributions to standard procedures in methods, drafted the manuscript, reviewed the paper, and approved the final manuscript. EAC: drafted the work and reviewed it critically for important intellectual content, as statistic consultant.

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7 **Roles and responsibilities:** ZSNR is the Principal Investigator and coordinator of the
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9 Directive Committee. JSG is the coordinator of the Data Management Team and will
10
11 continuously receive report adverse events of trial interventions or trial conduct. RAPLA
12
13 is the coordinator of the Clinical Trial Quality Committee, responsible for important
14
15 protocol modifications, if necessary.
16

17 18 19 20 **Conflict of interests statement**

21
22 Authors declare a patent deposit on behalf of the Universidade Federal de Minas Gerais
23
24 and Fundação de Amparo a Pesquisa de Minas Gerais, Brazil,
25
26 <http://www.fapemig.br/en/>. The inventors were Reis, Zilma Silveira Nogueira and
27
28 Guimaraes, Rodney Nascimento: BR1020170235688 (CTIT-PN862).
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35 Figure 1. Secondary outcome comparisons between the reference GA and the
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37 Preemie-Test in a simulated scenario without best pregnancy dating
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42 Legends: *Gestational age from crown-rump-length data adjusted to
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44 Intergrowth's 21st fetal standard¹⁹. R: reference. GA: gestational age. T: test. C1:
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46 comparator 1 is the gestational age calculated using the first ultrasound exam
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48 after 13 weeks and 6 days and before 22 weeks of gestation. C2: comparator 2
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50 is the gestational age based on a reliable last menstrual period.
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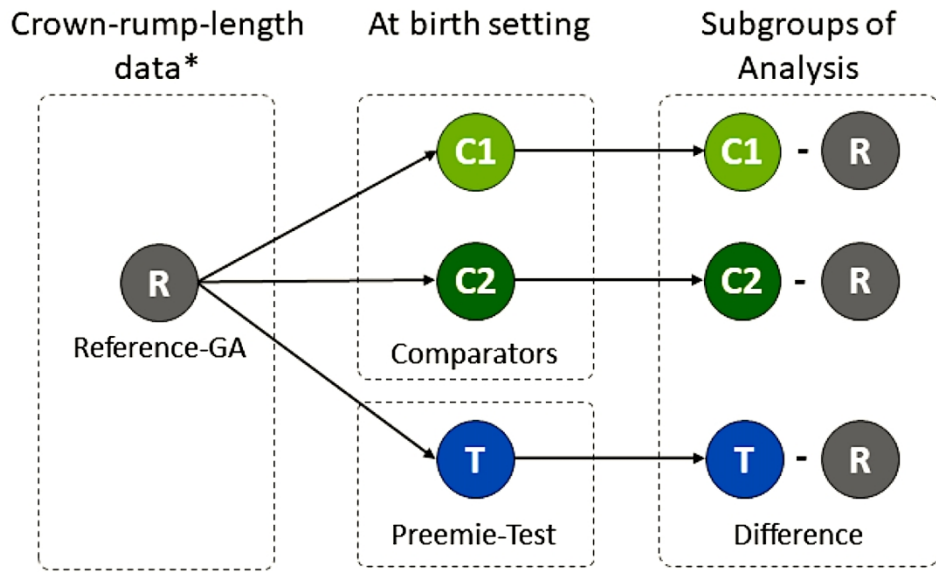
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56 Figure 2. Participant timeline of the study

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58 Legends: GA: gestational age. R: reference. LMP: last menstrual period.
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Word Count: 3415 words

For peer review only



Secondary outcome comparisons between the reference GA and the Premie-Test in a simulated scenario without best pregnancy dating

Legends: *Gestational age from crown-rump-length data adjusted to Intergrowth’s 21st fetal standard¹⁹. R: reference. GA: gestational age. T: test. C1: comparator 1 is the gestational age calculated using the first ultrasound exam after 13 weeks and 6 days and before 22 weeks of gestation. C2: comparator 2 is the gestational age based on a reliable last menstrual period.

143x90mm (300 x 300 DPI)

	STUDY PERIOD			
	Enrollment	Assessment	Close-out	Allocation
TIMEPOINT	0	0	72 hours	Analysis
ENROLLMENT:				
Eligibility screen	X			
Informed consent	X			
INTERVENTION:				
Preemie-Test		X		
ASSESSMENTS AND ANALYSIS:				
Preemie-Test: data acquisition		X		
Reference GA: calculated by obstetric ultrasound at <14 weeks of gestation	X			X
Comparator 1: GA calculated by obstetric ultrasound at ≥ 14 and <22 weeks	X			X
Comparator 2: GA calculated by reliable LMP	X			X
Case-control nested study: lung maturity		←————→		

Participant timeline of the study

Legends: GA: gestational age. R: reference. LMP: last menstrual period.

157x123mm (300 x 300 DPI)

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Detecção da prematuridade através da interação entre a luz e a pele neonatal: a validação do Premie-Teste

Sob responsabilidade da pesquisadora Profa Zilma Silveira Nogueira Reis

Cara senhora, você está sendo convidada a participar deste estudo porque acaba de ter um parto no hospital (nome do hospital do centro colaborador) _____.

Apresentação do estudo

O objetivo deste estudo é descobrir novas técnicas para estimar a idade de um bebê ao nascer e identificar aqueles que nasceram antes de nove meses, os prematuros. A idade gestacional desconhecida pode aumentar o risco dos bebês no momento de seu nascimento. As técnicas atuais para se estimar a idade do bebê possuem grande margem de erro.

Acreditamos que a pele possui características que, se bem estudadas, podem refletir a idade das pessoas, e também dos bebês. Por isso, estamos desenvolvendo um novo equipamento médico que se encontra em teste. Ele utiliza a luz para avaliar a composição da pele do bebê e detectar sua idade. Os resultados poderão beneficiar os bebês que nascem sem a informação confiável da idade gestacional.

Instituições envolvidas no estudo

O estudo é desenvolvido pela Faculdade de Medicina da Universidade Federal de Minas Gerais (UFMG), em cooperação com maternidades brasileiras, entre elas a que você se encontra internada. A previsão deste estudo é que 787 crianças recém-nascidas sejam examinadas.

A participação no estudo, riscos e cuidados

Convidamos você e seu bebê para participar deste estudo. Isso incluirá um exame na pele do bebê com a luz, uma breve entrevista com você e a consulta aos registros de saúde sobre a gravidez e os do seu bebê neste hospital. Na entrevista serão tomados todos os cuidados a fim de minimizar os constrangimentos para você. A consulta ao prontuário médico será realizada resguardando o direito de sigilo da informação. Pedimos sua permissão para fotografar a caderneta da gestante ou outro documento equivalente, para conferir a idade gestacional calculada pelos ciclos menstruais e pelos exames de ultrassom. As partes da fotografia que contenham sua identificação serão retiradas da imagem e a manteremos até o final do estudo, quando o arquivo será apagado dos registros da pesquisa.

Pedimos sua permissão para fazer um exame na pele de seu bebê, na região da sola do pé, usando um equipamento em teste. O exame é indolor e externo ao corpo, considerado não-invasivo. A parte que encosta no bebê é pequena e não apresenta pontas que possam ferir a sua pele. Outros equipamentos parecidos, que emitem luz, já são usados nos bebês de forma segura. Por exemplo o oxímetro que faz teste do coraçãozinho. Assim como esse, não se espera que ocorram efeitos imediatos ou futuros na saúde do bebê. Os riscos do teste que faremos incluem a exposição do pé do bebê com perda temporária de calor do corpo e estresse. Cuidados serão tomados a fim de minimizar estes desconfortos. Esclarecemos que o teste dura alguns segundos reduzindo ao mínimo chance de causar marcas ou irritação no local. Caso seu bebê apresente sinais de desconforto durante o exame, o mesmo será interrompido. Você ou familiares poderão permanecer junto ao seu filho durante o exame. Nas crianças que estiverem na Unidade Neonatal, o exame será realizado onde ela já está sendo cuidada, acompanhado pelo profissional de saúde que já está cuidando dela. Caso o seu bebê seja prematuro, todos os devidos cuidados serão tomados antes de cada exame para reduzir a chance de perda de calor, seguindo todas as recomendações de um bebê que fica em incubadora.

Esclarecemos que este estudo não trará benefícios diretos a você ou seu filho, entretanto auxiliará na validação de um novo teste que poderá no futuro identificar o bebê prematuro. Os resultados poderão também gerar informações que ajudem a melhorar os cuidados com outros bebês, quando a idade gestacional é desconhecida. Informamos que os resultados da pesquisa serão publicados em revistas científicas e apresentados em congressos, sem contudo revelar sua identidade ou a do bebê.

As informações obtidas durante a pesquisa serão confidenciais, guardadas em computadores, protegidos por senha e não serão usadas para outros fins. O roubo das informações que coletaremos no estudo é um risco remoto. Para isso, as melhores práticas em segurança de dados serão empregadas. Também poderão ter acesso aos dados da pesquisa o comitê que coordena o estudo, assim como a agência reguladora ANVISA, sem jamais violar a confidencialidade e privacidade dos dados, para que seja possível monitorar se os procedimentos de qualidade e segurança da pesquisa estão sendo seguidos.

Seus direitos como participante

Informamos que a sua participação deve ser voluntária, ou seja, não é obrigatória e caso não concorde ou resolva desistir a qualquer momento isto não trará nenhum constrangimento para você ou para a forma como você será tratada neste hospital. Também não está previsto nenhum tipo de pagamento por sua participação na pesquisa. Este estudo não implica em gastos para você, pois não terá que se deslocar para outro local, permanecer mais tempo no hospital, uma vez que o exame é feito durante sua internação e de seu bebê na maternidade. Caso seja de seu interesse, os resultados do exame que estarão guardados com o pesquisador e lhe serão entregues assim que você solicitar.

Os pesquisadores garantem que acompanharão gratuitamente seu bebê durante a realização do exame e a qualquer momento que se fizer necessário, em qualquer problema que por ventura esteja associado ao estudo ou efeito do teste com a luz.

Este Termo de Consentimento está elaborado em duas vias iguais. Ambas devem ser assinadas por você, pelo pai da criança e pelo pesquisador. Uma via ficará com o participante e a outra com o pesquisador.

O Comitê de Ética em Pesquisa da UFMG pode ser contatado em caso de haver dúvidas quanto aos aspectos éticos da pesquisa, através do telefone (31) 3409-4592 ou endereço completo apresentado a seguir.

Meu nome	
Documento de identidade	
Data de hoje	

Eu declaro que estou em condições de tomar esta decisão e ciente do que foi exposto acima. Autorizo o uso de minhas informações de saúde e as do meu bebê para este projeto de pesquisa, assim como a realização do novo teste. Participo voluntariamente deste estudo e estou ciente que o exame na pele do meu bebê com a luz não traz prejuízo à sua saúde

Assinatura da puérpera:
Assinatura do pai da criança:
Assinatura do pesquisador:

Telefones de contato:

Maternidade Hospital das Clínicas da UFMG – (31) 34099422

Hospital (nome e telefone do hospital colaborador)

Zilma Reis – (31) 985177473 e-mail: skinage.ufmg@gmail.com

Comitê de Ética em Pesquisa da UFMG – Av. Prof. Antônio Carlos, 6627, Unidade Administrativa II, 2º andar, sala 2005, Campus Pampulha, CEP: 31270-901. E-mail: coep@prpq.ufmg.br. Fone (31) 34094592.

Comitê de Ética em Pesquisa do centro colaborador e endereço completo, com e-mail.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. *Ann Intern Med.* 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	6
Funding	#4	Sources and types of financial, material, and other support	18
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	19

1	Roles and	#5b	Name and contact information for the trial sponsor	19
2	responsibilities:			
3	sponsor contact			
4	information			
5				
6				
7				
8	Roles and	#5c	Role of study sponsor and funders, if any, in study	18
9	responsibilities:		design; collection, management, analysis, and	
10	sponsor and funder		interpretation of data; writing of the report; and the	
11			decision to submit the report for publication, including	
12			whether they will have ultimate authority over any of	
13			these activities	
14				
15				
16				
17				
18	Roles and	#5d	Composition, roles, and responsibilities of the	18
19	responsibilities:		coordinating centre, steering committee, endpoint	
20	committees		adjudication committee, data management team, and	
21			other individuals or groups overseeing the trial, if	
22			applicable (see Item 21a for data monitoring committee)	
23				
24				
25				
26				
27	Background and	#6a	Description of research question and justification for	4
28	rationale		undertaking the trial, including summary of relevant	
29			studies (published and unpublished) examining benefits	
30			and harms for each intervention	
31				
32				
33				
34	Background and	#6b	Explanation for choice of comparators	4
35	rationale: choice of			
36	comparators			
37				
38				
39	Objectives	#7	Specific objectives or hypotheses	5
40				
41				
42	Trial design	#8	Description of trial design including type of trial (eg,	6
43			parallel group, crossover, factorial, single group),	
44			allocation ratio, and framework (eg, superiority,	
45			equivalence, non-inferiority, exploratory)	
46				
47				
48				
49	Study setting	#9	Description of study settings (eg, community clinic,	6
50			academic hospital) and list of countries where data will	
51			be collected. Reference to where list of study sites can	
52			be obtained	
53				
54				
55				
56	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If	7
57			applicable, eligibility criteria for study centres and	
58				
59				
60				

		individuals who will perform the interventions (eg, surgeons, psychotherapists)	
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3			
4	Interventions:	#11a Interventions for each group with sufficient detail to allow	7-8
5	description	replication, including how and when they will be administered	
6			
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8			
9	Interventions:	#11b Criteria for discontinuing or modifying allocated	9
10	modifications	interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	
11			
12			
13			
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15			
16	Interventions:	#11c Strategies to improve adherence to intervention	NA
17	adherence	protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	
18			
19			
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21			
22	Interventions:	#11d Relevant concomitant care and interventions that are	9
23	concomitant care	permitted or prohibited during the trial	
24			
25			
26	Outcomes	#12 Primary, secondary, and other outcomes, including the	9-10
27		specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	
28			
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38	Participant timeline	#13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11
39			
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44			
45	Sample size	#14 Estimated number of participants needed to achieve	11-12
46		study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	
47			
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52	Recruitment	#15 Strategies for achieving adequate participant enrolment	7
53		to reach target sample size	
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1	Allocation:	#16a	Method of generating the allocation sequence (eg,	NA
2			computer-generated random numbers), and list of any	
3	sequence		factors for stratification. To reduce predictability of a	
4	generation		random sequence, details of any planned restriction (eg,	
5			blocking) should be provided in a separate document that	
6			is unavailable to those who enrol participants or assign	
7			interventions	
8				
9				
10				
11				
12	Allocation	#16b	Mechanism of implementing the allocation sequence (eg,	NA
13	concealment		central telephone; sequentially numbered, opaque,	
14	mechanism		sealed envelopes), describing any steps to conceal the	
15			sequence until interventions are assigned	
16				
17				
18				
19				
20	Allocation:	#16c	Who will generate the allocation sequence, who will enrol	NA
21	implementation		participants, and who will assign participants to	
22			interventions	
23				
24				
25	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg,	8
26			trial participants, care providers, outcome assessors,	
27			data analysts), and how	
28				
29				
30				
31	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is	NA
32	emergency		permissible, and procedure for revealing a participant's	
33	unblinding		allocated intervention during the trial	
34				
35				
36	Data collection plan	#18a	Plans for assessment and collection of outcome,	12
37			baseline, and other trial data, including any related	
38			processes to promote data quality (eg, duplicate	
39			measurements, training of assessors) and a description	
40			of study instruments (eg, questionnaires, laboratory tests)	
41			along with their reliability and validity, if known.	
42			Reference to where data collection forms can be found, if	
43			not in the protocol	
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50	Data collection plan:	#18b	Plans to promote participant retention and complete	12
51	retention		follow-up, including list of any outcome data to be	
52			collected for participants who discontinue or deviate from	
53			intervention protocols	
54				
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57	Data management	#19	Plans for data entry, coding, security, and storage,	12
58			including any related processes to promote data quality	
59				
60				

1		7(eg, double data entry; range checks for data values).	
2		Reference to where details of data management	
3		procedures can be found, if not in the protocol	
4			
5			
6	Statistics: outcomes	#20a Statistical methods for analysing primary and secondary	12
7		outcomes. Reference to where other details of the	
8		statistical analysis plan can be found, if not in the	
9		protocol	
10			
11			
12			
13	Statistics: additional	#20b Methods for any additional analyses (eg, subgroup and	12
14	analyses	adjusted analyses)	
15			
16			
17	Statistics: analysis	#20c Definition of analysis population relating to protocol non-	NA
18	population and	adherence (eg, as randomised analysis), and any	
19	missing data	statistical methods to handle missing data (eg, multiple	
20		imputation)	
21			
22			
23			
24	Data monitoring:	#21a Composition of data monitoring committee (DMC);	18
25	formal committee	summary of its role and reporting structure; statement of	
26		whether it is independent from the sponsor and	
27		competing interests; and reference to where further	
28		details about its charter can be found, if not in the	
29		protocol. Alternatively, an explanation of why a DMC is	
30		not needed	
31			
32			
33			
34			
35			
36	Data monitoring:	#21b Description of any interim analyses and stopping	NA
37	interim analysis	guidelines, including who will have access to these	
38		interim results and make the final decision to terminate	
39		the trial	
40			
41			
42			
43	Harms	#22 Plans for collecting, assessing, reporting, and managing	19
44		solicited and spontaneously reported adverse events and	
45		other unintended effects of trial interventions or trial	
46		conduct	
47			
48			
49			
50	Auditing	#23 Frequency and procedures for auditing trial conduct, if	12
51		any, and whether the process will be independent from	
52		investigators and the sponsor	
53			
54			
55	Research ethics	#24 Plans for seeking research ethics committee / institutional	6
56	approval	review board (REC / IRB) approval	
57			
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59			
60			

1	Protocol	#25	Plans for communicating important protocol modifications	19
2	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to	
3			relevant parties (eg, investigators, REC / IRBs, trial	
4			participants, trial registries, journals, regulators)	
5				
6				
7				
8	Consent or assent	#26a	Who will obtain informed consent or assent from potential	6
9			trial participants or authorised surrogates, and how (see	
10			Item 32)	
11				
12				
13	Consent or assent:	#26b	Additional consent provisions for collection and use of	NA
14	ancillary studies		participant data and biological specimens in ancillary	
15			studies, if applicable	
16				
17				
18				
19	Confidentiality	#27	How personal information about potential and enrolled	6
20			participants will be collected, shared, and maintained in	
21			order to protect confidentiality before, during, and after	
22			the trial	
23				
24				
25				
26	Declaration of	#28	Financial and other competing interests for principal	18
27	interests		investigators for the overall trial and each study site	
28				
29				
30	Data access	#29	Statement of who will have access to the final trial	7
31			dataset, and disclosure of contractual agreements that	
32			limit such access for investigators	
33				
34				
35				
36	Ancillary and post	#30	Provisions, if any, for ancillary and post-trial care, and for	NA
37	trial care		compensation to those who suffer harm from trial	
38			participation	
39				
40				
41	Dissemination	#31a	Plans for investigators and sponsor to communicate trial	7
42	policy: trial results		results to participants, healthcare professionals, the	
43			public, and other relevant groups (eg, via publication,	
44			reporting in results databases, or other data sharing	
45			arrangements), including any publication restrictions	
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50	Dissemination	#31b	Authorship eligibility guidelines and any intended use of	NA
51	policy: authorship		professional writers	
52				
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54	Dissemination	#31c	Plans, if any, for granting public access to the full	7
55	policy: reproducible		protocol, participant-level dataset, and statistical code	
56	research			
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1	Informed consent	#32	Model consent form and other related documentation	6
2	materials		given to participants and authorised surrogates	
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5	Biological	#33	Plans for collection, laboratory evaluation, and storage of	NA
6	specimens		biological specimens for genetic or molecular analysis in	
7			the current trial and for future use in ancillary studies, if	
8			applicable	
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14 by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
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BMJ Open

Prematurity detection evaluating interaction between the skin of the newborn and light: Protocol for the Premie-Test multicenter clinical trial in Brazilians hospitals to validate a new medical device

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Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Global health, Diagnostics, Paediatrics
Keywords:	Gestational Age, Infant, Premature, Skin Physiological Phenomena, Photomedicine, Equipment and Supplies

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4 **Prematurity detection evaluating interaction between the skin of the**
5 **newborn and light: Protocol for the Preemie-Test multicenter clinical trial**
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7 **in Brazilians hospitals to validate a new medical device**
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57 **Abstract**
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6 **Introduction:** Recognizing prematurity is critical in order to attend to immediate needs
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8 in childbirth settings, guiding the extent of medical care provided for newborns. A new
9
10 medical device has been developed to carry out the Premie-Test, an innovative
11
12 approach to estimate gestational age (GA), based on the photobiological properties of
13
14 the newborn's skin. This study will validate the Premie-Test for GA estimation at birth
15
16 and its accuracy to detect prematurity. Secondly, the study intends to associate the
17
18 infant's skin reflectance with lung maturity, as well as evaluate safety, precision, and
19
20 usability of a new medical device to offer a suitable product for health professionals
21
22 during childbirth and in neonatal care settings.
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24
25 **Methods and analysis:** Research protocol for diagnosis, single-group, single-blinding,
26
27 and single-arm multicenter clinical trials with a reference standard. Alive newborns,
28
29 with 24 weeks or more of pregnancy age, will be enrolled during the first 24 hours of
30
31 life. Sample size is 787 subjects. The primary outcome is the difference between the
32
33 GA calculated by the photobiological neonatal skin assessment methodology and the
34
35 GA calculated by the comparator antenatal ultrasound or reliable last menstrual period.
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37 Immediate complications caused by pulmonary immaturity during the first 72 hours of
38
39 life will be associated with skin reflectance in a nested case-control study.
40
41

42 **Ethics and dissemination:** Each local independent ethics review board approved the
43
44 trial protocol. The authors intend to share the minimal anonymized data set necessary
45
46 to replicate study findings.
47

48 **Trial registration number:** WHO Clinical Trial RBR-3f5bm5.
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51
52 **Key-words:** Gestational Age, Infant, Premature; Skin Physiological Phenomena;
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54 Photomedicine; Equipment and Supplies.
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Article Summary

Strengths and limitations of this study:

- The study will provide high-quality data on prematurity detection, based on the newborn's skin assessment, using a photometer device.
- The gold standard comparator for pregnancy dating does not exist; instead a reference standard will be used with blinded primary outcome.
- The agreement endpoint between methods for gestational age determination precludes randomization of the intervention.

Introduction

In childbirth settings, health professionals continuously need to make timely decisions to provide proper neonatal care. The day of birth is the riskiest for newborns and mothers almost everywhere¹. Perinatal causes related to prematurity and complications during childbirth, which are generally preventable through qualified health care, are the primary causes of death among newborns^{1,2}. Most of these deaths took place in countries with low resources and a scarcity of health facilities³. The opportune recognition of prematurity is critical in order to judge the viability of the newborn and to attend to his/her immediate needs, guiding the complexity of the medical care provided for the newborn. Without reliable information on the age of the unborn phase, actions to preserve the potential for survival of the newborn can be neglected⁴. Indeed, the attempted management of the risk of mortality and severe complications are sensitive issues to the gestational age (GA), which involves temperature maintenance, ventilatory support, transport to a neonatal intensive care unit (NICU), and the early treatment of respiratory distress syndrome (RDS), the most severe complication of premature birth⁵. In addition to the GA information or birthweight, the prediction of neonatal respiratory morbidity may be critical in planning immediate medical care⁶, since the respiratory system is among the last of the fetal organ systems to mature, which is associated with enhanced morbidity and mortality⁶.

Current methods of dating pregnancy remain a worldwide challenge. Early obstetric ultrasound currently offers the best due date⁷. However, access to this type of exam is limited because of high equipment costs, poor training and skills of health professionals, or late prenatal care⁸. Despite a 10-days or more margin of error during the second and third trimester of gestation, ultrasound is still a reasonable methodology for GA determination, when the best opportunity was lost⁷. The calculation, based on the historical information of the last menstrual period (LMP), is

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4 impacted by the uncertainty of both the fertility days and date of conception⁹, due to the
5 bias of memory, the use of hormonal contraception, and breastfeeding¹⁰. After birth,
6 neurological scores, such as the New Ballard¹¹, show a tendency to overestimate GA in
7 preterm infants and underestimate GA in growth-restricted infants¹². Efforts to enhance
8 the reliability of pregnancy dating, through more accurate and accessible technologies,
9 seek to improve pregnancy outcomes and neonatal survival¹³.

10
11 A new medical device has been developed to carry out the Premie-Test, an innovative
12 approach used to estimate GA, based on the photobiological properties of the
13 newborn's skin. This reflective test is noninvasive, and the device automatically
14 processes the light, scattered by the constituents of the skin layers, when a small
15 optoelectronic light emitter/receiver sensor touches the newborn's skin¹⁴. The device
16 under test is easy to use and every effort is being made to ensure that it has excellent
17 accuracy, be it safe and low cost. The feasibility study provided a mathematical model
18 to predict GA based on the skin reflectance adjusted to clinical variables ($R^2 = 0.828$, P
19 <0.001)¹⁵. However, before the adoption or use of an innovation, an effectiveness trial
20 of intervention is a critical step in the research chain regarding its the social utility when
21 completing the translation from the proof of concept to clinical science¹⁶. The rationale
22 for the main hypothesis in this study is that the skin maturity of a newborn, obtained by
23 the analysis of its optical properties, is useful in pregnancy dating for clinical use and
24 respiratory prognosis, especially in a scenario with no reliable GA based on current
25 methods. This study aims to validate the photobiological model of the skin, called the
26 "Premie-test", in order to estimate GA at birth and determine its accuracy in detecting
27 prematurity. Secondly, it also seeks to associate the infant's skin reflectance with
28 lung maturity. Moreover, this study intends to evaluate the safety, precision, and the
29 usability of a new medical device to offer a suitable product to support health
30 professionals during childbirth and in neonatal care settings.

Methods

Study design

This study will use a protocol for diagnosis, single-group, single-blinding, and single-arm multicenter clinical trials with a reference standard. This new photobiological approach to the skin, gathered in a medical device, is currently in the pivotal phase of innovation development from the prototype to regulatory approval¹⁷. This step aims to provide the translation¹⁶ of the scientific model for GA detection based on skin maturity. This Protocol version is 1, July/10th/2018. Faculty of Medicine, Universidade Federal de Minas Gerais is the Coordinator Center.

Study Settings, Ethics and Dissemination

Selected Brazilian referral centers for high-risk pregnancy and neonatal care will participate in the study, according to this protocol: Hospital das Clínicas, Universidade Federal de Minas Gerais, as the Center for Coordination; Hospital Sofia Feldman, Minas Gerais State; Hospital da Universidade Luterana do Brasil, Rio Grande do Sul State; Hospital Materno-infantil de Brasília, Distrito Federal; and Hospital Universitário da Universidade Federal do Maranhão, Maranhão State. Each local independent ethics review board approved the trial protocol, and the Brazilian National Research Council (CONEP) approved all study activities and protocol prior to the commencement of study activities, in accordance with the Declaration of Helsinki (2008), good clinical practice as set forth by the International Organization for Standardization (ISO) 14155:2011, and the Brazilian regulatory health agency's recommendations¹⁸. This study was logged under both protocol number CAAE 81347817.6.1001.5149 and the International Clinical Trials Registry Platform under number RBR-3f5bm5. Parents will sign an informed consent form on behalf of the newborn before participating in the clinical trial (supplementary file).

Data Sharing Statement

The authors intend to share the minimal anonymized data set necessary to replicate study findings. Data sharing will include: the reference and comparators GA, GA estimated by the Premie-test, birth weight, RDS or transient tachypnea of the newborn (TTN) diagnosis, ventilatory support due to pulmonary immaturity, neonatal intensive care unit (NICU) admission due to RDS or TTN, and any adverse events regarding device's safety. Unidentified data and study-related documents as ethical approvals will be accessible by URLs for researchers, regulatory agencies, and sponsors.

Patient and Public Involvement

Patients and the public were not involved in the design of this study. The results will be disseminated to study parents of participants through scientific publications, non-scientific publications, and on the website of the project: <http://skinage.medicina.ufmg.br>.

Eligibility criteria and participant's timeline

A prospective sequential and concurrent enrollment process will select newborns in referral hospitals centers for neonatal care. Infants are eligible with the following inclusion criteria: (1) alive newborn; (2) enrollment during first 24 hours of life; (3) be 24 weeks or more of gestational age, at birth; (4) fetus underwent an obstetric ultrasound assessment before 14 weeks of pregnancy; (5) fetus also had obstetric ultrasound assessment between 14 and 22 gestational weeks. Exclusion criteria are: (1) malformation with structural skin alterations; (2) skin modifiers: anhydramnios, hydrops, congenital skin diseases or chorioamnionitis. Randomisation was not appropriate to assess the agreement between different methods to assess pregnancy dating.

In a nested case-control study, we will select newborns within the first 72 hours of life,

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4 discharge, or death, whichever occurs first, with the following inclusion criteria: (1) RDS
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6 or (2) TTN diagnosis. Ranges of gestational age will randomly pair controls. Exclusion
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8 criteria include: (1) the existence of extra pulmonary conditions with tachypnea not due
9
10 to prematurity and (2) diagnosis of Clinical or Laboratory-Confirmed Bloodstream
11
12 Infection.
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14 ***Intervention: The Premie-Test***

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18 The Premie-Test assessment occurs as soon as possible after birth, in the first 24
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20 hours, inside incubators, open heating crib, common crib or in the mother's lap, in order
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22 to ensure minimum manipulation and stable clinical conditions. The acquisitions of all
23
24 newborns will be stored in a database for further statistical analysis.
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27 A noninvasive, handheld optoelectronic prototype has been developed to measure the
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29 backscattered light signal from the skin¹⁵. The equipment regulates the emitted light
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31 and processes the received light signal in the sensor, resulting in the prediction of GA
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33 by a mathematical model, associated or not with clinical variables. According to the
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35 Brazilian regulatory health agency (ANVISA), this medical device is categorized as a
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37 Class II safety: noninvasive and medium risk. The prototype unit of measurement and
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39 the process of GA estimation were patented under number BR1020170235688 (CTIT-
40
41 PN862)¹⁴. An updated version of the invention received improvements in order to
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43 safeguard reliability and to minimize examiner interferences on the skin's
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45 backscattering acquisition. The light emitting-sensor touches the skin over the sole of
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47 the foot for a few seconds. The skin reflectance will be sensed once the light has been
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49 emitted by a light emitting diode (LED) at wavelengths from 400 nm to 1200 nm. Data
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51 acquisitions occur automatically, without operator influence, and are obtained three
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53 times per newborn, in the same site and sequentially. Digital recordings will be
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55 uploaded to a server for further analysis. The prototype will blind the examiner to the
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57 predicted GA value.
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7 The criterium for discontinuing the interventions for a given trial participant will be in
8 case of parents of the newborns' request.
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10 ***Training and monitoring***

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14 Systematic monitoring of data collection, through an electronic information system,
15 would trigger any adverse event. This medical team is still responsible for the training
16 of healthcare professionals to recruit participants, data collection, a safely performed
17 Premie-Test during the newborn's assessment, and the monitoring of data quality.
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19 The certification of co-participant centers involved the accomplishment of at least 30
20 simulated examinations by the participant health professionals in the study.
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26 ***Gestational age methods of calculation and comparators***

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30 Reference-GA (R) is calculated upon enrollment, using the embryo measurement
31 assessed by ultrasound exam at <14 weeks of gestation as a reference. Crown-rump-
32 length (CRL) data, recorded from the ultrasound report or prenatal care book-
33 document, will be considered the crude data, when available. Intergrowth's 21st
34 standard curve for ultrasound measurements from 7 weeks and 3 days up to 13 weeks
35 and 6 days will be adjusted to all GA data, according to CRL¹⁹.
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43 GA methods to calculate GA in the childbirth setting, and their comparators are as
44 follows:
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47 • Premie-Test-GA (T): data statistically determined by analyzing the acquired
48 information stored in the device's processor.
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- 50
51 • Comparators-GA (C): calculated using the first ultrasound exam after 13 weeks
52 and 6 days of gestation and before 22 weeks (C1). When available, a second
53 comparator is GA based on a reliable LMP (C2)¹³.
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4 We will take a scanning copy of the prenatal care book or the ultrasound report. After
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6 evaluating the data quality, the images will be discarded. To achieve a reliable LMP,
7
8 we will interview the woman, as suggested by Nguyen et al. (2000)¹³.
9

10 **Primary outcome measures**

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13 The primary target is the agreement between the GA offered by the Premie-Test (T)
14
15 and the GA calculated by the comparators (C1 and C2), so as to perform the new test
16
17 in scenarios without the Reference-GA (R). The outcome is the difference between the
18
19 GA calculated by the photobiological neonatal skin assessment methodology in relation
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21 to the age calculated by the comparators.
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25 Another measure for the primary target is the detection of preterm newborns,
26
27 considering the age before 37 weeks of pregnancy as the threshold between term and
28
29 preterm births, and analyzing sub-categories of preterm birth, based on GA⁴:
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- 31 • extremely preterm (less than 28 weeks)
- 32
- 33 • very preterm (28 to 32 weeks)
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- 35
- 36 • moderate to late preterm (more than 32 to less than 37 weeks).
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39 In this case, the outcome is the proportion of the preterm newborn correctly detected at
40
41 birth, based on the photobiological test of the skin, within a one-week error.
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44 **Secondary outcome measures**

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46 1. In a simulated scenario, in which the Reference-GA (R) is unknown, two groups
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48 will be randomly assigned from the complete database in order to compare
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50 differences among the Reference-GA (R), the GA obtained through the
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52 Premie-Test (T), and the GA calculated by the comparators. Figure 1 presents
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54 such subgroups and measures for comparison.
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2. To monitor the device's safety when in regular use by participants over a 72-hour period. Adverse events will be monitored, according to ISO 14155:2011 standards. This means any unexpected medical events, unintended disease or injury, or unfortunate clinical signs in subjects, users, or other people, whether related to the investigational medical device or not.
3. To establish the *ease of use* of the Preemie-Test measurement as a potential method for preterm newborn diagnosis.

The secondary outcome measures in the case-control nested study

Immediate complications, occurring during the first 72 hours of life due to pulmonary immaturity, are the secondary target. The outcome measures are as follows:

- To describe the relationship of the measurement of the newborn's skin reflectance with RDS and with diagnoses based on clinical and radiological findings and respiratory outcomes^{6,20}.
- To describe the relationship of the measurement of the newborn's skin reflectance with the TTN and with diagnoses based on clinical findings and respiratory outcomes⁶.
- To describe the relationship of the measurement of the newborn's skin reflectance with ventilatory support due to pulmonary immaturity.
- To describe the relationship of the measurement of the newborn's skin reflectance with NICU admission due to RDS or TTN.

Time schedule of enrollment, intervention, and outcome measurements are presented in a schematic diagram (see Figure 2). The assessment occurs during the first 24 hours of life, but participants will be followed up for 72 hours or until discharge or death, whichever occurs first, for the monitoring of neonatal outcomes and adverse events.

Sampling and sample size

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4 The sample size calculation is estimated based on the primary endpoint. To test the
5 hypothesis of equivalence between the Premie-Test GA and the comparators GA, a
6 sample of 787 subjects is necessary to detect an effect size of 10%. Using the G-
7 Power 3.1 software²¹, we assumed an alpha error of 0.05, and a power of test of 0.80
8 to support a paired t-test.
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15 Sampling intends to arrange three groups of GA enrollment to preserve enough
16 premature newborns with 3:2:1 proportion, similar to Wilson et al. (2017)²²: 392 term
17 newborns, 263 premature newborns from 32 to 36 weeks and six days of GA, and 132
18 extremely premature newborns from 24 to 31 weeks and six days of GA.
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23 **Usability**

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25 The usability assessment will be performed by applying a checklist to participants who
26 use the prototype device to perform the Premie-Test. The 10 heuristics proposed by
27 Nielsen and Marck (1994)²³ will be adapted to build a checklist to evaluate the device,
28 namely: (a) system visibility, (b) correspondence with the real world, (c) user control
29 and freedom, (d) consistency of results and standardization, (e) error prevention, (f)
30 visual recognition rather than memorization, (g) flexibility and efficiency of use, (h)
31 esthetic and minimalist design, (i) help for the user to recognize, diagnose, and recover
32 from errors, and (j) user documentation and help.
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44 **Data collection**

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46 Standard operational procedures set data entries in structured questionnaires. In this
47 concurrent clinical trial, an electronic information system was developed to collect data
48 in different hospitals, simultaneously. Entry forms validations were implemented with
49 data values ranges to ensure the quality of the information. An audit of the data will be
50 permanently performed and the data summary available on the project webpage.
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4 validity. Independent rater over-read all papers files and cross check with the electronic
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6 information from all patients.
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8 9 **Data analysis**

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11 Demographics and baseline characteristics of the study group, as well the intervention
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13 measurements, will be summarized by the frequencies and the mean and standard
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15 deviation (SD), the whereas median and interquartile range will be preferred for non-
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17 normally distributed continuous variables.
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20 To model the GA prediction, computational randomization will select two subsamples in
21
22 the database. One of them to train the prediction model of GA based on skin
23
24 reflectance and clinical variables, such as sex, time in an incubator, phototherapy, birth
25
26 weight, among others. Another part will be for the analytical validation of the predictive
27
28 model. Improvements in the existing prediction models for GA (Premie-Test), will be
29
30 conducted with conventional statistical and data mining analyses.
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34 Regarding the primary endpoint, the agreement among three methods for GA will be
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36 calculated using the Intraclass coefficient correlation and Bland & Altman plots²⁴, and
37
38 paired t-testing. The accuracy of the Premie-Test in identifying the premature
39
40 newborn, within a one-week margin of error, will be the target of the accuracy analysis.
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43 The relationship between the measurement of the newborn's skin reflectance and
44
45 complications due to pulmonary distress associated with immaturity will be evaluated
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47 by means of association tests and risk. The significance level for hypothesis tests will
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49 be 5%, together with 95% confidence intervals.
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51 52 53 54 **Results**

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4 The study begun with the training of health professionals in September 2018. It is
5 anticipated that the recruitment will take place from January to December 2019. Data
6 analysis will be finalized, the results of which are expected in May 2020.
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10 11 12 13 **Discussion**

14 15 16 ***Strengths and Limitations***

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18 Availability of trustworthy GA information is a prerequisite for preterm birth classification
19 and healthcare decisions²⁵. In this light, the results of this clinical study have the
20 potential to validate a new device for pregnancy dating. The Premie-Test was
21 prepared to operate with minimum operator intervention and for use by healthcare
22 professionals anywhere a birth takes place without a reliable GA.
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29
30 The purpose of medical research involving neonates is intended to improve clinical
31 procedures²⁶. In this context, a clinical trial is a research study in which subjects are
32 prospectively assigned to intervention and the effects of those interventions on health-
33 related outcomes are thereby evaluated²⁷. However, clinical trials on medical devices
34 face barriers when an effective standard procedure does not exist, as is the case of the
35 comparator procedure²⁸. Our challenge in preparing the present protocol was the
36 absence of a gold standard for pregnancy dating, since the fetal age begins upon
37 conception; however, this information is difficult to be accurately determined⁷.
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5 randomised clinical trials on medical devices. *Trials*. 2017;18(1):427.
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15 **Author statement:**

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17 ZSNR: designed the study, planned data collection, prepared the team for good clinical
18 practices, wrote and revised the paper. RNG, RAPLA, MASR, RMCR and JSG made
19 substantial contributions to study design, planned data collection, prepared the team
20 for good clinical practices, wrote and revised the paper. GLNV, MAAR, GSN, PJN,
21 MDRM, and MSV made contributions to standard procedures in methods, drafted the
22 manuscript, reviewed the paper, and approved the final manuscript. EAC: drafted the
23 work and reviewed it critically for important intellectual content, as statistic consultant.
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35 **Funding statement**

36
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42 Health Complex (PROCIS), project 23072.052747/2017-51, trial sponsor contact: Fotini
43 Toscas, e-mail fotini.toscas@saude.gov.br. The funders played no role in the study
44 design, data collection and analysis, decision to publish, or preparation of the
45 manuscript.
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Roles and responsibilities: ZSNR is the Principal Investigator and coordinator of the Directive Committee. JSG is the coordinator of the Data Management Team and will continuously receive report adverse events of trial interventions or trial conduct. RAPLA is the coordinator of the Clinical Trial Quality Committee, responsible for important protocol modifications, if necessary.

Conflict of interests statement

Authors declare a patent deposit on behalf of the Universidade Federal de Minas Gerais and Fundação de Amparo a Pesquisa de Minas Gerais, Brazil, <http://www.fapemig.br/en/>. The inventors were Reis, Zilma Silveira Nogueira and Guimaraes, Rodney Nascimento: BR1020170235688 (CTIT-PN862).

Figure 1. Secondary outcome comparisons between the reference GA and the Preemie-Test in a simulated scenario without best pregnancy dating

Legends: *Gestational age from crown-rump-length data adjusted to Intergrowth's 21st fetal standard¹⁹. R: reference. GA: gestational age. T: test. C1: comparator 1 is the gestational age calculated using the first ultrasound

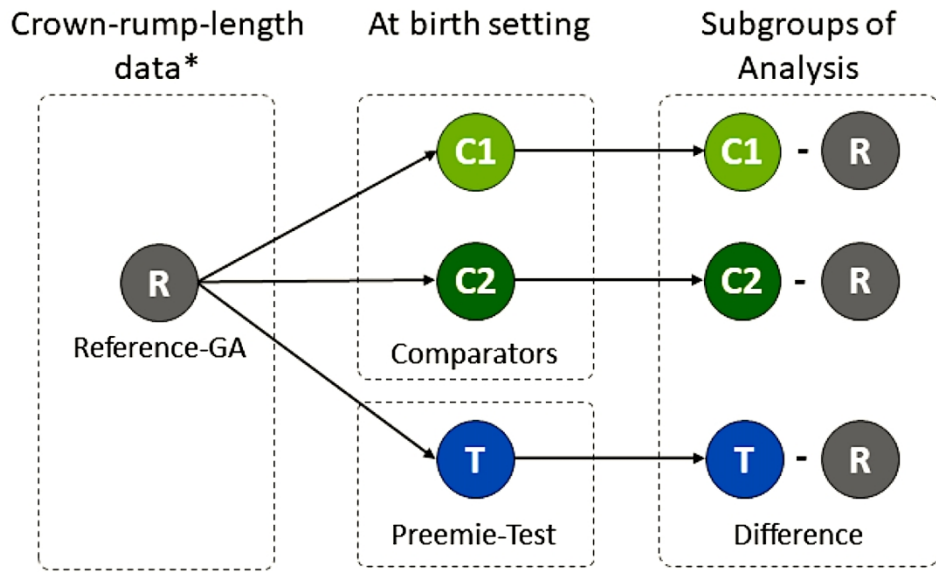
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4 exam after 13 weeks and 6 days and before 22 weeks of gestation. C2:
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6 comparator 2 is the gestational age based on a reliable last menstrual period.
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11 Figure 2. Participant timeline of the study

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14 Legends: GA: gestational age. R: reference. LMP: last menstrual period.
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For peer review only



Secondary outcome comparisons between the reference GA and the Premie-Test in a simulated scenario without best pregnancy dating

Legends: *Gestational age from crown-rump-length data adjusted to Intergrowth’s 21st fetal standard¹⁹. R: reference. GA: gestational age. T: test. C1: comparator 1 is the gestational age calculated using the first ultrasound exam after 13 weeks and 6 days and before 22 weeks of gestation. C2: comparator 2 is the gestational age based on a reliable last menstrual period.

143x90mm (300 x 300 DPI)

	STUDY PERIOD			
	Enrollment	Assessment	Close-out	Allocation
TIMEPOINT	0	0	72 hours	Analysis
ENROLLMENT:				
Eligibility screen	X			
Informed consent	X			
INTERVENTION:				
Preemie-Test		X		
ASSESSMENTS AND ANALYSIS:				
Preemie-Test: data acquisition		X		
Reference GA: calculated by obstetric ultrasound at <14 weeks of gestation	X			X
Comparator 1: GA calculated by obstetric ultrasound at ≥ 14 and <22 weeks	X			X
Comparator 2: GA calculated by reliable LMP	X			X
Case-control nested study: lung maturity		←————→		

Participant timeline of the study

Legends: GA: gestational age. R: reference. LMP: last menstrual period.

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TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Detecção da prematuridade através da interação entre a luz e a pele neonatal: a validação do Premie-Teste

Sob responsabilidade da pesquisadora Profa Zilma Silveira Nogueira Reis

Cara senhora, você está sendo convidada a participar deste estudo porque acaba de ter um parto no hospital (nome do hospital do centro colaborador) _____.

Apresentação do estudo

O objetivo deste estudo é descobrir novas técnicas para estimar a idade de um bebê ao nascer e identificar aqueles que nasceram antes de nove meses, os prematuros. A idade gestacional desconhecida pode aumentar o risco dos bebês no momento de seu nascimento. As técnicas atuais para se estimar a idade do bebê possuem grande margem de erro.

Acreditamos que a pele possui características que, se bem estudadas, podem refletir a idade das pessoas, e também dos bebês. Por isso, estamos desenvolvendo um novo equipamento médico que se encontra em teste. Ele utiliza a luz para avaliar a composição da pele do bebê e detectar sua idade. Os resultados poderão beneficiar os bebês que nascem sem a informação confiável da idade gestacional.

Instituições envolvidas no estudo

O estudo é desenvolvido pela Faculdade de Medicina da Universidade Federal de Minas Gerais (UFMG), em cooperação com maternidades brasileiras, entre elas a que você se encontra internada. A previsão deste estudo é que 787 crianças recém-nascidas sejam examinadas.

A participação no estudo, riscos e cuidados

Convidamos você e seu bebê para participar deste estudo. Isso incluirá um exame na pele do bebê com a luz, uma breve entrevista com você e a consulta aos registros de saúde sobre a gravidez e os do seu bebê neste hospital. Na entrevista serão tomados todos os cuidados a fim de minimizar os constrangimentos para você. A consulta ao prontuário médico será realizada resguardando o direito de sigilo da informação. Pedimos sua permissão para fotografar a caderneta da gestante ou outro documento equivalente, para conferir a idade gestacional calculada pelos ciclos menstruais e pelos exames de ultrassom. As partes da fotografia que contenham sua identificação serão retiradas da imagem e a manteremos até o final do estudo, quando o arquivo será apagado dos registros da pesquisa.

Pedimos sua permissão para fazer um exame na pele de seu bebê, na região da sola do pé, usando um equipamento em teste. O exame é indolor e externo ao corpo, considerado não-invasivo. A parte que encosta no bebê é pequena e não apresenta pontas que possam ferir a sua pele. Outros equipamentos parecidos, que emitem luz, já são usados nos bebês de forma segura. Por exemplo o oxímetro que faz teste do coraçãozinho. Assim como esse, não se espera que ocorram efeitos imediatos ou futuros na saúde do bebê. Os riscos do teste que faremos incluem a exposição do pé do bebê com perda temporária de calor do corpo e estresse. Cuidados serão tomados a fim de minimizar estes desconfortos. Esclarecemos que o teste dura alguns segundos reduzindo ao mínimo chance de causar marcas ou irritação no local. Caso seu bebê apresente sinais de desconforto durante o exame, o mesmo será interrompido. Você ou familiares poderão permanecer junto ao seu filho durante o exame. Nas crianças que estiverem na Unidade Neonatal, o exame será realizado onde ela já está sendo cuidada, acompanhado pelo profissional de saúde que já está cuidando dela. Caso o seu bebê seja prematuro, todos os devidos cuidados serão tomados antes de cada exame para reduzir a chance de perda de calor, seguindo todas as recomendações de um bebê que fica em incubadora.

Esclarecemos que este estudo não trará benefícios diretos a você ou seu filho, entretanto auxiliará na validação de um novo teste que poderá no futuro identificar o bebê prematuro. Os resultados poderão também gerar informações que ajudem a melhorar os cuidados com outros bebês, quando a idade gestacional é desconhecida. Informamos que os resultados da pesquisa serão publicados em revistas científicas e apresentados em congressos, sem contudo revelar sua identidade ou a do bebê.

As informações obtidas durante a pesquisa serão confidenciais, guardadas em computadores, protegidos por senha e não serão usadas para outros fins. O roubo das informações que coletaremos no estudo é um risco remoto. Para isso, as melhores práticas em segurança de dados serão empregadas. Também poderão ter acesso aos dados da pesquisa o comitê que coordena o estudo, assim como a agência reguladora ANVISA, sem jamais violar a confidencialidade e privacidade dos dados, para que seja possível monitorar se os procedimentos de qualidade e segurança da pesquisa estão sendo seguidos.

Seus direitos como participante

Informamos que a sua participação deve ser voluntária, ou seja, não é obrigatória e caso não concorde ou resolva desistir a qualquer momento isto não trará nenhum constrangimento para você ou para a forma como você será tratada neste hospital. Também não está previsto nenhum tipo de pagamento por sua participação na pesquisa. Este estudo não implica em gastos para você, pois não terá que se deslocar para outro local, permanecer mais tempo no hospital, uma vez que o exame é feito durante sua internação e de seu bebê na maternidade. Caso seja de seu interesse, os resultados do exame que estarão guardados com o pesquisador e lhe serão entregues assim que você solicitar.

Os pesquisadores garantem que acompanharão gratuitamente seu bebê durante a realização do exame e a qualquer momento que se fizer necessário, em qualquer problema que por ventura esteja associado ao estudo ou efeito do teste com a luz.

Este Termo de Consentimento está elaborado em duas vias iguais. Ambas devem ser assinadas por você, pelo pai da criança e pelo pesquisador. Uma via ficará com o participante e a outra com o pesquisador.

O Comitê de Ética em Pesquisa da UFMG pode ser contatado em caso de haver dúvidas quanto aos aspectos éticos da pesquisa, através do telefone (31) 3409-4592 ou endereço completo apresentado a seguir.

Meu nome	
Documento de identidade	
Data de hoje	

Eu declaro que estou em condições de tomar esta decisão e ciente do que foi exposto acima. Autorizo o uso de minhas informações de saúde e as do meu bebê para este projeto de pesquisa, assim como a realização do novo teste. Participo voluntariamente deste estudo e estou ciente que o exame na pele do meu bebê com a luz não traz prejuízo à sua saúde

Assinatura da puérpera:
Assinatura do pai da criança:
Assinatura do pesquisador:

Telefones de contato:

Maternidade Hospital das Clínicas da UFMG – (31) 34099422

Hospital (nome e telefone do hospital colaborador)

Zilma Reis – (31) 985177473 e-mail: skinage.ufmg@gmail.com

Comitê de Ética em Pesquisa da UFMG – Av. Prof. Antônio Carlos, 6627, Unidade Administrativa II, 2º andar, sala 2005, Campus Pampulha, CEP: 31270-901. E-mail: coep@prpq.ufmg.br. Fone (31) 34094592.

Comitê de Ética em Pesquisa do centro colaborador e endereço completo, com e-mail.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. *Ann Intern Med.* 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	6
Funding	#4	Sources and types of financial, material, and other support	18
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	19

1	Roles and	#5b	Name and contact information for the trial sponsor	19
2	responsibilities:			
3	sponsor contact			
4	information			
5				
6				
7				
8	Roles and	#5c	Role of study sponsor and funders, if any, in study	18
9	responsibilities:		design; collection, management, analysis, and	
10	sponsor and funder		interpretation of data; writing of the report; and the	
11			decision to submit the report for publication, including	
12			whether they will have ultimate authority over any of	
13			these activities	
14				
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16				
17				
18	Roles and	#5d	Composition, roles, and responsibilities of the	18
19	responsibilities:		coordinating centre, steering committee, endpoint	
20	committees		adjudication committee, data management team, and	
21			other individuals or groups overseeing the trial, if	
22			applicable (see Item 21a for data monitoring committee)	
23				
24				
25				
26				
27	Background and	#6a	Description of research question and justification for	4
28	rationale		undertaking the trial, including summary of relevant	
29			studies (published and unpublished) examining benefits	
30			and harms for each intervention	
31				
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33				
34	Background and	#6b	Explanation for choice of comparators	4
35	rationale: choice of			
36	comparators			
37				
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39	Objectives	#7	Specific objectives or hypotheses	5
40				
41				
42	Trial design	#8	Description of trial design including type of trial (eg,	6
43			parallel group, crossover, factorial, single group),	
44			allocation ratio, and framework (eg, superiority,	
45			equivalence, non-inferiority, exploratory)	
46				
47				
48				
49	Study setting	#9	Description of study settings (eg, community clinic,	6
50			academic hospital) and list of countries where data will	
51			be collected. Reference to where list of study sites can	
52			be obtained	
53				
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56	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If	7
57			applicable, eligibility criteria for study centres and	
58				
59				
60				

		individuals who will perform the interventions (eg, surgeons, psychotherapists)	
1			
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3			
4	Interventions:	#11a Interventions for each group with sufficient detail to allow	7-8
5	description	replication, including how and when they will be administered	
6			
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8			
9	Interventions:	#11b Criteria for discontinuing or modifying allocated	9
10	modifications	interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	
11			
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15			
16	Interventions:	#11c Strategies to improve adherence to intervention	NA
17	adherence	protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	
18			
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22	Interventions:	#11d Relevant concomitant care and interventions that are	9
23	concomitant care	permitted or prohibited during the trial	
24			
25			
26	Outcomes	#12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-10
27			
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38	Participant timeline	#13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11
39			
40			
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45	Sample size	#14 Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11-12
46			
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52	Recruitment	#15 Strategies for achieving adequate participant enrolment to reach target sample size	7
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1	Allocation:	#16a	Method of generating the allocation sequence (eg,	NA
2	sequence		computer-generated random numbers), and list of any	
3	generation		factors for stratification. To reduce predictability of a	
4			random sequence, details of any planned restriction (eg,	
5			blocking) should be provided in a separate document that	
6			is unavailable to those who enrol participants or assign	
7			interventions	
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12	Allocation	#16b	Mechanism of implementing the allocation sequence (eg,	NA
13	concealment		central telephone; sequentially numbered, opaque,	
14	mechanism		sealed envelopes), describing any steps to conceal the	
15			sequence until interventions are assigned	
16				
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20	Allocation:	#16c	Who will generate the allocation sequence, who will enrol	NA
21	implementation		participants, and who will assign participants to	
22			interventions	
23				
24				
25	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg,	8
26			trial participants, care providers, outcome assessors,	
27			data analysts), and how	
28				
29				
30				
31	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is	NA
32	emergency		permissible, and procedure for revealing a participant's	
33	unblinding		allocated intervention during the trial	
34				
35				
36	Data collection plan	#18a	Plans for assessment and collection of outcome,	12
37			baseline, and other trial data, including any related	
38			processes to promote data quality (eg, duplicate	
39			measurements, training of assessors) and a description	
40			of study instruments (eg, questionnaires, laboratory tests)	
41			along with their reliability and validity, if known.	
42			Reference to where data collection forms can be found, if	
43			not in the protocol	
44				
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50	Data collection plan:	#18b	Plans to promote participant retention and complete	12
51	retention		follow-up, including list of any outcome data to be	
52			collected for participants who discontinue or deviate from	
53			intervention protocols	
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57	Data management	#19	Plans for data entry, coding, security, and storage,	12
58			including any related processes to promote data quality	
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1		7(eg, double data entry; range checks for data values).	
2		Reference to where details of data management	
3		procedures can be found, if not in the protocol	
4			
5			
6	Statistics: outcomes	#20a Statistical methods for analysing primary and secondary	12
7		outcomes. Reference to where other details of the	
8		statistical analysis plan can be found, if not in the	
9		protocol	
10			
11			
12			
13	Statistics: additional	#20b Methods for any additional analyses (eg, subgroup and	12
14	analyses	adjusted analyses)	
15			
16			
17	Statistics: analysis	#20c Definition of analysis population relating to protocol non-	NA
18	population and	adherence (eg, as randomised analysis), and any	
19	missing data	statistical methods to handle missing data (eg, multiple	
20		imputation)	
21			
22			
23			
24	Data monitoring:	#21a Composition of data monitoring committee (DMC);	18
25	formal committee	summary of its role and reporting structure; statement of	
26		whether it is independent from the sponsor and	
27		competing interests; and reference to where further	
28		details about its charter can be found, if not in the	
29		protocol. Alternatively, an explanation of why a DMC is	
30		not needed	
31			
32			
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34			
35			
36	Data monitoring:	#21b Description of any interim analyses and stopping	NA
37	interim analysis	guidelines, including who will have access to these	
38		interim results and make the final decision to terminate	
39		the trial	
40			
41			
42			
43	Harms	#22 Plans for collecting, assessing, reporting, and managing	19
44		solicited and spontaneously reported adverse events and	
45		other unintended effects of trial interventions or trial	
46		conduct	
47			
48			
49			
50	Auditing	#23 Frequency and procedures for auditing trial conduct, if	12
51		any, and whether the process will be independent from	
52		investigators and the sponsor	
53			
54			
55	Research ethics	#24 Plans for seeking research ethics committee / institutional	6
56	approval	review board (REC / IRB) approval	
57			
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59			
60			

1	Protocol	#25	Plans for communicating important protocol modifications	19
2	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to	
3			relevant parties (eg, investigators, REC / IRBs, trial	
4			participants, trial registries, journals, regulators)	
5				
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7				
8	Consent or assent	#26a	Who will obtain informed consent or assent from potential	6
9			trial participants or authorised surrogates, and how (see	
10			Item 32)	
11				
12				
13	Consent or assent:	#26b	Additional consent provisions for collection and use of	NA
14	ancillary studies		participant data and biological specimens in ancillary	
15			studies, if applicable	
16				
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19	Confidentiality	#27	How personal information about potential and enrolled	6
20			participants will be collected, shared, and maintained in	
21			order to protect confidentiality before, during, and after	
22			the trial	
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26	Declaration of	#28	Financial and other competing interests for principal	18
27	interests		investigators for the overall trial and each study site	
28				
29				
30	Data access	#29	Statement of who will have access to the final trial	7
31			dataset, and disclosure of contractual agreements that	
32			limit such access for investigators	
33				
34				
35				
36	Ancillary and post	#30	Provisions, if any, for ancillary and post-trial care, and for	NA
37	trial care		compensation to those who suffer harm from trial	
38			participation	
39				
40				
41	Dissemination	#31a	Plans for investigators and sponsor to communicate trial	7
42	policy: trial results		results to participants, healthcare professionals, the	
43			public, and other relevant groups (eg, via publication,	
44			reporting in results databases, or other data sharing	
45			arrangements), including any publication restrictions	
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49				
50	Dissemination	#31b	Authorship eligibility guidelines and any intended use of	NA
51	policy: authorship		professional writers	
52				
53				
54	Dissemination	#31c	Plans, if any, for granting public access to the full	7
55	policy: reproducible		protocol, participant-level dataset, and statistical code	
56	research			
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1	Informed consent	#32	Model consent form and other related documentation	6
2	materials		given to participants and authorised surrogates	
3				
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5	Biological	#33	Plans for collection, laboratory evaluation, and storage of	NA
6	specimens		biological specimens for genetic or molecular analysis in	
7			the current trial and for future use in ancillary studies, if	
8			applicable	
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13 BY-ND 3.0. This checklist can be completed online using <https://www.goodreports.org/>, a tool made
14 by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
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BMJ Open

Prematurity detection evaluating interaction between the skin of the newborn and light: Protocol for the Premie-Test multicenter clinical trial in Brazilian hospitals to validate a new medical device

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Keywords:	Gestational Age, Infant, Premature, Skin Physiological Phenomena, Photomedicine, Equipment and Supplies

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4 **Prematurity detection evaluating interaction between the skin of the**
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6 **newborn and light: Protocol for the Premie-Test multicenter clinical trial**
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9 **in Brazilian hospitals to validate a new medical device**
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57 **Abstract**
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6 **Introduction:** Recognizing prematurity is critical in order to attend to immediate needs
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8 in childbirth settings, guiding the extent of medical care provided for newborns. A new
9
10 medical device has been developed to carry out the Preemie-Test, an innovative
11
12 approach to estimate gestational age (GA), based on the photobiological properties of
13
14 the newborn's skin. This study will validate the Preemie-Test for GA estimation at birth
15
16 and its accuracy to detect prematurity. Secondly, the study intends to associate the
17
18 infant's skin reflectance with lung maturity, as well as evaluate safety, precision, and
19
20 usability of a new medical device to offer a suitable product for health professionals
21
22 during childbirth and in neonatal care settings.
23

24
25 **Methods and analysis:** Research protocol for diagnosis, single-group, single-blinding,
26
27 and single-arm multicenter clinical trials with a reference standard. Alive newborns,
28
29 with 24 weeks or more of pregnancy age, will be enrolled during the first 24 hours of
30
31 life. Sample size is 787 subjects. The primary outcome is the difference between the
32
33 GA calculated by the photobiological neonatal skin assessment methodology and the
34
35 GA calculated by the comparator antenatal ultrasound or reliable last menstrual period.
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37 Immediate complications caused by pulmonary immaturity during the first 72 hours of
38
39 life will be associated with skin reflectance in a nested case-control study.
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41

42 **Ethics and dissemination:** Each local independent ethics review board approved the
43
44 trial protocol. The authors intend to share the minimal anonymized data set necessary
45
46 to replicate study findings.
47

48 **Trial registration number:** Brazilian Clinical Trials Registry (ReBec) [RBR-](#)
49
50 [3f5bm5](#).
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55 **Key-words:** Gestational Age, Infant, Premature; Skin Physiological Phenomena;
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57 Photomedicine; Equipment and Supplies.
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Article Summary

Strengths and limitations of this study:

- Prospective multicenter evaluation of a new medical device with training, and certification of collaborative centers.
- The gold standard comparator for pregnancy dating does not exist; instead a reference standard will be used with blinded primary outcome.
- The agreement endpoint between methods for gestational age determination precludes randomization of the intervention.

Introduction

In childbirth settings, health professionals continuously need to make timely decisions to provide proper neonatal care. The day of birth is the riskiest for newborns and mothers almost everywhere¹. Perinatal causes related to prematurity and complications during childbirth, which are generally preventable through qualified health care, are the primary causes of death among newborns^{1,2}. Most of these deaths took place in countries with low resources and a scarcity of health facilities³. The opportune recognition of prematurity is critical in order to judge the viability of the newborn and to attend to his/her immediate needs, guiding the complexity of the medical care provided for the newborn. Without reliable information on the age of the unborn phase, actions to preserve the potential for survival of the newborn can be neglected⁴. Indeed, the attempted management of the risk of mortality and severe complications are sensitive issues to the gestational age (GA), which involves temperature maintenance, ventilatory support, transport to a neonatal intensive care unit (NICU), and the early treatment of respiratory distress syndrome (RDS), the most severe complication of premature birth⁵. In addition to the GA information or birthweight, the prediction of neonatal respiratory morbidity may be critical in planning immediate medical care⁶, since the respiratory system is among the last of the fetal organ systems to mature, which is associated with enhanced morbidity and mortality⁶.

Current methods of dating pregnancy remain a worldwide challenge. Early obstetric ultrasound currently offers the best due date⁷. However, access to this type of exam is limited because of high equipment costs, poor training and skills of health professionals, or late prenatal care⁸. Despite a 10-days or more margin of error during the second and third trimester of gestation, ultrasound is still a reasonable methodology for GA determination, when the best opportunity was lost⁷. The calculation, based on the historical information of the last menstrual period (LMP), is

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4 impacted by the uncertainty of both the fertility days and date of conception⁹, due to the
5 bias of memory, the use of hormonal contraception, and breastfeeding¹⁰. After birth,
6 neurological scores, such as the New Ballard¹¹, show a tendency to overestimate GA in
7 preterm infants and underestimate GA in growth-restricted infants¹². Efforts to enhance
8 the reliability of pregnancy dating, through more accurate and accessible technologies,
9 seek to improve pregnancy outcomes and neonatal survival¹³.

10
11 A new medical device has been developed to carry out the Premie-Test, an innovative
12 approach used to estimate GA, based on the photobiological properties of the
13 newborn's skin. This reflective test is noninvasive, and the device automatically
14 processes the light, scattered by the constituents of the skin layers, when a small
15 optoelectronic light emitter/receiver sensor touches the newborn's skin¹⁴. The device
16 under test is easy to use and every effort is being made to ensure that it has excellent
17 accuracy, be it safe and low cost. The feasibility study provided a mathematical model
18 to predict GA based on the skin reflectance adjusted to clinical variables ($R^2 = 0.828$, P
19 <0.001)¹⁵. However, before the adoption or use of an innovation, an effectiveness trial
20 of intervention is a critical step in the research chain regarding its the social utility when
21 completing the translation from the proof of concept to clinical science¹⁶. The rationale
22 for the main hypothesis in this study is that the skin maturity of a newborn, obtained by
23 the analysis of its optical properties, is useful in pregnancy dating for clinical use and
24 respiratory prognosis, especially in a scenario with no reliable GA based on current
25 methods. This study aims to validate the photobiological model of the skin, called the
26 "Premie-test", in order to estimate GA at birth and determine its accuracy in detecting
27 prematurity. Secondly, it also seeks to associate the infant's skin reflectance with
28 lung maturity. Moreover, this study intends to evaluate the safety, precision, and the
29 usability of a new medical device to offer a suitable product to support health
30 professionals during childbirth and in neonatal care settings.

Methods

Study design

This study will use a protocol for diagnosis, single-group, single-blinding, and single-arm multicenter clinical trials with a reference standard. This new photobiological approach to the skin, gathered in a medical device, is currently in the pivotal phase of innovation development from the prototype to regulatory approval¹⁷. This step aims to provide the translation¹⁶ of the scientific model for GA detection based on skin maturity. This Protocol version is 1, July/10th/2018. Faculty of Medicine, Universidade Federal de Minas Gerais is the Coordinator Center.

Study Settings, Ethics and Dissemination

Selected Brazilian referral centers for high-risk pregnancy and neonatal care will participate in the study, according to this protocol: Hospital das Clínicas, Universidade Federal de Minas Gerais, as the Center for Coordination; Hospital Sofia Feldman, Minas Gerais State; Hospital da Universidade Luterana do Brasil, Rio Grande do Sul State; Hospital Materno-infantil de Brasília, Distrito Federal; and Hospital Universitário da Universidade Federal do Maranhão, Maranhão State. Each local independent ethics review board approved the trial protocol, and the Brazilian National Research Council (CONEP) approved all study activities and protocol prior to the commencement of study activities, in accordance with the Declaration of Helsinki (2008), good clinical practice as set forth by the International Organization for Standardization (ISO) 14155:2011, and the Brazilian regulatory health agency's recommendations¹⁸. This study was logged under both protocol number CAAE 81347817.6.1001.5149 and the International Clinical Trials Registry Platform under number RBR-3f5bm5. Parents will sign an informed consent form on behalf of the newborn before participating in the clinical trial (supplementary file).

Data Sharing Statement

The authors intend to share the minimal anonymized data set necessary to replicate study findings. Data sharing will include: the reference and comparators GA, GA estimated by the Premie-test, birth weight, RDS or transient tachypnea of the newborn (TTN) diagnosis, ventilatory support due to pulmonary immaturity, neonatal intensive care unit (NICU) admission due to RDS or TTN, and any adverse events regarding device's safety. Unidentified data and study-related documents as ethical approvals will be accessible by URLs for researchers, regulatory agencies, and sponsors.

Patient and Public Involvement

Patients and the public were not involved in the design of this study. The results will be disseminated to study parents of participants through scientific publications, non-scientific publications, and on the website of the project: <http://skinage.medicina.ufmg.br>.

Eligibility criteria and participant's timeline

A prospective sequential and concurrent enrollment process will select newborns in referral hospitals centers for neonatal care. Infants are eligible with the following inclusion criteria: (1) alive newborn; (2) enrollment during first 24 hours of life; (3) be 24 weeks or more of gestational age, at birth; (4) fetus underwent an obstetric ultrasound assessment before 14 weeks of pregnancy; (5) fetus also had obstetric ultrasound assessment between 14 and 22 gestational weeks. Exclusion criteria are: (1) malformation with structural skin alterations; (2) skin modifiers: anhydramnios, hydrops, congenital skin diseases or chorioamnionitis. Randomisation was not appropriate to assess the agreement between different methods to assess pregnancy dating.

In a nested case-control study, we will select newborns within the first 72 hours of life,

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4 discharge, or death, whichever occurs first, with the following inclusion criteria: (1) RDS
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6 or (2) TTN diagnosis. Ranges of gestational age will randomly pair controls. Exclusion
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8 criteria include: (1) the existence of extra pulmonary conditions with tachypnea not due
9
10 to prematurity and (2) diagnosis of Clinical or Laboratory-Confirmed Bloodstream
11
12 Infection.
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14 15 ***Intervention: The Premie-Test*** 16

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18 The Premie-Test assessment occurs as soon as possible after birth, in the first 24
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20 hours, inside incubators, open heating crib, common crib or in the mother's lap, in order
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22 to ensure minimum manipulation and stable clinical conditions. The acquisitions of all
23
24 newborns will be stored in a database for further statistical analysis.
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27 A noninvasive, handheld optoelectronic prototype has been developed to measure the
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29 backscattered light signal from the skin¹⁵. The equipment regulates the emitted light
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31 and processes the received light signal in the sensor, resulting in the prediction of GA
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33 by a mathematical model, associated or not with clinical variables. According to the
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35 Brazilian regulatory health agency (ANVISA), this medical device is categorized as a
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37 Class II safety: noninvasive and medium risk. The prototype unit of measurement and
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39 the process of GA estimation were patented under number BR1020170235688 (CTIT-
40
41 PN862)¹⁴. An updated version of the invention received improvements in order to
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43 safeguard reliability and to minimize examiner interferences on the skin's
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45 backscattering acquisition. The light emitting-sensor touches the skin over the sole of
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47 the foot for a few seconds. The skin reflectance will be sensed once the light has been
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49 emitted by a light emitting diode (LED) at wavelengths from 400 nm to 1200 nm. Data
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51 acquisitions occur automatically, without operator influence, and are obtained three
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53 times per newborn, in the same site and sequentially. Digital recordings will be
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55 uploaded to a server for further analysis. The prototype will blind the examiner to the
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57 predicted GA value.
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7 The criterium for discontinuing the interventions for a given trial participant will be in
8 case of parents of the newborns' request.
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10 ***Training and monitoring***

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14 Systematic monitoring of data collection, through an electronic information system,
15 would trigger any adverse event. This medical team is still responsible for the training
16 of healthcare professionals to recruit participants, data collection, a safely performed
17 Preemie-Test during the newborn's assessment, and the monitoring of data quality.
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19 The certification of co-participant centers involved the accomplishment of at least 30
20 simulated examinations by the participant health professionals in the study.
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27 ***Gestational age methods of calculation and comparators***

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30 Reference-GA (R) is calculated upon enrollment, using the embryo measurement
31 assessed by ultrasound exam at <14 weeks of gestation as a reference. Crown-rump-
32 length (CRL) data, recorded from the ultrasound report or prenatal care book-
33 document, will be considered the crude data, when available. Intergrowth's 21st
34 standard curve for ultrasound measurements from 7 weeks and 3 days up to 13 weeks
35 and 6 days will be adjusted to all GA data, according to CRL¹⁹.
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43 GA methods to calculate GA in the childbirth setting, and their comparators are as
44 follows:
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- 47 • Preemie-Test-GA (T): data statistically determined by analyzing the acquired
48 information stored in the device's processor.
49
- 50 • Comparators-GA (C): calculated using the first ultrasound exam after 13 weeks
51 and 6 days of gestation and before 22 weeks (C1). When available, a second
52 comparator is GA based on a reliable LMP (C2)¹³.
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4 We will take a scanning copy of the prenatal care book or the ultrasound report. After
5
6 evaluating the data quality, the images will be discarded. To achieve a reliable LMP,
7
8 we will interview the woman, as suggested by Nguyen et al. (2000)¹³.
9

10 **Primary outcome measures**

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13 The primary target is the agreement between the GA offered by the Premie-Test (T)
14
15 and the GA calculated by the comparators (C1 and C2), so as to perform the new test
16
17 in scenarios without the Reference-GA (R). The outcome is the difference between the
18
19 GA calculated by the photobiological neonatal skin assessment methodology in relation
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21 to the age calculated by the comparators.
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25 Another measure for the primary target is the detection of preterm newborns,
26
27 considering the age before 37 weeks of pregnancy as the threshold between term and
28
29 preterm births, and analyzing sub-categories of preterm birth, based on GA⁴:
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- 31 • extremely preterm (less than 28 weeks)
- 32
- 33 • very preterm (28 to 32 weeks)
- 34
- 35 • moderate to late preterm (more than 32 to less than 37 weeks).
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39 In this case, the outcome is the proportion of the preterm newborn correctly detected at
40
41 birth, based on the photobiological test of the skin, within a one-week error.
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43

44 **Secondary outcome measures**

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46 1. In a simulated scenario, in which the Reference-GA (R) is unknown, two groups
47
48 will be randomly assigned from the complete database in order to compare
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50 differences among the Reference-GA (R), the GA obtained through the
51
52 Premie-Test (T), and the GA calculated by the comparators. Figure 1 presents
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54 such subgroups and measures for comparison.
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2. To monitor the device's safety when in regular use by participants over a 72-hour period. Adverse events will be monitored, according to ISO 14155:2011 standards. This means any unexpected medical events, unintended disease or injury, or unfortunate clinical signs in subjects, users, or other people, whether related to the investigational medical device or not.
3. To establish the *ease of use* of the Preemie-Test measurement as a potential method for preterm newborn diagnosis.

The secondary outcome measures in the case-control nested study

Immediate complications, occurring during the first 72 hours of life due to pulmonary immaturity, are the secondary target. The outcome measures are as follows:

- To describe the relationship of the measurement of the newborn's skin reflectance with RDS and with diagnoses based on clinical and radiological findings and respiratory outcomes^{6,20}.
- To describe the relationship of the measurement of the newborn's skin reflectance with the TTN and with diagnoses based on clinical findings and respiratory outcomes⁶.
- To describe the relationship of the measurement of the newborn's skin reflectance with ventilatory support due to pulmonary immaturity.
- To describe the relationship of the measurement of the newborn's skin reflectance with NICU admission due to RDS or TTN.

Time schedule of enrollment, intervention, and outcome measurements are presented in a schematic diagram (see Figure 2). The assessment occurs during the first 24 hours of life, but participants will be followed up for 72 hours or until discharge or death, whichever occurs first, for the monitoring of neonatal outcomes and adverse events.

Sampling and sample size

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4 The sample size calculation is estimated based on the primary endpoint. To test the
5 hypothesis of equivalence between the Premie-Test GA and the comparators GA, a
6 sample of 787 subjects is necessary to detect an effect size of 10%. Using the G-
7 Power 3.1 software²¹, we assumed an alpha error of 0.05, and a power of test of 0.80
8 to support a paired t-test.
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15 Sampling intends to arrange three groups of GA enrollment to preserve enough
16 premature newborns with 3:2:1 proportion, similar to Wilson et al. (2017)²²: 392 term
17 newborns, 263 premature newborns from 32 to 36 weeks and six days of GA, and 132
18 extremely premature newborns from 24 to 31 weeks and six days of GA.
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23 **Usability**

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25 The usability assessment will be performed by applying a checklist to participants who
26 use the prototype device to perform the Premie-Test. The 10 heuristics proposed by
27 Nielsen and Marck (1994)²³ will be adapted to build a checklist to evaluate the device,
28 namely: (a) system visibility, (b) correspondence with the real world, (c) user control
29 and freedom, (d) consistency of results and standardization, (e) error prevention, (f)
30 visual recognition rather than memorization, (g) flexibility and efficiency of use, (h)
31 esthetic and minimalist design, (i) help for the user to recognize, diagnose, and recover
32 from errors, and (j) user documentation and help.
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44 **Data collection**

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46 Standard operational procedures set data entries in structured questionnaires. In this
47 concurrent clinical trial, an electronic information system was developed to collect data
48 in different hospitals, simultaneously. Entry forms validations were implemented with
49 data values ranges to ensure the quality of the information. An audit of the data will be
50 permanently performed and the data summary available on the project webpage.
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60 Double system, paper-based and electronic will permit audit concerning reliability and

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4 validity. Independent rater over-read all papers files and cross check with the electronic
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6 information from all patients.
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8 9 **Data analysis**

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11 Demographics and baseline characteristics of the study group, as well the intervention
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13 measurements, will be summarized by the frequencies and the mean and standard
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15 deviation (SD), the whereas median and interquartile range will be preferred for non-
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17 normally distributed continuous variables.
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20 To model the GA prediction, computational randomization will select two subsamples in
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22 the database. One of them to train the prediction model of GA based on skin
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24 reflectance and clinical variables, such as sex, time in an incubator, phototherapy, birth
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26 weight, among others. Another part will be for the analytical validation of the predictive
27
28 model. Improvements in the existing prediction models for GA (Premie-Test), will be
29
30 conducted with conventional statistical and data mining analyses.
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34 Regarding the primary endpoint, the agreement among three methods for GA will be
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36 calculated using the Intraclass coefficient correlation and Bland & Altman plots²⁴, and
37
38 paired t-testing. The accuracy of the Premie-Test in identifying the premature
39
40 newborn, within a one-week margin of error, will be the target of the accuracy analysis.
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43 The relationship between the measurement of the newborn's skin reflectance and
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45 complications due to pulmonary distress associated with immaturity will be evaluated
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47 by means of association tests and risk. The significance level for hypothesis tests will
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49 be 5%, together with 95% confidence intervals.
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51 52 53 54 **Discussion**

55 56 57 **Strengths and Limitations** 58 59 60

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4 Availability of trustworthy GA information is a prerequisite for preterm birth classification
5 and healthcare decisions²⁵. In this light, the results of this clinical study have the
6 potential to validate a new device for pregnancy dating. The Premie-Test was
7 prepared to operate with minimum operator intervention and for use by healthcare
8 professionals anywhere a birth takes place without a reliable GA.
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15 The purpose of medical research involving neonates is intended to improve clinical
16 procedures²⁶. In this context, a clinical trial is a research study in which subjects are
17 prospectively assigned to intervention and the effects of those interventions on health-
18 related outcomes are thereby evaluated²⁷. However, clinical trials on medical devices
19 face barriers when an effective standard procedure does not exist, as is the case of the
20 comparator procedure²⁸. Our challenge in preparing the present protocol was the
21 absence of a gold standard for pregnancy dating, since the fetal age begins upon
22 conception; however, this information is difficult to be accurately determined⁷.
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33 The study begun with the training of health professionals in September 2018. It is
34 anticipated that the recruitment will take place from January to December 2019. Data
35 analysis will be finalized, the results of which are expected in May 2020.
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52 randomised clinical trials on medical devices. *Trials.* 2017;18(1):427.
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Author statement:

ZSNR: designed the study, planned data collection, prepared the team for good clinical practices, wrote and revised the paper. RNG, RAPLA, MASR, RMCR and JSG made substantial contributions to study design, planned data collection, prepared the team for good clinical practices, wrote and revised the paper. GLNV, MAAR, GSN, PJN, MDRM, and MSV made contributions to standard procedures in methods, drafted the manuscript, reviewed the paper, and approved the final manuscript. EAC: drafted the work and reviewed it critically for important intellectual content, as statistic consultant.

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4 training; Fotini Toscas from the Brazilian Ministry of Health for the active intermediation
5
6 as the trial sponsor contact.
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11 **Roles and responsibilities:** ZSNR is the Principal Investigator and coordinator of the
12 Directive Committee. JSG is the coordinator of the Data Management Team and will
13 continuously receive report adverse events of trial interventions or trial conduct. RAPLA
14 is the coordinator of the Clinical Trial Quality Committee, responsible for important
15 protocol modifications, if necessary.
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23 24 **Conflict of interests statement**

25
26 Authors declare a patent deposit on behalf of the Universidade Federal de Minas
27 Gerais and Fundação de Amparo a Pesquisa de Minas Gerais, Brazil,
28 <http://www.fapemig.br/en/>. The inventors were Reis, Zilma Silveira Nogueira and
29 Guimaraes, Rodney Nascimento: BR1020170235688 (CTIT-PN862).
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39 Figure 1. Secondary outcome comparisons between the reference GA and the
40 Preemie-Test in a simulated scenario without best pregnancy dating
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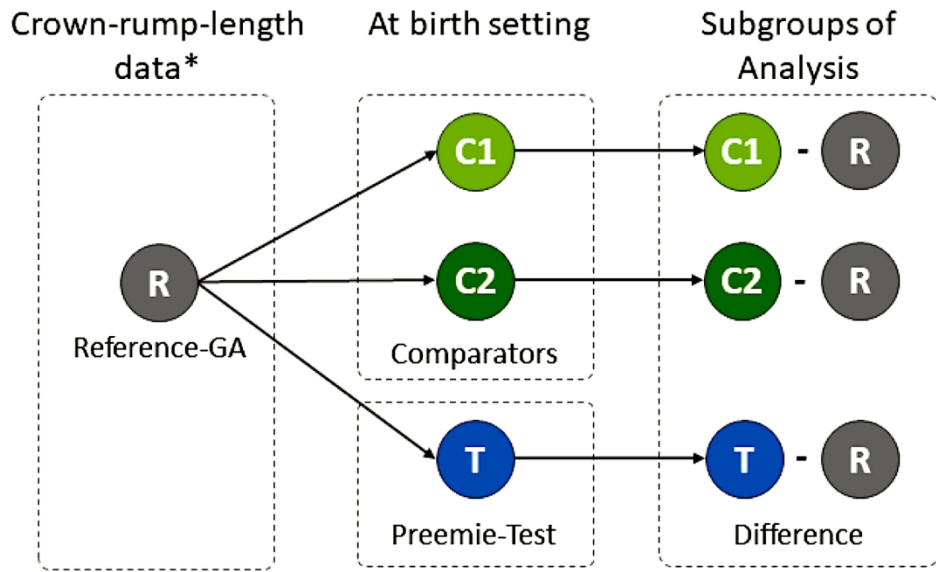
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46 Legends: *Gestational age from crown-rump-length data adjusted to
47 Intergrowth's 21st fetal standard¹⁹. R: reference. GA: gestational age. T: test.
48 C1: comparator 1 is the gestational age calculated using the first ultrasound
49 exam after 13 weeks and 6 days and before 22 weeks of gestation. C2:
50 comparator 2 is the gestational age based on a reliable last menstrual period.
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4 Figure 2. Participant timeline of the study
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6 Legends: GA: gestational age. R: reference. LMP: last menstrual period.
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12 **Word Count:** 3415 words
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For peer review only



Secondary outcome comparisons between the reference GA and the Premie-Test in a simulated scenario without best pregnancy dating

Legends: *Gestational age from crown-rump-length data adjusted to Intergrowth’s 21st fetal standard¹⁹. R: reference. GA: gestational age. T: test. C1: comparator 1 is the gestational age calculated using the first ultrasound exam after 13 weeks and 6 days and before 22 weeks of gestation. C2: comparator 2 is the gestational age based on a reliable last menstrual period.

143x90mm (300 x 300 DPI)

	STUDY PERIOD			
	Enrollment	Assessment	Close-out	Allocation
TIMEPOINT	0	0	72 hours	Analysis
ENROLLMENT:				
Eligibility screen	X			
Informed consent	X			
INTERVENTION:				
Preemie-Test		X		
ASSESSMENTS AND ANALYSIS:				
Preemie-Test: data acquisition		X		
Reference GA: calculated by obstetric ultrasound at <14 weeks of gestation	X			X
Comparator 1: GA calculated by obstetric ultrasound at ≥ 14 and <22 weeks	X			X
Comparator 2: GA calculated by reliable LMP	X			X
Case-control nested study: lung maturity		←—————→		

Participant timeline of the study

Legends: GA: gestational age. R: reference. LMP: last menstrual period.

157x123mm (300 x 300 DPI)

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Detecção da prematuridade através da interação entre a luz e a pele neonatal: a validação do Premie-Teste

Sob responsabilidade da pesquisadora Profa Zilma Silveira Nogueira Reis

Cara senhora, você está sendo convidada a participar deste estudo porque acaba de ter um parto no hospital (nome do hospital do centro colaborador) _____.

Apresentação do estudo

O objetivo deste estudo é descobrir novas técnicas para estimar a idade de um bebê ao nascer e identificar aqueles que nasceram antes de nove meses, os prematuros. A idade gestacional desconhecida pode aumentar o risco dos bebês no momento de seu nascimento. As técnicas atuais para se estimar a idade do bebê possuem grande margem de erro.

Acreditamos que a pele possui características que, se bem estudadas, podem refletir a idade das pessoas, e também dos bebês. Por isso, estamos desenvolvendo um novo equipamento médico que se encontra em teste. Ele utiliza a luz para avaliar a composição da pele do bebê e detectar sua idade. Os resultados poderão beneficiar os bebês que nascem sem a informação confiável da idade gestacional.

Instituições envolvidas no estudo

O estudo é desenvolvido pela Faculdade de Medicina da Universidade Federal de Minas Gerais (UFMG), em cooperação com maternidades brasileiras, entre elas a que você se encontra internada. A previsão deste estudo é que 787 crianças recém-nascidas sejam examinadas.

A participação no estudo, riscos e cuidados

Convidamos você e seu bebê para participar deste estudo. Isso incluirá um exame na pele do bebê com a luz, uma breve entrevista com você e a consulta aos registros de saúde sobre a gravidez e os do seu bebê neste hospital. Na entrevista serão tomados todos os cuidados a fim de minimizar os constrangimentos para você. A consulta ao prontuário médico será realizada resguardando o direito de sigilo da informação. Pedimos sua permissão para fotografar a caderneta da gestante ou outro documento equivalente, para conferir a idade gestacional calculada pelos ciclos menstruais e pelos exames de ultrassom. As partes da fotografia que contenham sua identificação serão retiradas da imagem e a manteremos até o final do estudo, quando o arquivo será apagado dos registros da pesquisa.

Pedimos sua permissão para fazer um exame na pele de seu bebê, na região da sola do pé, usando um equipamento em teste. O exame é indolor e externo ao corpo, considerado não-invasivo. A parte que encosta no bebê é pequena e não apresenta pontas que possam ferir a sua pele. Outros equipamentos parecidos, que emitem luz, já são usados nos bebês de forma segura. Por exemplo o oxímetro que faz teste do coraçãozinho. Assim como esse, não se espera que ocorram efeitos imediatos ou futuros na saúde do bebê. Os riscos do teste que faremos incluem a exposição do pé do bebê com perda temporária de calor do corpo e estresse. Cuidados serão tomados a fim de minimizar estes desconfortos. Esclarecemos que o teste dura alguns segundos reduzindo ao mínimo chance de causar marcas ou irritação no local. Caso seu bebê apresente sinais de desconforto durante o exame, o mesmo será interrompido. Você ou familiares poderão permanecer junto ao seu filho durante o exame. Nas crianças que estiverem na Unidade Neonatal, o exame será realizado onde ela já está sendo cuidada, acompanhado pelo profissional de saúde que já está cuidando dela. Caso o seu bebê seja prematuro, todos os devidos cuidados serão tomados antes de cada exame para reduzir a chance de perda de calor, seguindo todas as recomendações de um bebê que fica em incubadora.

Esclarecemos que este estudo não trará benefícios diretos a você ou seu filho, entretanto auxiliará na validação de um novo teste que poderá no futuro identificar o bebê prematuro. Os resultados poderão também gerar informações que ajudem a melhorar os cuidados com outros bebês, quando a idade gestacional é desconhecida. Informamos que os resultados da pesquisa serão publicados em revistas científicas e apresentados em congressos, sem contudo revelar sua identidade ou a do bebê.

As informações obtidas durante a pesquisa serão confidenciais, guardadas em computadores, protegidos por senha e não serão usadas para outros fins. O roubo das informações que coletaremos no estudo é um risco remoto. Para isso, as melhores práticas em segurança de dados serão empregadas. Também poderão ter acesso aos dados da pesquisa o comitê que coordena o estudo, assim como a agência reguladora ANVISA, sem jamais violar a confidencialidade e privacidade dos dados, para que seja possível monitorar se os procedimentos de qualidade e segurança da pesquisa estão sendo seguidos.

Seus direitos como participante

Informamos que a sua participação deve ser voluntária, ou seja, não é obrigatória e caso não concorde ou resolva desistir a qualquer momento isto não trará nenhum constrangimento para você ou para a forma como você será tratada neste hospital. Também não está previsto nenhum tipo de pagamento por sua participação na pesquisa. Este estudo não implica em gastos para você, pois não terá que se deslocar para outro local, permanecer mais tempo no hospital, uma vez que o exame é feito durante sua internação e de seu bebê na maternidade. Caso seja de seu interesse, os resultados do exame que estarão guardados com o pesquisador e lhe serão entregues assim que você solicitar.

Os pesquisadores garantem que acompanharão gratuitamente seu bebê durante a realização do exame e a qualquer momento que se fizer necessário, em qualquer problema que por ventura esteja associado ao estudo ou efeito do teste com a luz.

Este Termo de Consentimento está elaborado em duas vias iguais. Ambas devem ser assinadas por você, pelo pai da criança e pelo pesquisador. Uma via ficará com o participante e a outra com o pesquisador.

O Comitê de Ética em Pesquisa da UFMG pode ser contatado em caso de haver dúvidas quanto aos aspectos éticos da pesquisa, através do telefone (31) 3409-4592 ou endereço completo apresentado a seguir.

Meu nome	
Documento de identidade	
Data de hoje	

Eu declaro que estou em condições de tomar esta decisão e ciente do que foi exposto acima. Autorizo o uso de minhas informações de saúde e as do meu bebê para este projeto de pesquisa, assim como a realização do novo teste. Participo voluntariamente deste estudo e estou ciente que o exame na pele do meu bebê com a luz não traz prejuízo à sua saúde

Assinatura da puérpera:
Assinatura do pai da criança:
Assinatura do pesquisador:

Telefones de contato:

Maternidade Hospital das Clínicas da UFMG – (31) 34099422

Hospital (nome e telefone do hospital colaborador)

Zilma Reis – (31) 985177473 e-mail: skinage.ufmg@gmail.com

Comitê de Ética em Pesquisa da UFMG – Av. Prof. Antônio Carlos, 6627, Unidade Administrativa II, 2º andar, sala 2005, Campus Pampulha, CEP: 31270-901. E-mail: coep@prpq.ufmg.br. Fone (31) 34094592.

Comitê de Ética em Pesquisa do centro colaborador e endereço completo, com e-mail.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. *Ann Intern Med.* 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	6
Funding	#4	Sources and types of financial, material, and other support	18
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	19

1	Roles and	#5b	Name and contact information for the trial sponsor	19
2	responsibilities:			
3	sponsor contact			
4	information			
5				
6				
7				
8	Roles and	#5c	Role of study sponsor and funders, if any, in study	18
9	responsibilities:		design; collection, management, analysis, and	
10	sponsor and funder		interpretation of data; writing of the report; and the	
11			decision to submit the report for publication, including	
12			whether they will have ultimate authority over any of	
13			these activities	
14				
15				
16				
17				
18	Roles and	#5d	Composition, roles, and responsibilities of the	18
19	responsibilities:		coordinating centre, steering committee, endpoint	
20	committees		adjudication committee, data management team, and	
21			other individuals or groups overseeing the trial, if	
22			applicable (see Item 21a for data monitoring committee)	
23				
24				
25				
26				
27	Background and	#6a	Description of research question and justification for	4
28	rationale		undertaking the trial, including summary of relevant	
29			studies (published and unpublished) examining benefits	
30			and harms for each intervention	
31				
32				
33				
34	Background and	#6b	Explanation for choice of comparators	4
35	rationale: choice of			
36	comparators			
37				
38				
39	Objectives	#7	Specific objectives or hypotheses	5
40				
41				
42	Trial design	#8	Description of trial design including type of trial (eg,	6
43			parallel group, crossover, factorial, single group),	
44			allocation ratio, and framework (eg, superiority,	
45			equivalence, non-inferiority, exploratory)	
46				
47				
48				
49	Study setting	#9	Description of study settings (eg, community clinic,	6
50			academic hospital) and list of countries where data will	
51			be collected. Reference to where list of study sites can	
52			be obtained	
53				
54				
55				
56	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If	7
57			applicable, eligibility criteria for study centres and	
58				
59				
60				

		individuals who will perform the interventions (eg, surgeons, psychotherapists)	
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3			
4	Interventions:	#11a Interventions for each group with sufficient detail to allow	7-8
5	description	replication, including how and when they will be administered	
6			
7			
8			
9	Interventions:	#11b Criteria for discontinuing or modifying allocated	9
10	modifications	interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	
11			
12			
13			
14			
15			
16	Interventions:	#11c Strategies to improve adherence to intervention	NA
17	adherence	protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	
18			
19			
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21			
22	Interventions:	#11d Relevant concomitant care and interventions that are	9
23	concomitant care	permitted or prohibited during the trial	
24			
25			
26	Outcomes	#12 Primary, secondary, and other outcomes, including the	9-10
27		specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	
28			
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38	Participant timeline	#13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11
39			
40			
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44			
45	Sample size	#14 Estimated number of participants needed to achieve	11-12
46		study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	
47			
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52	Recruitment	#15 Strategies for achieving adequate participant enrolment	7
53		to reach target sample size	
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1	Allocation:	#16a	Method of generating the allocation sequence (eg,	NA
2	sequence		computer-generated random numbers), and list of any	
3	generation		factors for stratification. To reduce predictability of a	
4			random sequence, details of any planned restriction (eg,	
5			blocking) should be provided in a separate document that	
6			is unavailable to those who enrol participants or assign	
7			interventions	
8				
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10				
11				
12	Allocation	#16b	Mechanism of implementing the allocation sequence (eg,	NA
13	concealment		central telephone; sequentially numbered, opaque,	
14	mechanism		sealed envelopes), describing any steps to conceal the	
15			sequence until interventions are assigned	
16				
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19				
20	Allocation:	#16c	Who will generate the allocation sequence, who will enrol	NA
21	implementation		participants, and who will assign participants to	
22			interventions	
23				
24				
25	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg,	8
26			trial participants, care providers, outcome assessors,	
27			data analysts), and how	
28				
29				
30				
31	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is	NA
32	emergency		permissible, and procedure for revealing a participant's	
33	unblinding		allocated intervention during the trial	
34				
35				
36	Data collection plan	#18a	Plans for assessment and collection of outcome,	12
37			baseline, and other trial data, including any related	
38			processes to promote data quality (eg, duplicate	
39			measurements, training of assessors) and a description	
40			of study instruments (eg, questionnaires, laboratory tests)	
41			along with their reliability and validity, if known.	
42			Reference to where data collection forms can be found, if	
43			not in the protocol	
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50	Data collection plan:	#18b	Plans to promote participant retention and complete	12
51	retention		follow-up, including list of any outcome data to be	
52			collected for participants who discontinue or deviate from	
53			intervention protocols	
54				
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57	Data management	#19	Plans for data entry, coding, security, and storage,	12
58			including any related processes to promote data quality	
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1		7(eg, double data entry; range checks for data values).	
2		Reference to where details of data management	
3		procedures can be found, if not in the protocol	
4			
5			
6	Statistics: outcomes	#20a Statistical methods for analysing primary and secondary	12
7		outcomes. Reference to where other details of the	
8		statistical analysis plan can be found, if not in the	
9		protocol	
10			
11			
12			
13	Statistics: additional	#20b Methods for any additional analyses (eg, subgroup and	12
14	analyses	adjusted analyses)	
15			
16			
17	Statistics: analysis	#20c Definition of analysis population relating to protocol non-	NA
18	population and	adherence (eg, as randomised analysis), and any	
19	missing data	statistical methods to handle missing data (eg, multiple	
20		imputation)	
21			
22			
23			
24	Data monitoring:	#21a Composition of data monitoring committee (DMC);	18
25	formal committee	summary of its role and reporting structure; statement of	
26		whether it is independent from the sponsor and	
27		competing interests; and reference to where further	
28		details about its charter can be found, if not in the	
29		protocol. Alternatively, an explanation of why a DMC is	
30		not needed	
31			
32			
33			
34			
35			
36	Data monitoring:	#21b Description of any interim analyses and stopping	NA
37	interim analysis	guidelines, including who will have access to these	
38		interim results and make the final decision to terminate	
39		the trial	
40			
41			
42			
43	Harms	#22 Plans for collecting, assessing, reporting, and managing	19
44		solicited and spontaneously reported adverse events and	
45		other unintended effects of trial interventions or trial	
46		conduct	
47			
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49			
50	Auditing	#23 Frequency and procedures for auditing trial conduct, if	12
51		any, and whether the process will be independent from	
52		investigators and the sponsor	
53			
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55	Research ethics	#24 Plans for seeking research ethics committee / institutional	6
56	approval	review board (REC / IRB) approval	
57			
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1	Protocol	#25	Plans for communicating important protocol modifications	19
2	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to	
3			relevant parties (eg, investigators, REC / IRBs, trial	
4			participants, trial registries, journals, regulators)	
5				
6				
7				
8	Consent or assent	#26a	Who will obtain informed consent or assent from potential	6
9			trial participants or authorised surrogates, and how (see	
10			Item 32)	
11				
12				
13	Consent or assent:	#26b	Additional consent provisions for collection and use of	NA
14	ancillary studies		participant data and biological specimens in ancillary	
15			studies, if applicable	
16				
17				
18				
19	Confidentiality	#27	How personal information about potential and enrolled	6
20			participants will be collected, shared, and maintained in	
21			order to protect confidentiality before, during, and after	
22			the trial	
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26	Declaration of	#28	Financial and other competing interests for principal	18
27	interests		investigators for the overall trial and each study site	
28				
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30	Data access	#29	Statement of who will have access to the final trial	7
31			dataset, and disclosure of contractual agreements that	
32			limit such access for investigators	
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36	Ancillary and post	#30	Provisions, if any, for ancillary and post-trial care, and for	NA
37	trial care		compensation to those who suffer harm from trial	
38			participation	
39				
40				
41	Dissemination	#31a	Plans for investigators and sponsor to communicate trial	7
42	policy: trial results		results to participants, healthcare professionals, the	
43			public, and other relevant groups (eg, via publication,	
44			reporting in results databases, or other data sharing	
45			arrangements), including any publication restrictions	
46				
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50	Dissemination	#31b	Authorship eligibility guidelines and any intended use of	NA
51	policy: authorship		professional writers	
52				
53				
54	Dissemination	#31c	Plans, if any, for granting public access to the full	7
55	policy: reproducible		protocol, participant-level dataset, and statistical code	
56	research			
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1	Informed consent	#32	Model consent form and other related documentation	6
2	materials		given to participants and authorised surrogates	
3				
4				
5	Biological	#33	Plans for collection, laboratory evaluation, and storage of	NA
6	specimens		biological specimens for genetic or molecular analysis in	
7			the current trial and for future use in ancillary studies, if	
8			applicable	
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14 by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
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BMJ Open

Prematurity detection evaluating interaction between the skin of the newborn and light: Protocol for the Premie-Test multicenter clinical trial in Brazilian hospitals to validate a new medical device

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Secondary Subject Heading:	Global health, Diagnostics, Paediatrics
Keywords:	Gestational Age, Infant, Premature, Skin Physiological Phenomena, Photomedicine, Equipment and Supplies

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4 **Prematurity detection evaluating interaction between the skin of the**
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6 **newborn and light: Protocol for the Preemie-Test multicenter clinical trial**
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9 **in Brazilian hospitals to validate a new medical device**
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Abstract

Introduction: Recognizing prematurity is critical in order to attend to immediate needs in childbirth settings, guiding the extent of medical care provided for newborns. A new medical device has been developed to carry out the Preemie-Test, an innovative approach to estimate gestational age (GA), based on the photobiological properties of the newborn's skin. This study will validate the Preemie-Test for GA estimation at birth and its accuracy to detect prematurity. Secondly, the study intends to associate the infant's skin reflectance with lung maturity, as well as evaluate safety, precision, and usability of a new medical device to offer a suitable product for health professionals during childbirth and in neonatal care settings.

Methods and analysis: Research protocol for diagnosis, single-group, single-blinding, and single-arm multicenter clinical trials with a reference standard. Alive newborns, with 24 weeks or more of pregnancy age, will be enrolled during the first 24 hours of life. Sample size is 787 subjects. The primary outcome is the difference between the GA calculated by the photobiological neonatal skin assessment methodology and the GA calculated by the comparator antenatal ultrasound or reliable last menstrual period. Immediate complications caused by pulmonary immaturity during the first 72 hours of life will be associated with skin reflectance in a nested case-control study.

Ethics and dissemination: Each local independent ethics review board approved the trial protocol. The authors intend to share the minimal anonymized data set necessary to replicate study findings.

Trial registration number: Brazilian Clinical Trials Registry (ReBec) [RBR-3f5bm5](https://rebec.clinicaltrials.gov/record/RBR-3f5bm5).

Key-words: Gestational Age, Infant, Premature; Skin Physiological Phenomena; Photomedicine; Equipment and Supplies.

Article Summary

Strengths and limitations of this study:

- Prospective multicenter evaluation of a new medical device with training, and certification of collaborative centers.
- The gold standard comparator for pregnancy dating does not exist; instead a reference standard will be used with blinded primary outcome.
- The agreement endpoint between methods for gestational age determination precludes randomization of the intervention.

Introduction

In childbirth settings, health professionals continuously need to make timely decisions to provide proper neonatal care. The day of birth is the riskiest for newborns and mothers almost everywhere¹. Perinatal causes related to prematurity and complications during childbirth, which are generally preventable through qualified health care, are the primary causes of death among newborns^{1,2}. Most of these deaths took place in countries with low resources and a scarcity of health facilities³. The opportune recognition of prematurity is critical in order to judge the viability of the newborn and to attend to his/her immediate needs, guiding the complexity of the medical care provided for the newborn. Without reliable information on the age of the unborn phase, actions to preserve the potential for survival of the newborn can be neglected⁴. Indeed, the attempted management of the risk of mortality and severe complications are sensitive issues to the gestational age (GA), which involves temperature maintenance, ventilatory support, transport to a neonatal intensive care unit (NICU), and the early treatment of respiratory distress syndrome (RDS), the most severe complication of premature birth⁵. In addition to the GA information or birthweight, the prediction of neonatal respiratory morbidity may be critical in planning immediate medical care⁶, since the respiratory system is among the last of the fetal organ systems to mature, which is associated with enhanced morbidity and mortality⁶.

Current methods of dating pregnancy remain a worldwide challenge. Early obstetric ultrasound currently offers the best due date⁷. However, access to this type of exam is limited because of high equipment costs, poor training and skills of health professionals, or late prenatal care⁸. Despite a 10-days or more margin of error during the second and third trimester of gestation, ultrasound is still a reasonable methodology for GA determination, when the best opportunity was lost⁷. The calculation, based on the historical information of the last menstrual period (LMP), is

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4 impacted by the uncertainty of both the fertility days and date of conception⁹, due to the
5 bias of memory, the use of hormonal contraception, and breastfeeding¹⁰. After birth,
6 neurological scores, such as the New Ballard¹¹, show a tendency to overestimate GA in
7 preterm infants and underestimate GA in growth-restricted infants¹². Efforts to enhance
8 the reliability of pregnancy dating, through more accurate and accessible technologies,
9 seek to improve pregnancy outcomes and neonatal survival¹³.

10
11 A new medical device has been developed to carry out the Premie-Test, an innovative
12 approach used to estimate GA, based on the photobiological properties of the
13 newborn's skin. This reflective test is noninvasive, and the device automatically
14 processes the light, scattered by the constituents of the skin layers, when a small
15 optoelectronic light emitter/receiver sensor touches the newborn's skin¹⁴. The device
16 under test is easy to use and every effort is being made to ensure that it has excellent
17 accuracy, be it safe and low cost. The feasibility study provided a mathematical model
18 to predict GA based on the skin reflectance adjusted to clinical variables ($R^2 = 0.828$, P
19 <0.001)¹⁵. However, before the adoption or use of an innovation, an effectiveness trial
20 of intervention is a critical step in the research chain regarding its the social utility when
21 completing the translation from the proof of concept to clinical science¹⁶. The rationale
22 for the main hypothesis in this study is that the skin maturity of a newborn, obtained by
23 the analysis of its optical properties, is useful in pregnancy dating for clinical use and
24 respiratory prognosis, especially in a scenario with no reliable GA based on current
25 methods. This study aims to validate the photobiological model of the skin, called the
26 "Premie-test", in order to estimate GA at birth and determine its accuracy in detecting
27 prematurity. Secondly, it also seeks to associate the infant's skin reflectance with
28 lung maturity. Moreover, this study intends to evaluate the safety, precision, and the
29 usability of a new medical device to offer a suitable product to support health
30 professionals during childbirth and in neonatal care settings.

Methods

Study design

This study will use a protocol for diagnosis, single-group, single-blinding, and single-arm multicenter clinical trials with a reference standard. This new photobiological approach to the skin, gathered in a medical device, is currently in the pivotal phase of innovation development from the prototype to regulatory approval¹⁷. This step aims to provide the translation¹⁶ of the scientific model for GA detection based on skin maturity. This Protocol version is 2, January/15th/2019. Faculty of Medicine, Universidade Federal de Minas Gerais is the Coordinator Center.

Study Settings, Ethics and Dissemination

Selected Brazilian referral centers for high-risk pregnancy and neonatal care will participate in the study, according to this protocol: Hospital das Clínicas, Universidade Federal de Minas Gerais, as the Center for Coordination; Hospital Sofia Feldman, Minas Gerais State; Hospital da Universidade Luterana do Brasil, Rio Grande do Sul State; Hospital Materno-infantil de Brasília, Distrito Federal; and Hospital Universitário da Universidade Federal do Maranhão, Maranhão State. Each local independent ethics review board approved the trial protocol, and the Brazilian National Research Council (CONEP) approved all study activities and protocol prior to the commencement of study activities, in accordance with the Declaration of Helsinki (2008), good clinical practice as set forth by the International Organization for Standardization (ISO) 14155:2011, and the Brazilian regulatory health agency's recommendations¹⁸. This study was logged under both protocol number CAAE 81347817.6.1001.5149 and the International Clinical Trials Registry Platform under number RBR-3f5bm5. Parents will sign an informed consent form on behalf of the newborn before participating in the clinical trial (supplementary file).

Data Sharing Statement

The authors intend to share the minimal deidentified data set necessary to replicate study findings. Data sharing will include: the reference and comparators GA, GA estimated by the Premie-test, birth weight, RDS or transient tachypnea of the newborn (TTN) diagnosis, ventilatory support due to pulmonary immaturity, neonatal intensive care unit (NICU) admission due to RDS or TTN, and any adverse events regarding device's safety. Unidentified data and study-related documents as ethical approvals will be accessible by URLs for researchers, regulatory agencies, and sponsors. The correspondent author, orcid.org/0000-0001-6374-9295, will provide data access under reasonable request since the original study citation is warranted.

Patient and Public Involvement

Patients and the public were not involved in the design of this study. The results will be disseminated to study parents of participants through scientific publications, non-scientific publications, and on the website of the project: <http://skinage.medicina.ufmg.br>.

Eligibility criteria and participant's timeline

A prospective sequential and concurrent enrollment process will select newborns in referral hospitals centers for neonatal care. Infants are eligible with the following inclusion criteria: (1) alive newborn; (2) enrollment during first 24 hours of life; (3) be 24 weeks or more of gestational age, at birth; (4) fetus underwent an obstetric ultrasound assessment before 14 weeks of pregnancy; (5) fetus also had obstetric ultrasound assessment between 14 and 22 gestational weeks. Exclusion criteria are: (1) malformation with structural skin alterations; (2) skin modifiers: anhydramnios, hydrops, congenital skin diseases or chorioamnionitis. Randomisation was not appropriate to assess the agreement between different methods to assess pregnancy dating.

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4 In a nested case-control study, we will select newborns within the first 72 hours of life,
5 discharge, or death, whichever occurs first, with the following inclusion criteria: (1) RDS
6 or (2) TTN diagnosis. Ranges of gestational age will randomly pair controls. Exclusion
7 criteria include: (1) the existence of extra pulmonary conditions with tachypnea not due
8 to prematurity and (2) diagnosis of Clinical or Laboratory-Confirmed Bloodstream
9 Infection.

17 ***Intervention: The Premie-Test***

20 The Premie-Test assessment occurs as soon as possible after birth, in the first 24
21 hours, inside incubators, open heating crib, common crib or in the mother's lap, in order
22 to ensure minimum manipulation and stable clinical conditions. The acquisitions of all
23 newborns will be stored in a database for further statistical analysis.

29 A noninvasive, handheld optoelectronic prototype has been developed to measure the
30 backscattered light signal from the skin¹⁵. The equipment regulates the emitted light
31 and processes the received light signal in the sensor, resulting in the prediction of GA
32 by a mathematical model, associated or not with clinical variables. According to the
33 Brazilian regulatory health agency (ANVISA), this medical device is categorized as a
34 Class II safety: noninvasive and medium risk. The prototype unit of measurement and
35 the process of GA estimation were patented under number BR1020170235688 (CTIT-
36 PN862)¹⁴. An updated version of the invention received improvements in order to
37 safeguard reliability and to minimize examiner interferences on the skin's
38 backscattering acquisition. The light emitting-sensor touches the skin over the sole of
39 the foot for a few seconds. The skin reflectance will be sensed once the light has been
40 emitted by a light emitting diode (LED) at wavelengths from 400 nm to 1200 nm. Data
41 acquisitions occur automatically, without operator influence, and are obtained three
42 times per newborn, in the same site and sequentially. Digital recordings will be
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4 uploaded to a server for further analysis. The prototype will blind the examiner to the
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6 predicted GA value.
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11 The criterium for discontinuing the interventions for a given trial participant will be in
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13 case of parents of the newborns' request.
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15 ***Training and monitoring***

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17 Systematic monitoring of data collection, through an electronic information system,
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19 would trigger any adverse event. This medical team is still responsible for the training
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21 of healthcare professionals to recruit participants, data collection, a safely performed
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23 Premie-Test during the newborn's assessment, and the monitoring of data quality.
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25 The certification of co-participant centers involved the accomplishment of at least 30
26
27 simulated examinations by the participant health professionals in the study.
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31 ***Gestational age methods of calculation and comparators***

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33 Reference-GA (R) is calculated upon enrollment, using the embryo measurement
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35 assessed by ultrasound exam at <14 weeks of gestation as a reference. Crown-rump-
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37 length (CRL) data, recorded from the ultrasound report or prenatal care book-
38
39 document, will be considered the crude data, when available. Intergrowth's 21st
40
41 standard curve for ultrasound measurements from 7 weeks and 3 days up to 13 weeks
42
43 and 6 days will be adjusted to all GA data, according to CRL¹⁹.
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47 GA methods to calculate GA in the childbirth setting, and their comparators are as
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49 follows:
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- 51 • Premie-Test-GA (T): data statistically determined by analyzing the acquired
52 information stored in the device's processor.
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- 54 • Comparators-GA (C): calculated using the first ultrasound exam after 13 weeks
55 and 6 days of gestation and before 22 weeks (C1). When available, a second
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4 comparator is GA based on a reliable LMP (C2)¹³.
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7 We will take a scanning copy of the prenatal care book or the ultrasound report. After
8 evaluating the data quality, the images will be discarded. To achieve a reliable LMP,
9 we will interview the woman, as suggested by Nguyen et al. (2000)¹³.
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13 **Primary outcome measures**

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16 The primary target is the agreement between the GA offered by the Premie-Test (T)
17 and the GA calculated by the comparators (C1 and C2), so as to perform the new test
18 in scenarios without the Reference-GA (R). The outcome is the difference between the
19 GA calculated by the photobiological neonatal skin assessment methodology in relation
20 to the age calculated by the comparators.
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27 Another measure for the primary target is the detection of preterm newborns,
28 considering the age before 37 weeks of pregnancy as the threshold between term and
29 preterm births, and analyzing sub-categories of preterm birth, based on GA⁴:
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- 33 • extremely preterm (less than 28 weeks)
- 34 • very preterm (28 to 32 weeks)
- 35 • moderate to late preterm (more than 32 to less than 37 weeks).
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42 In this case, the outcome is the proportion of the preterm newborn correctly detected at
43 birth, based on the photobiological test of the skin, within a one-week error.
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47 **Secondary outcome measures**

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49 1. In a simulated scenario, in which the Reference-GA (R) is unknown, two groups
50 will be randomly assigned from the complete database in order to compare
51 differences among the Reference-GA (R), the GA obtained through the
52 Premie-Test (T), and the GA calculated by the comparators. Figure 1 presents
53 such subgroups and measures for comparison.
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2. To monitor the device's safety when in regular use by participants over a 72-hour period. Adverse events will be monitored, according to ISO 14155:2011 standards. This means any unexpected medical events, unintended disease or injury, or unfortunate clinical signs in subjects, users, or other people, whether related to the investigational medical device or not.
3. To establish the *ease of use* of the Preemie-Test measurement as a potential method for preterm newborn diagnosis.

The secondary outcome measures in the case-control nested study

Immediate complications, occurring during the first 72 hours of life due to pulmonary immaturity, are the secondary target. The outcome measures are as follows:

- To describe the relationship of the measurement of the newborn's skin reflectance with RDS and with diagnoses based on clinical and radiological findings and respiratory outcomes^{6,20}.
- To describe the relationship of the measurement of the newborn's skin reflectance with the TTN and with diagnoses based on clinical findings and respiratory outcomes⁶.
- To describe the relationship of the measurement of the newborn's skin reflectance with ventilatory support due to pulmonary immaturity.
- To describe the relationship of the measurement of the newborn's skin reflectance with NICU admission due to RDS or TTN.

Time schedule of enrollment, intervention, and outcome measurements are presented in a schematic diagram (see Figure 2). The assessment occurs during the first 24 hours of life, but participants will be followed up for 72 hours or until discharge or death, whichever occurs first, for the monitoring of neonatal outcomes and adverse events.

Sampling and sample size

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4 The sample size calculation is estimated based on the primary endpoint. To test the
5 hypothesis of equivalence between the Premie-Test GA and the comparators GA, a
6 sample of 787 subjects is necessary to detect an effect size of 10%. Using the G-
7 Power 3.1 software²¹, we assumed an alpha error of 0.05, and a power of test of 0.80
8 to support a paired t-test.
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15 Sampling intends to arrange three groups of GA enrollment to preserve enough
16 premature newborns with 3:2:1 proportion, similar to Wilson et al. (2017)²²: 392 term
17 newborns, 263 premature newborns from 32 to 36 weeks and six days of GA, and 132
18 extremely premature newborns from 24 to 31 weeks and six days of GA.
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23 **Usability**

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25 The usability assessment will be performed by applying a checklist to participants who
26 use the prototype device to perform the Premie-Test. The 10 heuristics proposed by
27 Nielsen and Marck (1994)²³ will be adapted to build a checklist to evaluate the device,
28 namely: (a) system visibility, (b) correspondence with the real world, (c) user control
29 and freedom, (d) consistency of results and standardization, (e) error prevention, (f)
30 visual recognition rather than memorization, (g) flexibility and efficiency of use, (h)
31 esthetic and minimalist design, (i) help for the user to recognize, diagnose, and recover
32 from errors, and (j) user documentation and help.
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44 **Data collection**

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46 Standard operational procedures set data entries in structured questionnaires. In this
47 concurrent clinical trial, an electronic information system was developed to collect data
48 in different hospitals, simultaneously. Entry forms validations were implemented with
49 data values ranges to ensure the quality of the information. An audit of the data will be
50 permanently performed and the data summary available on the project webpage.
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61 Double system, paper-based and electronic will permit audit concerning reliability and

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4 validity. Independent rater over-read all papers files and cross check with the electronic
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6 information from all patients.
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8 9 **Data analysis**

10 Demographics and baseline characteristics of the study group, as well the intervention
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12 measurements, will be summarized by the frequencies and the mean and standard
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14 deviation (SD), the whereas median and interquartile range will be preferred for non-
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16 normally distributed continuous variables.
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19 To model the GA prediction, computational randomization will select two subsamples in
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21 the database. One of them to train the prediction model of GA based on skin
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23 reflectance and clinical variables, such as sex, time in an incubator, phototherapy, birth
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25 weight, among others. Another part will be for the analytical validation of the predictive
26
27 model. Improvements in the existing prediction models for GA (Premie-Test), will be
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29 conducted with conventional statistical and data mining analyses.
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33 Regarding the primary endpoint, the agreement among three methods for GA will be
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35 calculated using the Intraclass coefficient correlation and Bland & Altman plots²⁴, and
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37 paired t-testing. The accuracy of the Premie-Test in identifying the premature
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39 newborn, within a one-week margin of error, will be the target of the accuracy analysis.
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42 The relationship between the measurement of the newborn's skin reflectance and
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44 complications due to pulmonary distress associated with immaturity will be evaluated
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46 by means of association tests and risk. The significance level for hypothesis tests will
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48 be 5%, together with 95% confidence intervals.
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51 52 53 54 **Discussion**

55 56 57 **Strengths and Limitations** 58 59 60

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4 Availability of trustworthy GA information is a prerequisite for preterm birth classification
5 and healthcare decisions²⁵. In this light, the results of this clinical study have the
6 potential to validate a new device for pregnancy dating. The Premie-Test was
7 prepared to operate with minimum operator intervention and for use by healthcare
8 professionals anywhere a birth takes place without a reliable GA.
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15 The purpose of medical research involving neonates is intended to improve clinical
16 procedures²⁶. In this context, a clinical trial is a research study in which subjects are
17 prospectively assigned to intervention and the effects of those interventions on health-
18 related outcomes are thereby evaluated²⁷. However, clinical trials on medical devices
19 face barriers when an effective standard procedure does not exist, as is the case of the
20 comparator procedure²⁸. Our challenge in preparing the present protocol was the
21 absence of a gold standard for pregnancy dating, since the fetal age begins upon
22 conception; however, this information is difficult to be accurately determined⁷.
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32 The study began with the training of health professionals in September 2018.
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35 Planned Date of First Enrollment: 2019-01-02.
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38 Planned Date of Last Enrollment: 2019-12-31.
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40 Data analysis will be finalized, the results of which are expected in May 2020.
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5 randomised clinical trials on medical devices. *Trials*. 2017;18(1):427.
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15 **Author statement:**

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17 ZSNR: designed the study, planned data collection, prepared the team for good clinical
18 practices, wrote and revised the paper. RNG, RAPLA, MASR, RMCR and JSG made
19 substantial contributions to study design, planned data collection, prepared the team
20 for good clinical practices, wrote and revised the paper. GLNV, MAAR, GSN, PJN,
21 MDRM, and MSV made contributions to standard procedures in methods, drafted the
22 manuscript, reviewed the paper, and approved the final manuscript. EAC: drafted the
23 work and reviewed it critically for important intellectual content, as statistic consultant.
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35 **Funding statement**

36
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42 Health Complex (PROCIS), project 23072.052747/2017-51, trial sponsor contact: Fotini
43 Toscas, e-mail fotini.toscas@saude.gov.br. The funders played no role in the study
44 design, data collection and analysis, decision to publish, or preparation of the
45 manuscript.
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Roles and responsibilities: ZSNR is the Principal Investigator and coordinator of the Directive Committee. JSG is the coordinator of the Data Management Team and will continuously receive report adverse events of trial interventions or trial conduct. RAPLA is the coordinator of the Clinical Trial Quality Committee, responsible for important protocol modifications, if necessary.

Conflict of interests statement

Authors declare a patent deposit on behalf of the Universidade Federal de Minas Gerais and Fundação de Amparo a Pesquisa de Minas Gerais, Brazil, <http://www.fapemig.br/en/>. The inventors were Reis, Zilma Silveira Nogueira and Guimaraes, Rodney Nascimento: BR1020170235688 (CTIT-PN862).

Figure 1. Secondary outcome comparisons between the reference GA and the Preemie-Test in a simulated scenario without best pregnancy dating

Legends: *Gestational age from crown-rump-length data adjusted to Intergrowth's 21st fetal standard¹⁹. R: reference. GA: gestational age. T: test. C1: comparator 1 is the gestational age calculated using the first ultrasound

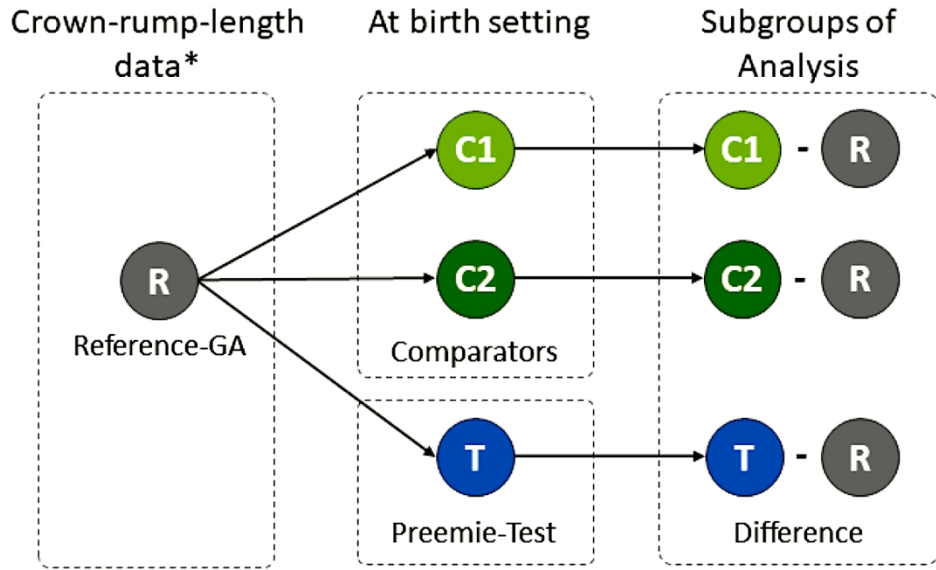
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4 exam after 13 weeks and 6 days and before 22 weeks of gestation. C2:
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6 comparator 2 is the gestational age based on a reliable last menstrual period.
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11 Figure 2. Participant timeline of the study

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14 Legends: GA: gestational age. R: reference. LMP: last menstrual period.
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20 **Word Count:** 3415 words
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For peer review only



Secondary outcome comparisons between the reference GA and the Premie-Test in a simulated scenario without best pregnancy dating

Legends: *Gestational age from crown-rump-length data adjusted to Intergrowth’s 21st fetal standard¹⁹. R: reference. GA: gestational age. T: test. C1: comparator 1 is the gestational age calculated using the first ultrasound exam after 13 weeks and 6 days and before 22 weeks of gestation. C2: comparator 2 is the gestational age based on a reliable last menstrual period.

143x90mm (300 x 300 DPI)

	STUDY PERIOD			
	Enrollment	Assessment	Close-out	Allocation
TIMEPOINT	0	0	72 hours	Analysis
ENROLLMENT:				
Eligibility screen	X			
Informed consent	X			
INTERVENTION:				
Preemie-Test		X		
ASSESSMENTS AND ANALYSIS:				
Preemie-Test: data acquisition		X		
Reference GA: calculated by obstetric ultrasound at <14 weeks of gestation	X			X
Comparator 1: GA calculated by obstetric ultrasound at ≥ 14 and <22 weeks	X			X
Comparator 2: GA calculated by reliable LMP	X			X
Case-control nested study: lung maturity		←————→		

Participant timeline of the study

Legends: GA: gestational age. R: reference. LMP: last menstrual period.

157x123mm (300 x 300 DPI)

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Detecção da prematuridade através da interação entre a luz e a pele neonatal: a validação do Premie-Teste

Sob responsabilidade da pesquisadora Profa Zilma Silveira Nogueira Reis

Cara senhora, você está sendo convidada a participar deste estudo porque acaba de ter um parto no hospital (nome do hospital do centro colaborador) _____.

Apresentação do estudo

O objetivo deste estudo é descobrir novas técnicas para estimar a idade de um bebê ao nascer e identificar aqueles que nasceram antes de nove meses, os prematuros. A idade gestacional desconhecida pode aumentar o risco dos bebês no momento de seu nascimento. As técnicas atuais para se estimar a idade do bebê possuem grande margem de erro.

Acreditamos que a pele possui características que, se bem estudadas, podem refletir a idade das pessoas, e também dos bebês. Por isso, estamos desenvolvendo um novo equipamento médico que se encontra em teste. Ele utiliza a luz para avaliar a composição da pele do bebê e detectar sua idade. Os resultados poderão beneficiar os bebês que nascem sem a informação confiável da idade gestacional.

Instituições envolvidas no estudo

O estudo é desenvolvido pela Faculdade de Medicina da Universidade Federal de Minas Gerais (UFMG), em cooperação com maternidades brasileiras, entre elas a que você se encontra internada. A previsão deste estudo é que 787 crianças recém-nascidas sejam examinadas.

A participação no estudo, riscos e cuidados

Convidamos você e seu bebê para participar deste estudo. Isso incluirá um exame na pele do bebê com a luz, uma breve entrevista com você e a consulta aos registros de saúde sobre a gravidez e os do seu bebê neste hospital. Na entrevista serão tomados todos os cuidados a fim de minimizar os constrangimentos para você. A consulta ao prontuário médico será realizada resguardando o direito de sigilo da informação. Pedimos sua permissão para fotografar a caderneta da gestante ou outro documento equivalente, para conferir a idade gestacional calculada pelos ciclos menstruais e pelos exames de ultrassom. As partes da fotografia que contenham sua identificação serão retiradas da imagem e a manteremos até o final do estudo, quando o arquivo será apagado dos registros da pesquisa.

Pedimos sua permissão para fazer um exame na pele de seu bebê, na região da sola do pé, usando um equipamento em teste. O exame é indolor e externo ao corpo, considerado não-invasivo. A parte que encosta no bebê é pequena e não apresenta pontas que possam ferir a sua pele. Outros equipamentos parecidos, que emitem luz, já são usados nos bebês de forma segura. Por exemplo o oxímetro que faz teste do coraçãozinho. Assim como esse, não se espera que ocorram efeitos imediatos ou futuros na saúde do bebê. Os riscos do teste que faremos incluem a exposição do pé do bebê com perda temporária de calor do corpo e estresse. Cuidados serão tomados a fim de minimizar estes desconfortos. Esclarecemos que o teste dura alguns segundos reduzindo ao mínimo chance de causar marcas ou irritação no local. Caso seu bebê apresente sinais de desconforto durante o exame, o mesmo será interrompido. Você ou familiares poderão permanecer junto ao seu filho durante o exame. Nas crianças que estiverem na Unidade Neonatal, o exame será realizado onde ela já está sendo cuidada, acompanhado pelo profissional de saúde que já está cuidando dela. Caso o seu bebê seja prematuro, todos os devidos cuidados serão tomados antes de cada exame para reduzir a chance de perda de calor, seguindo todas as recomendações de um bebê que fica em incubadora.

Esclarecemos que este estudo não trará benefícios diretos a você ou seu filho, entretanto auxiliará na validação de um novo teste que poderá no futuro identificar o bebê prematuro. Os resultados poderão também gerar informações que ajudem a melhorar os cuidados com outros bebês, quando a idade gestacional é desconhecida. Informamos que os resultados da pesquisa serão publicados em revistas científicas e apresentados em congressos, sem contudo revelar sua identidade ou a do bebê.

As informações obtidas durante a pesquisa serão confidenciais, guardadas em computadores, protegidos por senha e não serão usadas para outros fins. O roubo das informações que coletaremos no estudo é um risco remoto. Para isso, as melhores práticas em segurança de dados serão empregadas. Também poderão ter acesso aos dados da pesquisa o comitê que coordena o estudo, assim como a agência reguladora ANVISA, sem jamais violar a confidencialidade e privacidade dos dados, para que seja possível monitorar se os procedimentos de qualidade e segurança da pesquisa estão sendo seguidos.

Seus direitos como participante

Informamos que a sua participação deve ser voluntária, ou seja, não é obrigatória e caso não concorde ou resolva desistir a qualquer momento isto não trará nenhum constrangimento para você ou para a forma como você será tratada neste hospital. Também não está previsto nenhum tipo de pagamento por sua participação na pesquisa. Este estudo não implica em gastos para você, pois não terá que se deslocar para outro local, permanecer mais tempo no hospital, uma vez que o exame é feito durante sua internação e de seu bebê na maternidade. Caso seja de seu interesse, os resultados do exame que estarão guardados com o pesquisador e lhe serão entregues assim que você solicitar.

Os pesquisadores garantem que acompanharão gratuitamente seu bebê durante a realização do exame e a qualquer momento que se fizer necessário, em qualquer problema que por ventura esteja associado ao estudo ou efeito do teste com a luz.

Este Termo de Consentimento está elaborado em duas vias iguais. Ambas devem ser assinadas por você, pelo pai da criança e pelo pesquisador. Uma via ficará com o participante e a outra com o pesquisador.

O Comitê de Ética em Pesquisa da UFMG pode ser contatado em caso de haver dúvidas quanto aos aspectos éticos da pesquisa, através do telefone (31) 3409-4592 ou endereço completo apresentado a seguir.

Meu nome	
Documento de identidade	
Data de hoje	

Eu declaro que estou em condições de tomar esta decisão e ciente do que foi exposto acima. Autorizo o uso de minhas informações de saúde e as do meu bebê para este projeto de pesquisa, assim como a realização do novo teste. Participo voluntariamente deste estudo e estou ciente que o exame na pele do meu bebê com a luz não traz prejuízo à sua saúde

Assinatura da puérpera:
Assinatura do pai da criança:
Assinatura do pesquisador:

Telefones de contato:

Maternidade Hospital das Clínicas da UFMG – (31) 34099422

Hospital (nome e telefone do hospital colaborador)

Zilma Reis – (31) 985177473 e-mail: skinage.ufmg@gmail.com

Comitê de Ética em Pesquisa da UFMG – Av. Prof. Antônio Carlos, 6627, Unidade Administrativa II, 2º andar, sala 2005, Campus Pampulha, CEP: 31270-901. E-mail: coep@prpq.ufmg.br. Fone (31) 34094592.

Comitê de Ética em Pesquisa do centro colaborador e endereço completo, com e-mail.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. *Ann Intern Med.* 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	6
Funding	#4	Sources and types of financial, material, and other support	18
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	19

1	Roles and	#5b	Name and contact information for the trial sponsor	19
2	responsibilities:			
3	sponsor contact			
4	information			
5				
6				
7				
8	Roles and	#5c	Role of study sponsor and funders, if any, in study	18
9	responsibilities:		design; collection, management, analysis, and	
10	sponsor and funder		interpretation of data; writing of the report; and the	
11			decision to submit the report for publication, including	
12			whether they will have ultimate authority over any of	
13			these activities	
14				
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16				
17				
18	Roles and	#5d	Composition, roles, and responsibilities of the	18
19	responsibilities:		coordinating centre, steering committee, endpoint	
20	committees		adjudication committee, data management team, and	
21			other individuals or groups overseeing the trial, if	
22			applicable (see Item 21a for data monitoring committee)	
23				
24				
25				
26				
27	Background and	#6a	Description of research question and justification for	4
28	rationale		undertaking the trial, including summary of relevant	
29			studies (published and unpublished) examining benefits	
30			and harms for each intervention	
31				
32				
33				
34	Background and	#6b	Explanation for choice of comparators	4
35	rationale: choice of			
36	comparators			
37				
38				
39	Objectives	#7	Specific objectives or hypotheses	5
40				
41				
42	Trial design	#8	Description of trial design including type of trial (eg,	6
43			parallel group, crossover, factorial, single group),	
44			allocation ratio, and framework (eg, superiority,	
45			equivalence, non-inferiority, exploratory)	
46				
47				
48				
49	Study setting	#9	Description of study settings (eg, community clinic,	6
50			academic hospital) and list of countries where data will	
51			be collected. Reference to where list of study sites can	
52			be obtained	
53				
54				
55				
56	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If	7
57			applicable, eligibility criteria for study centres and	
58				
59				
60				

		individuals who will perform the interventions (eg, surgeons, psychotherapists)	
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2			
3			
4	Interventions:	#11a Interventions for each group with sufficient detail to allow	7-8
5	description	replication, including how and when they will be administered	
6			
7			
8			
9	Interventions:	#11b Criteria for discontinuing or modifying allocated	9
10	modifications	interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	
11			
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16	Interventions:	#11c Strategies to improve adherence to intervention	NA
17	adherence	protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	
18			
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22	Interventions:	#11d Relevant concomitant care and interventions that are	9
23	concomitant care	permitted or prohibited during the trial	
24			
25			
26	Outcomes	#12 Primary, secondary, and other outcomes, including the	9-10
27		specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	
28			
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37			
38	Participant timeline	#13 Time schedule of enrolment, interventions (including any	11
39		run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	
40			
41			
42			
43			
44			
45	Sample size	#14 Estimated number of participants needed to achieve	11-12
46		study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	
47			
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52	Recruitment	#15 Strategies for achieving adequate participant enrolment	7
53		to reach target sample size	
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1	Allocation:	#16a	Method of generating the allocation sequence (eg,	NA
2			computer-generated random numbers), and list of any	
3	sequence		factors for stratification. To reduce predictability of a	
4	generation		random sequence, details of any planned restriction (eg,	
5			blocking) should be provided in a separate document that	
6			is unavailable to those who enrol participants or assign	
7			interventions	
8				
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11				
12	Allocation	#16b	Mechanism of implementing the allocation sequence (eg,	NA
13	concealment		central telephone; sequentially numbered, opaque,	
14	mechanism		sealed envelopes), describing any steps to conceal the	
15			sequence until interventions are assigned	
16				
17				
18				
19				
20	Allocation:	#16c	Who will generate the allocation sequence, who will enrol	NA
21	implementation		participants, and who will assign participants to	
22			interventions	
23				
24				
25	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg,	8
26			trial participants, care providers, outcome assessors,	
27			data analysts), and how	
28				
29				
30				
31	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is	NA
32	emergency		permissible, and procedure for revealing a participant's	
33	unblinding		allocated intervention during the trial	
34				
35				
36	Data collection plan	#18a	Plans for assessment and collection of outcome,	12
37			baseline, and other trial data, including any related	
38			processes to promote data quality (eg, duplicate	
39			measurements, training of assessors) and a description	
40			of study instruments (eg, questionnaires, laboratory tests)	
41			along with their reliability and validity, if known.	
42			Reference to where data collection forms can be found, if	
43			not in the protocol	
44				
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50	Data collection plan:	#18b	Plans to promote participant retention and complete	12
51	retention		follow-up, including list of any outcome data to be	
52			collected for participants who discontinue or deviate from	
53			intervention protocols	
54				
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57	Data management	#19	Plans for data entry, coding, security, and storage,	12
58			including any related processes to promote data quality	
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1		7(eg, double data entry; range checks for data values).	
2		Reference to where details of data management	
3		procedures can be found, if not in the protocol	
4			
5			
6	Statistics: outcomes	#20a Statistical methods for analysing primary and secondary	12
7		outcomes. Reference to where other details of the	
8		statistical analysis plan can be found, if not in the	
9		protocol	
10			
11			
12			
13	Statistics: additional	#20b Methods for any additional analyses (eg, subgroup and	12
14	analyses	adjusted analyses)	
15			
16			
17	Statistics: analysis	#20c Definition of analysis population relating to protocol non-	NA
18	population and	adherence (eg, as randomised analysis), and any	
19	missing data	statistical methods to handle missing data (eg, multiple	
20		imputation)	
21			
22			
23			
24	Data monitoring:	#21a Composition of data monitoring committee (DMC);	18
25	formal committee	summary of its role and reporting structure; statement of	
26		whether it is independent from the sponsor and	
27		competing interests; and reference to where further	
28		details about its charter can be found, if not in the	
29		protocol. Alternatively, an explanation of why a DMC is	
30		not needed	
31			
32			
33			
34			
35			
36	Data monitoring:	#21b Description of any interim analyses and stopping	NA
37	interim analysis	guidelines, including who will have access to these	
38		interim results and make the final decision to terminate	
39		the trial	
40			
41			
42			
43	Harms	#22 Plans for collecting, assessing, reporting, and managing	19
44		solicited and spontaneously reported adverse events and	
45		other unintended effects of trial interventions or trial	
46		conduct	
47			
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49			
50	Auditing	#23 Frequency and procedures for auditing trial conduct, if	12
51		any, and whether the process will be independent from	
52		investigators and the sponsor	
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55	Research ethics	#24 Plans for seeking research ethics committee / institutional	6
56	approval	review board (REC / IRB) approval	
57			
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1	Protocol	#25	Plans for communicating important protocol modifications	19
2	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to	
3			relevant parties (eg, investigators, REC / IRBs, trial	
4			participants, trial registries, journals, regulators)	
5				
6				
7				
8	Consent or assent	#26a	Who will obtain informed consent or assent from potential	6
9			trial participants or authorised surrogates, and how (see	
10			Item 32)	
11				
12				
13	Consent or assent:	#26b	Additional consent provisions for collection and use of	NA
14	ancillary studies		participant data and biological specimens in ancillary	
15			studies, if applicable	
16				
17				
18				
19	Confidentiality	#27	How personal information about potential and enrolled	6
20			participants will be collected, shared, and maintained in	
21			order to protect confidentiality before, during, and after	
22			the trial	
23				
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25				
26	Declaration of	#28	Financial and other competing interests for principal	18
27	interests		investigators for the overall trial and each study site	
28				
29				
30	Data access	#29	Statement of who will have access to the final trial	7
31			dataset, and disclosure of contractual agreements that	
32			limit such access for investigators	
33				
34				
35				
36	Ancillary and post	#30	Provisions, if any, for ancillary and post-trial care, and for	NA
37	trial care		compensation to those who suffer harm from trial	
38			participation	
39				
40				
41	Dissemination	#31a	Plans for investigators and sponsor to communicate trial	7
42	policy: trial results		results to participants, healthcare professionals, the	
43			public, and other relevant groups (eg, via publication,	
44			reporting in results databases, or other data sharing	
45			arrangements), including any publication restrictions	
46				
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49				
50	Dissemination	#31b	Authorship eligibility guidelines and any intended use of	NA
51	policy: authorship		professional writers	
52				
53				
54	Dissemination	#31c	Plans, if any, for granting public access to the full	7
55	policy: reproducible		protocol, participant-level dataset, and statistical code	
56	research			
57				
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1	Informed consent	#32	Model consent form and other related documentation	6
2	materials		given to participants and authorised surrogates	
3				
4				
5	Biological	#33	Plans for collection, laboratory evaluation, and storage of	NA
6	specimens		biological specimens for genetic or molecular analysis in	
7			the current trial and for future use in ancillary studies, if	
8			applicable	
9				
10				
11				

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