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Protocol for the prospective observational clinical study: Estimation of fetal weight by MR imaging to PREdict neonatal MACROsomia (PREMACRO study)

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Keywords: Large-for-date fetuses, macrosomia, magnetic resonance imaging, estimation of weight, 2D ultrasound.

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Abstract

Introduction: Macrosomia refers to growth beyond a specific threshold, regardless of gestational age. These fetuses are also frequently referred to as large for gestational age (LGA). Various cut-offs have been used but for research purposes, a cut-off above the 95th centile is often preferred because it defines 90% of the population as normal weight. The use of centiles, rather than estimated weights, also accommodates preterm macrosomic infants, although most of the complications, maternal and fetal, arise during the delivery of large babies at term. This means that accurate identification of LGA fetuses (≥ 95th centile) may play an important role in guiding obstetric interventions, such as induction of labor or cesarean section. Traditionally, identification of fetuses suspected of macrosomia, has been based on biometric measurements using 2D ultrasound (US), yet this method is rather sub-optimal. We present a protocol (V.2.1, date 19-May 2016) for the estimation of fetal weight (EFW) by magnetic resonance imaging (MRI) to PREdict neonatal MACROsomia (PREMACRO study), which is a prospective observational clinical study designed to determine whether MRI at 36+0 to 36+6 weeks of gestation, as compared to 2D US, can improve the identification of LGA neonates ≥ 95th centile.

Methods and analysis: All eligible women attending the 36-week clinic will be invited to participate in the screening study for LGA fetuses ≥ 95th centile and will undergo US-EFW and MRI-EFW within minutes of each other. From these estimations, a centile will be derived which will be compared to the centile of birth weight used as the gold standard. Besides birth weight, other pregnancy and neonatal outcomes will be collected and analyzed. The first enrolment for the study was in May 2016. As of September 2018, 2004 women have been screened and recruited to the study. The study is registered on ClinicalTrials.gov.

Registration number: NCT01334489.

Word count: 300.

Ethics and dissemination: The study will be conducted in accordance with the International Conference on Harmonization for Good Clinical Practice and the appropriate regulatory requirement(s). A favorable ethical opinion was obtained from the Ethics Committee of the University Hospital Brugmann, reference number CE2016/44. Results will be published in peer-reviewed journals and disseminated at international conferences.

Article Summary

Strengths and limitations of this study:

This is the first prospective head-to-head comparison of US-EFW and MRI-EFW at 36 weeks of gestation in a large cohort to evaluate whether MRI can improve detection of large-for-gestational age neonates ≥ 95th centile.

Both US and MRI for EFW are performed within minutes of each other at 36+0 to 36+6 weeks of gestation.

This is a prospective clinical study and in contrast to the US-EFW, MRI-EFW will not be communicated to patients or to patients' caregivers.

This is a single-center study and the extrapolation of our findings to other perinatal centers needs further evaluation.

BACKGROUND

Macrosomia and growth restriction are important causes of perinatal morbidity (1-3), at or near to term. However, clear identification of 'at-risk' fetuses is difficult and clinical estimates of fetal weight are poor (4,5).

Ultrasound (US) is used as a second-line when an abnormality of growth is suspected, but the accuracy of this imaging modality in the mid- to late third trimester is also limited (6).

Estimated fetal weight (EFW) is an important part of the clinical assessment and is used to guide obstetric interventions, when a fetus is small or large for gestational age. When a diagnosis of intrauterine growth restriction (IUGR) is made, the decision-making process is complex, particularly at very early gestation and involves multiple factors, including maternal status, cardiotocography, liquor volume and Doppler imaging (7). However, a large body of research is now available to assist with the management of both early and late-onset IUGR, but there is a paucity of evidence to guide clinical practice, once macrosomia has been diagnosed, so EFW is frequently the single most important component guiding interventions, such as induction of labor or cesarean section (8).

Fetal macrosomia is associated with a higher incidence of perinatal morbidity, including shoulder dystocia and brachial plexus injury in the fetus and anal sphincter tears, uterine atony and hemorrhage in the mother (1). A recent multicenter randomized controlled trial appears to confirm the advantages of a policy of induction of labor for suspected macrosomia, demonstrating a clear reduction in the rates of shoulder dystocia and composite perinatal morbidity (8). A meta-analyses and systematic review, including this publication, supports the validity of this option (9). However, some earlier but lower quality, observational studies have questioned the benefit of EFW by ultrasonography in the last trimester, for suspected macrosomia, demonstrating that this practice can increase the risk of cesarean and instrumental delivery, without reducing perinatal morbidity.

Despite these conflicting data and a lack of evidence to support routine third-trimester ultrasound (10), the absence of specific guidance, coupled with concerns regarding perinatal outcomes, means that obstetricians will increasingly request an ultrasound scan at around 34-36 weeks of gestation to identify fetuses above the 90th or below the 10th centile. This practice will inevitably lead to increased and potentially harmful interventions based on relatively inaccurate data (11).

Due to the imprecision of ultrasound-derived EFW, particularly in cases of suspected macrosomia in the third trimester (12, 13), we believe that these estimates should not be used to make important obstetric decisions regarding mode and timing of delivery and that a more accurate method of assessment could produce better *outcomes* by restricting interventions to those fetuses at greatest risk. Some publications have already demonstrated that magnetic resonance imaging (MRI)-derived EFW close to delivery is more accurate than ultrasound, with a mean percentage error superior to that of ultrasound (14-23), and a recent meta-analysis has confirmed this promising accuracy (24).

HYPOTHESIS

We hypothesize that MRI-EFW at 36+0-36+6 weeks of gestation is significantly more accurate than US-EFW in prediction of large-for-gestational-age (LGA) neonates (≥ 95th centile for gestational age).

AIM

To examine whether MRI-EFW at 36+0-36+6 weeks of gestation is more accurate than US-EFW in prediction of LGA neonates.

OBJECTIVES

Primary objective

To compare MRI-EFW with US-EFW using the Hadlock formula (25,26), by comparing the Area Under the Receiver Operating Curve (AUROC) for the prediction of LGA neonates (≥ 95th centile for gestational age).

Secondary objectives

To compare MRI-EFW with US-EFW by comparing AUROC for the prediction of LGA neonates:

- ≥ 90th centile for gestational age.
- ≥ 97th centile for gestational age.
- ≥ 99th centile for gestational age.

To compare MRI-EFW with US measurement of abdominal circumference for the prediction of LGA neonates (≥ 90th and ≥ 95th centile for gestational age).

To compare MRI-EFW with US-EFW by comparing AUROC for the prediction of small-for-gestational age neonates:

- ≤ 10th centile for gestational age.
- ≤ 5th centile for gestational age.
- ≤ 3rd centile for gestational age.

To determine the ability of MRI-EFW versus US-EFW to predict significant shoulder dystocia, fracture of the clavicle or a long bone, brachial plexus injury, intracranial hemorrhage, or death.

To determine the ability of MRI-EFW versus US-EFW to predict neonatal morbidity, defined as arterial cord blood pH less than 7.10, Apgar score at 5 min less than 7, and admission to the neonatal intensive care unit (NICU).

To determine the ability of MRI-EFW versus US-EFW to predict maternal morbidity, defined as cesarean section, operative vaginal delivery (vacuum or forceps), postpartum hemorrhage (1000 mL or more), blood transfusion, and anal sphincter tear.

CENTERS

This is a single-center study conducted at the Department of Obstetrics and Gynecology and Radiology of the University Hospital Brugmann, Université Libre de Bruxelles in Brussels, Belgium.

DESIGN

This is a prospective observational clinical head-to-head comparison study of MR-EFW versus US-EFW for the prediction of LGA neonates. Randomization was not appropriate since all patients undergo both examinations.

INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria

Age ≥ 18 years;

Singleton pregnancy;

Live fetus at 36+0-36+6 weeks of gestation;

Subject is planning a delivery at our maternity at the University Hospital Brugmann, in Brussels, Belgium;

French- or Dutch-speaking (otherwise interpreters will be used);

Informed and written consent.

Exclusion Criteria

Multiple pregnancy;

Pregnancies complicated by major fetal abnormality identified at the 11-13, 20-22 or 30-35 week routine scans;

Women presenting with an imprecise pregnancy dating due to absence of first-trimester scan;

Women presenting at a gestational age < 36 or ≥ 37 weeks of gestation;

Subject is known to have a contraindication to MRI, such as:

- Carrying a pacemaker or a metallic cardiac valve.
- Having metallic material inside the head.
- Having metallic fragments inside the eye following an accident.
- Having any type of implant including ear implant.
- Having a hip prosthesis.

Women presenting with painful regular uterine contractions or history of ruptured membranes;

Women who are unconscious, severely ill, those with learning difficulties, or mentally handicapped;

Women presenting for the study but who have been previously included in the study in a previous pregnancy;

Women who deliver before MRI and US evaluation;

If the neonate's weight is not measured within 6 hours after birth for any reason, including the need for emergency care immediately after delivery;

Pregnancies ending with a stillborn;

Women who deliver outside our network of hospitals in Brussels where a full pediatric report is not available and where there is uncertainty whether the neonate's weight is measured within 6 hours after birth.

METHODS

We will recruit women attending their routine third-trimester scan in pregnancy at 30-35 weeks of gestation as well as women attending our antenatal clinic after 30 weeks of gestation at the university hospital Brugmann, in Brussels, Belgium. The patient information sheet concerning the PREMACRO study will be given to them and they will be invited to attend the 36-week clinic.

If women attend the 36-week clinic, detailed counseling about the study is provided and women who agree to participate, after obtaining a written informed consent, will undergo 15 minutes apart a US scan for fetal biometric measurement and MRI for fetal body volume (FBV) measurement. There is no prespecified order for these examinations, which are performed according to which machine is available first. For the purpose of the study, 2 ultrasound machines have been installed in the Radiology Department on the same floor as the MRI machine.

US examination and US-EFW:

Prenatal US examinations will be carried out using transabdominal sonography by one of 4 experienced consultants in Maternal Fetal Medicine Department. US-EFW will be obtained between 36.0-36+6 weeks of gestation, according to Hadlock *et al.* (25,26), based on measurements of biparietal diameter, head circumference, abdominal circumference and femoral length. Two Voluson E8 machines will be used for the purpose of the study (GE Medical Systems, Zipf, Austria). A percentile for the US-EFW will be obtained after plotting the weight estimation on the curves as described by Yudkin *et al.* (27). All data will be entered in ASTRAIA software gmbh (Munich, Germany). The participants, general practitioners, obstetricians and midwives of the patients will be aware of the results of US-EFW which will be used for clinical management.

MRI examination

MRI will be performed using a clinical 1.5 T whole-body unit with a gradient field strength of 45 mT/m. Patients will be scanned in the supine position, with a combination of a six-channel phased-array body and six elements of the spine coil positioned over the lower pelvic area. The MRI protocol consists of a 'scout' scan in order to gather information about the orientation of the fetus. Subsequently, we will perform T2-weighted imaging (WI) using fast imaging with steady-state free procession (True FISP) sequences in the fetal sagittal plane: 9-15 adjacent slices average-adjusted according to fetal size with a 4 mm slice thickness, an intersection gap of 20, a field-of-view of 380 x 309 mm^2, matrix 166 x 256, TR (repetition time)/TE (echo time) = 4.65 ms/2.33 ms, resulting voxel resolution of 1.9 x 1.5 x 4.0 mm^3 and a bandwidth of 399 Hz/pixel.

For further research, other sequences with be acquired in the following order: True FISP sequences in the fetal sagittal plane with a 4 mm slice thickness and an intersection gap of 4

mm, followed by sequences for pelvimetric measurements. Sequences degraded by fetal motion or following maternal movements will be repeated with the same parameters. For the PREMACRO study, total examination time will be kept under 5 minutes.

MRI will be performed using one of 2 MRI magnets: Siemens Magnetom Avanto with a bore diameter of 60 cm or Aera with a bore diameter of 70 cm (Erlangen, Germany).

MRI planimetric measurements and MRI-EFW:

Total FBV planimetric measurements will be performed by one of 5 trainees in the Maternal Fetal Medicine Department or the Radiology Department. Prior to the PREMACRO study, all trainees will receive extensive training in planimetric measurements by an expert (CK or MMC) with at least 100 FBV measured per trainee. All but one of the trainees performing the FBV measurements are different from those performing the US-EFW. However, for the only trainee performing both US-EFW and FBV measurements, we made sure that the trainee never evaluated the same woman using both imaging modalities. FBV will be measured on the day of MRI or on the following 2 days by the available trainee without a specific order. FBV will be measured using semi-automatic software on a picture archiving and communication system (PACS) (Impax, Agfa-Gevaert, Mortsel, Belgium) as previously described (18). This semi-automatic software was designed for volumetric measurements, but was validated by our research team in collaboration with Agfa HealthCare.

Operators performing FBV measurements will be blinded to the US-EFW results. If the total FBV cannot be measured on MRI, this will be noted. The time required to perform the FBV measurements with 4 mm slice thickness and an intersection gap of 20 mm will also be recorded. FBV measurements will be entered in the ASTRAIA database. MRI-EFW will be calculated using the equation 0.12+1.031*FBV = MRI-EFW (kg) developed by Baker *et al.* (14), where FBV is entered in liters. MRI-EFW will not be entered in the ASTRAIA database, but will be kept in a secure database by the principal investigator. Data will be transmitted to the Independent Data Monitoring Committee (IDMC) on a monthly basis.

In contrast to the US-EFW, the participants, general practitioners, obstetricians and midwives of the patients will be blinded to the results of the MRI-EFW.

A percentile for the MRI-EFW will be obtained after plotting the weight estimation on the curves as described by Yudkin *et al.* (27).

MRI-EFW will be defined as successful if all the following conditions are met:

- Patient did not feel any discomfort during the MRI or felt discomfort but the acquisition of the main sequence was successful.
- MRI acquisition of the main sequence: True FISP sequence with a 4 mm slice thickness, an intersection gap of 20 mm, could be performed.
- FBV acquisition was complete and allowed MRI planimetric measurement.

MRI-EFW will be defined as a failure if any of these conditions are met:

- Women could not be accommodated in the magnet because of a high body mass index.
- Women did not undergo MRI due to claustrophobia, discomfort resulting in interruption of the examination before the main sequence of the True FISP with a 4 mm slice thickness and an intersection gap of 20 mm could be performed.
- Women presenting with a contraindication to MRI.

- The examination could not be started or continued because of an incident with the magnet.

The characteristics of women in both groups will be detailed and compared.

Measurement of neonatal weight at birth:

We will aim to measure neonatal weight immediately after birth or within 6 hours of delivery. A percentile for the birth weight will be obtained after plotting the actual weight on the curves as described by Yudkin *et al.* (27) and this will be considered as the gold standard for the US-EFW and MRI-EFW-derived percentile at 36.0-36+6 weeks of gestation.

Data collection:

Data on study participants will be entered in an electronic case report form (CRF) in the ASTRAIA database. Data on pregnancy and neonatal outcomes will be collected from our obstetrical electronic database MOSOS (BMA B.V., Houten, The Netherlands) and hospital maternity records. If neonates are admitted to NICU, additional neonatal outcomes will be collected from the discharge summary.

OUTCOMES

Primary outcome

LGA neonate ≥ 95th centile for gestational age, based on the curves as described by Yudkin *et al.* (27).

Secondary outcomes

As defined above in the Secondary objectives section.

SIDE EFFECTS AND ADVERSE EVENT REPORTING

This study is considered a minimal risk study. However, investigators are required to report any suspected or actual Unexpected Adverse Events (UAEs) that patients have while they are participating. Subject study participation begins at the time of consent and ends when the results of the neonatal weight are received. A UAE is defined as any event that meets the following conditions:

- The event is **not** a known or reasonably foreseeable risk associated with the study procedures (includes risks related to breaches of confidential information specified in the informed consent), and
- The event, in the investigator's opinion, is or could be directly related to the subject's participation in this research protocol/protocol procedure. Please note that the only procedures in this protocol are US and MRI and measuring neonatal weight at birth. Any other care delivered as part of a subject's regular plan of care are not study-related activities.
- Clinical outcomes (e.g. adverse birth outcome, pregnancy complications) experienced by patients other than those associated with the study procedures will not be considered as UAEs.

Events that are the result of a natural progression of an underlying disease, disorder, condition, or a predisposing risk factor profile for the patient do not qualify as UAEs. UAEs should be reported to the study sponsor within 24 hours of discovery. The study site at the University Hospital Brugmann, Brussels, Belgium is responsible for complying with local IRB requirements for the reporting of UAEs.

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Procedure for reporting SAEs and SUSARs

If an adverse event is considered to be serious, it must be documented and reported to the trial coordinator, whether attributed to the treatment or not. SAEs will be reported to the IDMC and all events will be followed up until resolution.

All suspected adverse reactions that are both unexpected and serious are subject to expedited reporting. If the trial coordinator is notified of an SAE which qualifies as a suspected unexpected adverse reaction (SUSAR), then details will immediately be passed to the sponsor. The sponsor will report all SUSARs that are fatal or life-threatening to the Ethics Committee not later than 7 days after the sponsor is first made aware of the reaction.

An annual safety report for the study will be submitted to the Ethics Committee, including listings of all suspected serious adverse reactions.

STATISTICAL ANALYSIS PLAN INCLUDING SAMPLE SIZE AND POWER CALCULATION

On the basis of results of a pilot study conducted in our department before the PREMACRO study and assumptions with respect to the performance of MRI-EFW and US-EFW in the prediction of neonatal macrosomia as well as on the basis of the prevalence of neonates born in our department ≥ 95th centile (available data from 5920 deliveries between 2011 and 2016), we determined that a sample size of 90 cases of macrosomic fetuses (≥ P95) and 2250 negative controls would provide a power of 90% to determine the primary outcome of detecting a difference between the AUROC of MRI-EFW and US-EFW at significance level of 5%.

Assuming that 70% of women with singleton pregnancies who fulfill the entry criteria agree to participate in the study and provide follow-up data and also allow for loss to follow-up (~ 5%), we would need to approach about 3,500 such women to meet our primary outcome.

The first enrolment for the study was in May 2016. As of September 2018, 2004 women have been screened and recruited to the study. So far, the rate of women refusing the study at the 36-week clinic is only 8.5% rather than 30%. Yet, this is an underestimation of the proportion of women refusing the study from those that were approached during the third-trimester scan and/or the antenatal clinic when the patient information sheet was given to them. Thus, the proportion of women receiving the patient information sheet and not attending our 36-week clinic is probably even higher than 30%.

Type of analysis and statistical tests

MRI-EFW and US-EFW each produce a measured value and classify the fetus as macrosomic or not. The ROC curve is generated by computing sensitivity and specificity for each technique (US and MRI) as compared to the actual classification of a neonate being macrosomic or not at birth. The differences between the ROC curves will be calculated as the primary outcome, taking into account the paired nature of the data. AUC values will be compared with the use of

a z-test according to the method of DeLong *et al.* (28). A *p* value of less than 0.05 will be considered to indicate statistical significance.

Confidence intervals will be computed with the use of the Clopper-Pearson method. The exact binomial test (29) for paired comparisons will be used in sensitivity and specificity and will use the generalized score statistic (30) to analyze positive and negative predictive values. We will compare the sensitivity, specificity, positive and negative predictive values, and likelihood ratios of MRI-EFW and US-EFW for the detection of neonatal macrosomia for a fixed false-positive rate of 5 and 10%.

Descriptive statistics

For categorical variables, summary tabulations of the number and percentage of patients in each category (with a category for missing data) of the parameter will be presented. For continuous variables, the number of patients, mean, median, standard deviation, minimum, and maximum values or interquartile ranges will be presented. Graphical displays will be produced as appropriate.

The SPIRIT reporting guidelines were used (31).

COMMITTEE OVERSIGHTS

The IDMC is independent of the trial and is responsible for monitoring the progress of the trial, including recruitment, protocol adherence, SAEs as well as the result of the comparison between the 2 estimations to the primary outcome measure. The IDMC is the only oversight body that has access to unblinded data. The IDMC is responsible for safeguarding the interests of trial participants, monitoring the accumulating data and making recommendations to the Trial Steering Committee (TSC) on whether the trial should continue as planned.

The TSC is the independent group responsible for oversight of the trial in order to safeguard the interests of trial participants. The TSC provides advice to the chief investigator, Brugmann CTU, the funder and sponsor on all aspects of the trial through its independent chair.

ETHICS AND DISSEMINATION

The study will be conducted in accordance with the International Conference on Harmonization (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). A favorable ethical opinion was obtained from the Ethics Committee of the University Hospital Brugmann, reference number CE2016/44. Results will be published in peer-reviewed journals and disseminated at international conferences.

DISCUSSION

Macrosomia is a risk factor for unfavorable delivery outcomes, including operative vaginal or cesarean delivery and shoulder dystocia (1,32). Shoulder dystocia can cause neonatal morbidity, including fracture of the clavicle, brachial plexus injury, or asphyxia and maternal complications such as vaginal tears and postpartum haemorrhage. The traditional approach to screening for macrosomia is based on clinical measurement of fundal height or US-EFW using the Hadlock formula, but such an approach identifies only 73% of LGA neonates > 95th centile, for a fixed 10% false-positive rate (33).

Findings from a decision analysis suggested that the number of elective cesarean sections needed to avoid one permanent brachial plexus injury is quite high (12). This strategy is thus

recommended only when fetal weight is estimated to exceed 4500 g for women with diabetes and 5000 g for those without diabetes (34). Another approach would be to induce labor between 37^0 and 38^6 weeks, which effectively arrests the problem of continued fetal overgrowth, thereby reducing the associated risks of fetal and maternal morbidity (8). Induction of labor for suspected LGA fetuses above the 95^{th} percentile was shown to be associated with a reduced risk of shoulder dystocia and associated morbidity compared with expectant management (8,9). However, these benefits should be balanced against the effects of early-term induction of labor, including neonatal respiratory morbidity (8) therefore this proposed strategy remains the subject of much ongoing debate .

The problem is that any strategy to detect macrosomic fetuses is limited by the imprecision of the methods for estimation of fetal weight (35). Fundal height is imprecise, subject to measurement errors, and dependent on the thickness of the maternal abdominal wall and the amount of amniotic fluid (36). Ultrasound is also imprecise in estimation of fetal weight, especially for LGA fetuses (37).

There is evidence that MRI-EFW is more precise than US-EFW. So far, published data comparing the two techniques have been collected from a limited number of cases, mainly by comparing their ability to predict absolute weight estimation, rather than LGA neonates. Also, the data are retrospective, the evaluation has been done within hours of delivery rather than remote from delivery, and in most cases a time-consuming method has been used for planimetric FBV measurement. The present study is a large prospective study, using a simplified method for planimetric FBV evaluation, designed to streamline the process, thus making it more practical in the clinical setting. Furthermore, the study was also designed to evaluate women several weeks prior to the expected date of confinement, which would give more time to make further evaluations if necessary and implement clinical decisions, should this method be adopted into routine clinical practice in the future.

This study will assess whether MRI-EFW is more accurate than US-EFW in prediction of LGA and small-for-gestational-age neonates, and if our hypothesis is correct, by how much is the performance improved. The latter will determine if the introduction of MRI for the prediction of macrosomia or small-for-gestational-age neonates is cost-effective and may form the basis for the design of future interventional studies based on a more accurate method of fetal weight estimation. The results of the study could also be used to develop new recommendations for elective cesarean section, in cases of suspected macrosomia in both diabetic and non-diabetic pregnancies.

Author Contributions: CK, AC and JCJ conceived and designed the study, drafted the original grant proposal and trial protocol. JCJ provided methodological and statistical expertise. CK provide expertise in the pregnancy clinical outcomes. CK and JCJ drafted the original protocol and the manuscript. All authors have responsibilities for day-to-day running of the trial including participant recruitment and data collection. All authors critically reviewed and approved the final version of the manuscript.

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Disclaimer: The views expressed in this publication are those of the authors and not necessarily those of the FMFB, Brugmann Foundation, healthcare systems or competent authorities.

Competing interests: None declared.

Acknowledgements: None.

Ethical approval: This study will be conducted in accordance with the principles of Good Clinical Practice. This protocol was submitted to the University Hospital Brugmann Research Ethics Committee, in Brussels, Belgium and a favorable opinion was granted. The reference number is CE2016/44.

Provenance and peer review: Not commissioned; externally peer-reviewed.

Data statement section: Technical appendix, statistical code, and dataset available from the Dryad repository, DOI: [will be available soon].

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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:

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		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	13
Protocol version	#3	Date and version identifier	2
		Initially V.2.0, date 26-Feb-2016 followed by V.2.1, date 19-May 2016, which is the last version where we asked a minor amendment adding among the secondary outcomes prediction by ultrasound and MRI of the neonates above the 97th centile for gestational age.	
Funding	#4	Sources and types of financial, material, and other support	13
		Support was mainly for financing the MRI examinations.	

Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 13
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	10
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	11
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4,5
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained.	6

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7,8
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	11
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	N/A
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
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	5,9
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)	7
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	10
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	10
Allocation: sequence	#16a	Method of generating the allocation sequence (eg,	N/A

generation		computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7,8
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial No unblinding for MRI results are permissible, or needed.	8
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	9
Data collection plan: retention	#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	9
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	8

		found, if not in the protocol	
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	10,11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10,11
Statistics: analysis population and missing data	#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)	N/A
Data monitoring: formal committee	#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 found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9,10
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor The Trial Steering Committee meets every 6 months.	
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	2
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7

Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers All authors should have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.	
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code The full protocol will be published with article on Journal site	
Informed consent	#32	Model consent form and other related documentation given	

materials		to participants and authorised surrogates Given in annexes	
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

BMJ Open

Protocol for the prospective observational clinical study: Estimation of fetal weight by MR imaging to PREdict neonatal MACROsomia (PREMACRO study) and small-for-gestational age neonates

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Protocol for the prospective observational clinical study: Estimation of fetal weight by MR imaging to PREdict neonatal MACROsomia (PREMACRO study) and small-for-gestational age neonates.

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Abstract

Introduction: Macrosomia refers to growth beyond a specific threshold, regardless of gestational age. These fetuses are also frequently referred to as large for gestational age (LGA). Various cut-offs have been used but for research purposes, a cut-off above the 95th centile for birth weight is often preferred because it defines 90% of the population as normal weight. The use of centiles, rather than estimated weights, also accommodates preterm macrosomic infants, although most of the complications, maternal and fetal, arise during the delivery of large babies at term. This means that accurate identification of LGA fetuses (≥ 95th centile) may play an important role in guiding obstetric interventions, such as induction of labor or cesarean section. Traditionally, identification of fetuses suspected of macrosomia, has been based on biometric measurements using 2D ultrasound (US), yet this method is rather sub-optimal. We present a protocol (V.2.1, date 19-May 2016) for the estimation of fetal weight (EFW) by magnetic resonance imaging (MRI) to PREdict neonatal MACROsomia (PREMACRO study), which is a prospective observational clinical study designed to determine whether MRI at 36+0 to 36+6 weeks of gestation, as compared to 2D US, can improve the identification of LGA neonates ≥ 95th centile.

Methods and analysis: All eligible women attending the 36-week clinic will be invited to participate in the screening study for LGA fetuses ≥ 95th centile and will undergo US-EFW and MRI-EFW within minutes of each other. From these estimations, a centile will be derived which will be compared to the centile of birth weight used as the gold standard. Besides birth weight, other pregnancy and neonatal outcomes will be collected and analyzed. The first enrolment for the study was in May 2016. As of September 2018, 2004 women have been screened and recruited to the study. The study is due to end in April 2019. The study is registered on ClinicalTrials.gov.

Ethics and dissemination: The study will be conducted in accordance with the International Conference on Harmonization for Good Clinical Practice and the appropriate regulatory requirement(s). A favorable ethical opinion was obtained from the Ethics Committee of the University Hospital Brugmann, reference number CE2016/44. Results will be published in peer-reviewed journals and disseminated at international conferences.

Registration number: NCT02713568.

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Article Summary

Strengths and limitations of this study:

This is the first prospective head-to-head comparison of US-EFW and MRI-EFW at 36 weeks of gestation in a large cohort to evaluate whether MRI can improve detection of large-for-gestational age neonates ≥ 95th centile.

Both US and MRI for EFW are performed within minutes of each other at 36+0 to 36+6 weeks of gestation.

This is a prospective clinical study and in contrast to the US-EFW, MRI-EFW will not be communicated to patients or to patients' caregivers.

This is a single-center study and the extrapolation of our findings to other perinatal centers needs further evaluation.

BACKGROUND

Macrosomia and growth restriction are important causes of perinatal morbidity (1-3), at or near to term. However, clear identification of 'at-risk' fetuses is difficult and clinical estimates of fetal weight are poor (4,5).

Ultrasound (US) is used as a second-line when an abnormality of growth is suspected, but the accuracy of this imaging modality in the mid- to late third trimester is also limited (6).

Estimated fetal weight (EFW) is an important part of the clinical assessment and is used to guide obstetric interventions, when a fetus is small or large for gestational age. When a diagnosis of intrauterine growth restriction (IUGR) is made, the decision-making process is complex, particularly at very early gestation and involves multiple factors, including maternal status, cardiotocography, liquor volume and Doppler imaging (7). While a large body of research is now available to assist with the management of both early and late-onset IUGR, once macrosomia has been diagnosed there is a paucity of evidence to guide clinical practice. In the management of fetuses suspected with macrosomia, EFW is frequently the single most important component guiding interventions, such as induction of labor or cesarean section (8).

Fetal macrosomia is associated with a higher incidence of perinatal morbidity, including shoulder dystocia and brachial plexus injury in the fetus and anal sphincter tears, uterine atony and hemorrhage in the mother (1). A recent multicenter randomized controlled trial appears to confirm the advantages of a policy of induction of labor for suspected macrosomia, demonstrating a clear reduction in the rates of shoulder dystocia and composite perinatal morbidity (8). A meta-analyses and systematic review, including this publication, supports the validity of this option (9). However, some earlier but lower quality, observational studies have questioned the benefit of EFW by ultrasonography in the last trimester, for suspected macrosomia, demonstrating that this practice can increase the risk of cesarean and instrumental delivery, without reducing perinatal morbidity.

Despite these conflicting data and a lack of evidence to support routine third-trimester ultrasound (10), the absence of specific guidance, coupled with concerns regarding perinatal outcomes, obstetricians still request an ultrasound scan at around 34-36 weeks of gestation to identify fetuses above the 90th or below the 10th centile. This practice will inevitably lead to increased and potentially harmful interventions based on relatively inaccurate data (11).

Due to the imprecision of ultrasound-derived EFW, particularly in cases of suspected macrosomia in the third trimester (12, 13), we believe that these estimates should not be used to make important obstetric decisions regarding mode and timing of delivery. A more accurate method of EFW could produce better *outcomes* by restricting interventions such as induction of labor and cesarean section to those fetuses at greatest risk of suspected macrosomia. Some publications have already demonstrated that magnetic resonance imaging (MRI)-derived EFW close to delivery is more accurate than ultrasound, with a precision superior to that of ultrasound using birth weight as a golden standard (14-23), and a recent meta-analysis has confirmed this promising accuracy (24).

HYPOTHESIS

We hypothesize that MRI-EFW at 36+0-36+6 weeks of gestation is significantly more accurate than US-EFW in prediction of large-for-gestational-age (LGA) neonates (≥ 95th centile for gestational age), using birth weight as a golden standard.

AIM

To evaluate the accuracy of MRI-EFW at 36+0-36+6 weeks of gestation in comparison to US-EFW in prediction of LGA neonates.

OBJECTIVES

Primary objective

To compare MRI-EFW with US-EFW using the Hadlock formula (25,26), by comparing the Area Under the Receiver Operating Curve (AUROC) for the prediction of LGA neonates (≥ 95th centile for gestational age), using the normal ranges as described by Yudkin *et al.* (27).

Secondary objectives

To compare MRI-EFW with US-EFW by comparing AUROC for the prediction of LGA neonates:

- ≥ 90th centile for gestational age.
- ≥ 97th centile for gestational age.
- ≥ 99th centile for gestational age.

To compare MRI-EFW with US measurement of abdominal circumference for the prediction of LGA neonates (≥ 90th and ≥ 95th centile for gestational age).

To compare MRI-EFW with US-EFW by comparing AUROC for the prediction of small-for-gestational age neonates:

- ≤ 10th centile for gestational age.
- ≤ 5th centile for gestational age.
- ≤ 3rd centile for gestational age.

To determine the ability of MRI-EFW versus US-EFW to predict significant shoulder dystocia, fracture of the clavicle or a long bone, brachial plexus injury, intracranial hemorrhage, or death.

To determine the ability of MRI-EFW versus US-EFW to predict neonatal morbidity, defined as arterial cord blood pH less than 7.10, Apgar score at 5 min less than 7, and admission to the neonatal intensive care unit (NICU).

To determine the ability of MRI-EFW versus US-EFW to predict maternal morbidity, defined as cesarean section, operative vaginal delivery (vacuum or forceps), postpartum hemorrhage (1000 mL or more), blood transfusion, and anal sphincter tear.

CENTERS

This is a single-center study conducted at the Department of Obstetrics and Gynecology and Radiology of the University Hospital Brugmann, Université Libre de Bruxelles in Brussels, Belgium.

DESIGN

This is a prospective observational clinical head-to-head comparison study of MR-EFW versus US-EFW for the prediction of LGA neonates. Randomization was not appropriate since all patients undergo both examinations.

INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria

Age ≥ 18 years;

Singleton pregnancy;

Live fetus at 36+0-36+6 weeks of gestation;

Subject is planning a delivery at our maternity at the University Hospital Brugmann, in Brussels, Belgium;

French- or Dutch-speaking (otherwise interpreters will be used);

Informed and written consent.

Exclusion Criteria

Multiple pregnancy;

Pregnancies complicated by major fetal abnormality identified at the 11-13, 20-22 or 30-35 week routine scans;

Women presenting with an imprecise pregnancy dating due to absence of first-trimester scan;

Women presenting at a gestational age < 36 or ≥ 37 weeks of gestation;

Subject is known to have a contraindication to MRI, such as:

- Carrying a pacemaker or a metallic cardiac valve.
- Having metallic material inside the head.
- Having metallic fragments inside the eye following an accident.
- Having any type of implant including ear implant.
- Having a hip prosthesis.

Women presenting with painful regular uterine contractions or history of premature ruptured membranes;

Women who are unconscious, severely ill, those with learning difficulties, or mentally handicapped;

Women presenting for the study but who have been previously included in the study in a previous pregnancy;

Women who deliver before MRI and US evaluation;

If the neonate's weight is not measured within 6 hours after birth for any reason, including the need for emergency care immediately after delivery;

Pregnancies ending with a stillborn;

Women who deliver outside our network of hospitals in Brussels where a full pediatric report is not available and where there is uncertainty whether the neonate's weight is measured within 6 hours after birth.

METHODS

We will recruit women attending their routine third-trimester scan in pregnancy at 30-35 weeks of gestation as well as women attending our antenatal clinic after 30 weeks of gestation at the university hospital Brugmann, in Brussels, Belgium. The patient information sheet concerning the PREMACRO study will be given to them and they will be invited to attend the 36-week clinic.

If women attend the 36-week clinic, detailed counseling about the study is provided and women who agree to participate, after obtaining a written informed consent, will undergo 15 minutes apart a US scan for fetal biometric measurement and MRI for fetal body volume (FBV) measurement. There is no prespecified order for these examinations, which are performed according to which machine is available first. For the purpose of the study, 2 ultrasound machines have been installed in the Radiology Department on the same floor as the MRI machine.

US examination and US-EFW:

Prenatal US examinations will be carried out using transabdominal sonography by one of 4 experienced consultants in Maternal Fetal Medicine Department. US-EFW will be obtained between 36.0-36+6 weeks of gestation, according to Hadlock *et al.* (25,26), based on measurements of biparietal diameter, head circumference, abdominal circumference and femoral length. Two Voluson E8 machines will be used for the purpose of the study (GE Medical Systems, Zipf, Austria). A percentile for the US-EFW will be obtained after plotting the weight estimation on the curves as described by Yudkin *et al.* (27). All data will be entered in ASTRAIA software gmbh (Munich, Germany). The participants, general practitioners, obstetricians and midwives of the patients will be aware of the results of US-EFW which will be used for clinical management.

MRI examination

MRI will be performed using a clinical 1.5 T whole-body unit with a gradient field strength of 45 mT/m. Patients will be scanned in the supine position, with a combination of a six-channel phased-array body and six elements of the spine coil positioned over the lower pelvic area. The MRI protocol consists of a 'scout' scan in order to gather information about the orientation of the fetus. Subsequently, we will perform T2-weighted imaging (WI) using fast imaging with steady-state free procession (True FISP) sequences in the fetal sagittal plane: 9-15 adjacent slices average-adjusted according to fetal size with a 4 mm slice thickness, an intersection gap of 20, a field-of-view of 380 x 309 mm^2, matrix 166 x 256, TR (repetition time)/TE (echo time) = 4.65 ms/2.33 ms, resulting voxel resolution of 1.9 x 1.5 x 4.0 mm^3 and a bandwidth of 399 Hz/pixel.

For further research, other sequences with be acquired in the following order: True FISP sequences in the fetal sagittal plane with a 4 mm slice thickness and an intersection gap of 4

mm, followed by sequences for pelvimetric measurements. Sequences degraded by fetal motion or following maternal movements will be repeated with the same parameters. For the PREMACRO study, total examination time will be kept under 5 minutes.

MRI will be performed using one of 2 MRI magnets: Siemens Magnetom Avanto with a bore diameter of 60 cm or Aera with a bore diameter of 70 cm (Erlangen, Germany).

MRI planimetric measurements and MRI-EFW:

Total FBV planimetric measurements will be performed by one of 5 trainees in the Maternal Fetal Medicine Department or the Radiology Department. Prior to the PREMACRO study, all trainees will receive extensive training in planimetric measurements by an expert (CK or MMC) with at least 100 FBV measured per trainee. All but one of the trainees performing the FBV measurements are different from those performing the US-EFW. However, for the only trainee performing both US-EFW and FBV measurements, we made sure that the trainee never evaluated the same woman using both imaging modalities. FBV will be measured on the day of MRI or on the following 2 days by the available trainee without a specific order. FBV will be measured using semi-automatic software on a picture archiving and communication system (PACS) (Impax, Agfa-Gevaert, Mortsel, Belgium) as previously described (18). This semi-automatic software was designed for volumetric measurements, but was validated by our research team in collaboration with Agfa HealthCare.

Operators performing FBV measurements will be blinded to the US-EFW results. If the total FBV cannot be measured on MRI, this will be noted. The time required to perform the FBV measurements with 4 mm slice thickness and an intersection gap of 20 mm will also be recorded. FBV measurements will be entered in the ASTRAIA database. MRI-EFW will be calculated using the equation 0.12+1.031*FBV = MRI-EFW (kg) developed by Baker *et al.* (14), where FBV is entered in liters. MRI-EFW will not be entered in the ASTRAIA database, but will be kept in a secure database by the principal investigator. Data will be transmitted to the Independent Data Monitoring Committee (IDMC) on a monthly basis.

In contrast to the US-EFW, the participants, general practitioners, obstetricians and midwives of the patients will be blinded to the results of the MRI-EFW.

A percentile for the MRI-EFW will be obtained after plotting the weight estimation on the curves as described by Yudkin *et al.* (27).

MRI-EFW will be defined as successful if all the following conditions are met:

- Patient did not feel any discomfort during the MRI or felt discomfort but the acquisition of the main sequence was successful.
- MRI acquisition of the main sequence: True FISP sequence with a 4 mm slice thickness, an intersection gap of 20 mm, could be performed.
- FBV acquisition was complete and allowed MRI planimetric measurement.

MRI-EFW will be defined as a failure if any of these conditions are met:

- Women could not be accommodated in the magnet because of a high body mass index.
- Women did not undergo MRI due to claustrophobia, discomfort resulting in interruption of the examination before the main sequence of the True FISP with a 4 mm slice thickness and an intersection gap of 20 mm could be performed.
- Women presenting with a contraindication to MRI.

- The examination could not be started or continued because of an incident with the magnet.

The characteristics of women in both groups will be detailed and compared.

Measurement of neonatal weight at birth:

We will aim to measure neonatal weight immediately after birth or within 6 hours of delivery. A percentile for the birth weight will be obtained after plotting the actual weight on the curves as described by Yudkin *et al.* (27) and this will be considered as the gold standard for the US-EFW and MRI-EFW-derived percentile at 36.0-36+6 weeks of gestation.

Data collection:

Data on study participants will be entered in an electronic case report form (CRF) in the ASTRAIA database. Data on pregnancy and neonatal outcomes will be collected from our obstetrical electronic database MOSOS (BMA B.V., Houten, The Netherlands) and hospital maternity records. If neonates are admitted to NICU, additional neonatal outcomes will be collected from the discharge summary.

Patient and Public Involvement:

Patients and or public were not involved in the design, recruitment or conduct of the study. However, while all study participants were informed that MREFW will not be disclosed to them or their health care providers before delivery and during the study period, study participants were informed that after completion of the study and publication of the data, they were free to contact us and we would inform them about their MRI-EFW.

OUTCOMES

Primary outcome

LGA neonate ≥ 95th centile for gestational age, based on the curves as described by Yudkin *et al.* (27).

Secondary outcomes

As defined above in the Secondary objectives section.

SIDE EFFECTS AND ADVERSE EVENT REPORTING

This study is considered a minimal risk study. However, investigators are required to report any suspected or actual Unexpected Adverse Events (UAEs) that patients have while they are participating. Subject study participation begins at the time of consent and ends when the results of the neonatal weight are received. A UAE is defined as any event that meets the following conditions:

- The event is **not** a known or reasonably foreseeable risk associated with the study procedures (includes risks related to breaches of confidential information specified in the informed consent), and

- The event, in the investigator's opinion, is or could be directly related to the subject's participation in this research protocol/protocol procedure. Please note that the only procedures in this protocol are US and MRI and measuring neonatal weight at birth. Any other care delivered as part of a subject's regular plan of care are not study-related activities.
- Clinical outcomes (e.g. adverse birth outcome, pregnancy complications) experienced by patients other than those associated with the study procedures will not be considered as UAEs.

Events that are the result of a natural progression of an underlying disease, disorder, condition, or a predisposing risk factor profile for the patient do not qualify as UAEs. UAEs should be reported to the study sponsor within 24 hours of discovery. The study site at the University Hospital Brugmann, Brussels, Belgium is responsible for complying with local IRB requirements for the reporting of UAEs.

UAE Sponsor Contact: Tatiana Besse-Hammer, MD
Physician Clinical Study Coordinator at UH Brugmann.
Tatiana.besse-hammer@chu-brugmann.be
Office: +32 2 477 33.10.

Procedure for reporting SAEs and SUSARs

If an adverse event is considered to be serious, it must be documented and reported to the trial coordinator, whether attributed to the treatment or not. SAEs will be reported to the IDMC and all events will be followed up until resolution.

All suspected adverse reactions that are both unexpected and serious are subject to expedited reporting. If the trial coordinator is notified of an SAE which qualifies as a suspected unexpected adverse reaction (SUSAR), then details will immediately be passed to the sponsor. The sponsor will report all SUSARs that are fatal or life-threatening to the Ethics Committee not later than 7 days after the sponsor is first made aware of the reaction.

An annual safety report for the study will be submitted to the Ethics Committee, including listings of all suspected serious adverse reactions.

STATISTICAL ANALYSIS PLAN INCLUDING SAMPLE SIZE AND POWER CALCULATION

On the basis of results of a pilot study conducted in our department before the PREMACRO study and assumptions with respect to the performance of MRI-EFW (AUROC 0.981) and US-EFW (AUROC 0.921) in the prediction of neonatal macrosomia as well as on the basis of the prevalence of neonates born in our department ≥ 95th centile (available data from 5920 deliveries between 2011 and 2016), we determined that a sample size of 90 cases of macrosomic fetuses (≥ P95) and 2250 negative controls would provide a power of 90% to determine the primary outcome of detecting a difference between the AUROC of MRI-EFW and US-EFW (of 0.06) at significance level of 5%.

Assuming that 70% of women with singleton pregnancies who fulfill the entry criteria agree to participate in the study and provide follow-up data and also allow for loss to follow-up (~ 5%), we would need to approach about 3,500 such women to meet our primary outcome.

The first enrolment for the study was in May 2016. As of September 2018, 2004 women have been screened and recruited to the study. So far, the rate of women refusing the study at the 36-week clinic is only 8.5% rather than 30%. Yet, this is an underestimation of the proportion of women refusing the study from those that were approached during the third-trimester scan and/or

the antenatal clinic when the patient information sheet was given to them. Thus, the proportion of women receiving the patient information sheet and not attending our 36-week clinic is probably even higher than 30%.

Type of analysis and statistical tests

MRI-EFW and US-EFW each produce a measured value and classify the fetus as macrosomic or not. The ROC curve is generated by computing sensitivity and specificity for each technique (US and MRI) as compared to the actual classification of a neonate being macrosomic or not at birth. The differences between the ROC curves will be calculated as the primary outcome, taking into account the paired nature of the data. AUC values will be compared with the use of a z-test according to the method of DeLong *et al.* (28). A *p* value of less than 0.05 will be considered to indicate statistical significance.

Confidence intervals will be computed with the use of the Clopper-Pearson method. The exact binomial test (29) for paired comparisons will be used in sensitivity and specificity and will use the generalized score statistic (30) to analyze positive and negative predictive values. We will compare the sensitivity, specificity, positive and negative predictive values, and likelihood ratios of MRI-EFW and US-EFW for the detection of neonatal macrosomia for a fixed false-positive rate of 5 and 10%.

Descriptive statistics

For categorical variables, summary tabulations of the number and percentage of patients in each category (with a category for missing data) of the parameter will be presented. For continuous variables, the number of patients, mean, median, standard deviation, minimum, and maximum values or interquartile ranges will be presented. Graphical displays will be produced as appropriate.

The SPIRIT reporting guidelines were used (31).

COMMITTEE OVERSIGHTS

The IDMC is independent of the trial and is responsible for monitoring the progress of the trial, including recruitment, protocol adherence, SAEs as well as the result of the comparison between the 2 estimations to the primary outcome measure. The IDMC is the only oversight body that has access to unblinded data. The IDMC is responsible for safeguarding the interests of trial participants, monitoring the accumulating data and making recommendations to the Trial Steering Committee (TSC) on whether the trial should continue as planned.

The TSC is the independent group responsible for oversight of the trial in order to safeguard the interests of trial participants. The TSC provides advice to the chief investigator, Brugmann CTU, the funder and sponsor on all aspects of the trial through its independent chair.

ETHICS AND DISSEMINATION

The study will be conducted in accordance with the International Conference on Harmonization (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). A favorable ethical opinion was obtained from the Ethics Committee of the University Hospital Brugmann, reference number CE2016/44. Results will be published in peer-reviewed journals and disseminated at international conferences.

DISCUSSION

Macrosomia is a risk factor for unfavorable delivery outcomes, including operative vaginal or cesarean delivery and shoulder dystocia (1,32). Shoulder dystocia can cause neonatal morbidity, including fracture of the clavicle, brachial plexus injury, or asphyxia and maternal complications such as vaginal tears and postpartum haemorrhage. The traditional approach to screening for macrosomia is based on clinical measurement of fundal height or US-EFW using the Hadlock formula, but such an approach identifies only 73% of LGA neonates > 95th centile, for a fixed 10% false-positive rate (33).

Findings from a decision analysis suggested that the number of elective cesarean sections needed to avoid one permanent brachial plexus injury is quite high (12). This strategy is thus recommended only when fetal weight is estimated to exceed 4500 g for women with diabetes and 5000 g for those without diabetes (34). Another approach would be to induce labor between 37^{0} and 38^{6} weeks, which effectively arrests the problem of continued fetal overgrowth, thereby reducing the associated risks of fetal and maternal morbidity (8). Induction of labor for suspected LGA fetuses above the 95th percentile was shown to be associated with a reduced risk of shoulder dystocia and associated morbidity compared with expectant management (8,9). However, these benefits should be balanced against the effects of early-term induction of labor, including neonatal respiratory morbidity (8) therefore this proposed strategy remains the subject of much ongoing debate .

The problem is that any strategy to detect macrosomic fetuses is limited by the imprecision of the methods for estimation of fetal weight (35). Fundal height is imprecise, subject to measurement errors, and dependent on the thickness of the maternal abdominal wall and the amount of amniotic fluid (36). Ultrasound is also imprecise in estimation of fetal weight, especially for LGA fetuses (37).

There is evidence that MRI-EFW is more precise than US-EFW. So far, published data comparing the two techniques have been collected from a limited number of cases, mainly by comparing their ability to predict absolute weight estimation, rather than LGA neonates. Also, the data are retrospective, the evaluation has been done within hours of delivery rather than remote from delivery, and in most cases a time-consuming method has been used for planimetric FBV measurement. The present study is a large prospective study, using a simplified method for planimetric FBV evaluation, designed to streamline the process, thus making it more practical in the clinical setting. Furthermore, the study was also designed to evaluate women several weeks prior to the expected date of confinement, which would give more time to make further evaluations if necessary and implement clinical decisions, should this method be adopted into routine clinical practice in the future.

This study will assess whether MRI-EFW is more accurate than US-EFW in prediction of LGA and small-for-gestational-age neonates, and if our hypothesis is correct, by how much is the performance improved. The latter will determine if the introduction of MRI for the prediction of macrosomia or small-for-gestational-age neonates is cost-effective and may form the basis for the design of future interventional studies based on a more accurate method of fetal weight estimation. The results of the study could also be used to develop new recommendations for elective cesarean section, in cases of suspected macrosomia in both diabetic and non-diabetic pregnancies.

Author Contributions: CK, MMC, AC and JCJ conceived and designed the study, drafted the original grant proposal and trial protocol. JCJ provided methodological and statistical expertise. CK provide expertise in the pregnancy clinical outcomes. CK and JCJ drafted the original protocol and the manuscript. All authors have responsibilities for day-to-day running of the trial including participant recruitment and data collection. All authors critically reviewed and approved the final version of the manuscript.

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Disclaimer: The views expressed in this publication are those of the authors and not necessarily those of the FMFB, Brugmann Foundation, healthcare systems or competent authorities.

Competing interests: None declared.

Acknowledgements: None.

Ethical approval: This study will be conducted in accordance with the principles of Good Clinical Practice. This protocol was submitted to the University Hospital Brugmann Research Ethics Committee, in Brussels, Belgium and a favorable opinion was granted. The reference number is CE2016/44.

Provenance and peer review: Not commissioned; externally peer-reviewed.

Data statement section: Technical appendix, statistical code, and dataset available from the Dryad repository, DOI: [will be available soon].

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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	13
Protocol version	#3	Date and version identifier	2
		Initially V.2.0, date 26-Feb-2016 followed by V.2.1, date 19-May 2016, which is the last version where we asked a minor amendment adding among the secondary outcomes prediction by ultrasound and MRI of the neonates above the 97th centile for gestational age.	
Funding	#4	Sources and types of financial, material, and other support	13
		Support was mainly for financing the MRI examinations.	

Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 13
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	10
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	11
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4,5
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained.	6

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7,8
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	11
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	N/A
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
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	5,9
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)	7
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	10
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	10
Allocation: sequence	#16a	Method of generating the allocation sequence (eg,	N/A

generation		computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7,8
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial No unblinding for MRI results are permissible, or needed.	8
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	9
Data collection plan: retention	#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	9
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	8

		found, if not in the protocol	
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	10,11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10,11
Statistics: analysis population and missing data	#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)	N/A
Data monitoring: formal committee	#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 found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9,10
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor The Trial Steering Committee meets every 6 months.	
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	2
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7

Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers All authors should have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.	
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code The full protocol will be published with article on Journal site	
Informed consent	#32	Model consent form and other related documentation given	

materials		to participants and authorised surrogates Given in annexes	
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

BMJ Open

Protocol for the prospective observational clinical study: Estimation of fetal weight by MR imaging to PREdict neonatal MACROsomia (PREMACRO study) and small-for-gestational age neonates

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Protocol for the prospective observational clinical study: Estimation of fetal weight by MR imaging to PREdict neonatal MACROsomia (PREMACRO study) and small-for-gestational age neonates.

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Abstract

Introduction: Macrosomia refers to growth beyond a specific threshold, regardless of gestational age. These fetuses are also frequently referred to as large for gestational age (LGA). Various cut-offs have been used but for research purposes, a cut-off above the 95th centile for birth weight is often preferred because it defines 90% of the population as normal weight. The use of centiles, rather than estimated weights, also accommodates preterm macrosomic infants, although most of the complications, maternal and fetal, arise during the delivery of large babies at term. This means that accurate identification of LGA fetuses (≥ 95th centile) may play an important role in guiding obstetric interventions, such as induction of labor or cesarean section. Traditionally, identification of fetuses suspected of macrosomia, has been based on biometric measurements using 2D ultrasound (US), yet this method is rather sub-optimal. We present a protocol (V.2.1, date 19-May 2016) for the estimation of fetal weight (EFW) by magnetic resonance imaging (MRI) to PREdict neonatal MACROsomia (PREMACRO study), which is a prospective observational clinical study designed to determine whether MRI at 36+0 to 36+6 weeks of gestation, as compared to 2D US, can improve the identification of LGA neonates ≥ 95th centile.

Methods and analysis: All eligible women attending the 36-week clinic will be invited to participate in the screening study for LGA fetuses ≥ 95th centile and will undergo US-EFW and MRI-EFW within minutes of each other. From these estimations, a centile will be derived which will be compared to the centile of birth weight used as the gold standard. Besides birth weight, other pregnancy and neonatal outcomes will be collected and analyzed. The first enrolment for the study was in May 2016. As of September 2018, 2004 women have been screened and recruited to the study. The study is due to end in April 2019. The study is registered on ClinicalTrials.gov.

Ethics and dissemination: The study will be conducted in accordance with the International Conference on Harmonization for Good Clinical Practice and the appropriate regulatory requirement(s). A favorable ethical opinion was obtained from the Ethics Committee of the University Hospital Brugmann, reference number CE2016/44. Results will be published in peer-reviewed journals and disseminated at international conferences.

Registration number: NCT02713568.

Word count: 361.

Article Summary

Strengths and limitations of this study:

This is the first prospective head-to-head comparison of US-EFW and MRI-EFW at 36 weeks of gestation in a large cohort to evaluate whether MRI can improve detection of large-for-gestational age neonates ≥ 95th centile.

Both US and MRI for EFW are performed within minutes of each other at 36+0 to 36+6 weeks of gestation.

This is a prospective clinical study and in contrast to the US-EFW, MRI-EFW will not be communicated to patients or to patients' caregivers.

This is a single-center study and the extrapolation of our findings to other perinatal centers needs further evaluation.

BACKGROUND

Macrosomia and growth restriction are important causes of perinatal morbidity (1-3), at or near to term. However, clear identification of 'at-risk' fetuses is difficult and clinical estimates of fetal weight are poor (4,5).

Ultrasound (US) is used as a second-line when an abnormality of growth is suspected, but the accuracy of this imaging modality in the mid- to late third trimester is also limited (6).

Estimated fetal weight (EFW) is an important part of the clinical assessment and is used to guide obstetric interventions, when a fetus is small or large for gestational age. When a diagnosis of intrauterine growth restriction (IUGR) is made, the decision-making process is complex, particularly at very early gestation and involves multiple factors, including maternal status, cardiotocography, liquor volume and Doppler imaging (7). While a large body of research is now available to assist with the management of both early and late-onset IUGR, once macrosomia has been diagnosed there is a paucity of evidence to guide clinical practice. In the management of fetuses suspected with macrosomia, EFW is frequently the single most important component guiding interventions, such as induction of labor or cesarean section (8).

Fetal macrosomia is associated with a higher incidence of perinatal morbidity, including shoulder dystocia and brachial plexus injury in the fetus and anal sphincter tears, uterine atony and hemorrhage in the mother (1). A recent multicenter randomized controlled trial appears to confirm the advantages of a policy of induction of labor for suspected macrosomia, demonstrating a clear reduction in the rates of shoulder dystocia and composite perinatal morbidity (8). A meta-analyses and systematic review, including this publication, supports the validity of this option (9). However, some earlier but lower quality, observational studies have questioned the benefit of EFW by ultrasonography in the last trimester, for suspected macrosomia, demonstrating that this practice can increase the risk of cesarean and instrumental delivery, without reducing perinatal morbidity.

Despite these conflicting data and a lack of evidence to support routine third-trimester ultrasound (10), the absence of specific guidance, coupled with concerns regarding perinatal outcomes, obstetricians still request an ultrasound scan at around 34-36 weeks of gestation to identify fetuses above the 90th or below the 10th centile. This practice will inevitably lead to increased and potentially harmful interventions based on relatively inaccurate data (11).

Due to the inaccuracy of ultrasound-derived EFW, particularly in cases of suspected macrosomia in the third trimester (12, 13), we believe that these estimates should not be used to make important obstetric decisions regarding mode and timing of delivery. A more accurate method of EFW could produce better *outcomes* by restricting interventions such as induction of labor and cesarean section to those fetuses at greatest risk of suspected macrosomia. Some publications have already demonstrated that magnetic resonance imaging (MRI)-derived EFW close to delivery is more accurate than ultrasound, with a precision superior to that of ultrasound using birth weight as a golden standard (14-23), and a recent meta-analysis has confirmed this promising accuracy (24).

HYPOTHESIS

We hypothesize that MRI-EFW at 36+0-36+6 weeks of gestation is significantly more accurate than US-EFW in prediction of large-for-gestational-age (LGA) neonates (≥ 95th centile for gestational age), using birth weight as a golden standard.

AIM

To evaluate the accuracy of MRI-EFW at 36+0-36+6 weeks of gestation in comparison to US-EFW in prediction of LGA neonates.

OBJECTIVES

Primary objective

To compare MRI-EFW with US-EFW using the Hadlock formula (25,26), by comparing the Area Under the Receiver Operating Curve (AUROC) for the prediction of LGA neonates (≥ 95th centile for gestational age), using the normal ranges as described by Yudkin *et al.* (27).

Secondary objectives

To compare MRI-EFW with US-EFW by comparing AUROC for the prediction of LGA neonates:

- ≥ 90th centile for gestational age.
- ≥ 97th centile for gestational age.
- ≥ 99th centile for gestational age.

To compare MRI-EFW with US measurement of abdominal circumference for the prediction of LGA neonates (≥ 90th and ≥ 95th centile for gestational age).

To compare MRI-EFW with US-EFW by comparing AUROC for the prediction of small-for-gestational age neonates:

- ≤ 10th centile for gestational age.
- ≤ 5th centile for gestational age.
- ≤ 3rd centile for gestational age.

To determine the ability of MRI-EFW versus US-EFW to predict significant shoulder dystocia, fracture of the clavicle or a long bone, brachial plexus injury, intracranial hemorrhage, or death.

To determine the ability of MRI-EFW versus US-EFW to predict neonatal morbidity, defined as arterial cord blood pH less than 7.10, Apgar score at 5 min less than 7, and admission to the neonatal intensive care unit (NICU).

To determine the ability of MRI-EFW versus US-EFW to predict maternal morbidity, defined as cesarean section, operative vaginal delivery (vacuum or forceps), postpartum hemorrhage (1000 mL or more), blood transfusion, and anal sphincter tear.

CENTERS

This is a single-center study conducted at the Department of Obstetrics and Gynecology and Radiology of the University Hospital Brugmann, Université Libre de Bruxelles in Brussels, Belgium.

DESIGN

This is a prospective observational clinical head-to-head comparison study of MR-EFW versus US-EFW for the prediction of LGA neonates. Randomization was not appropriate since all patients undergo both examinations.

INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria

Age ≥ 18 years;

Singleton pregnancy;

Live fetus at 36+0-36+6 weeks of gestation;

Subject is planning a delivery at our maternity at the University Hospital Brugmann, in Brussels, Belgium;

French- or Dutch-speaking (otherwise interpreters will be used);

Informed and written consent.

Exclusion Criteria

Multiple pregnancy;

Pregnancies complicated by major fetal abnormality identified at the 11-13, 20-22 or 30-35 week routine scans;

Women presenting with an imprecise pregnancy dating due to absence of first-trimester scan;

Women presenting at a gestational age < 36 or ≥ 37 weeks of gestation;

Subject is known to have a contraindication to MRI, such as:

- Carrying a pacemaker or a metallic cardiac valve.
- Having metallic material inside the head.
- Having metallic fragments inside the eye following an accident.
- Having any type of implant including ear implant.
- Having a hip prosthesis.

Women presenting with painful regular uterine contractions or history of premature ruptured membranes;

Women who are unconscious, severely ill, those with learning difficulties, or mentally handicapped;

Women presenting for the study but who have been previously included in the study in a previous pregnancy;

Women who deliver before MRI and US evaluation;

If the neonate's weight is not measured within 6 hours after birth for any reason, including the need for emergency care immediately after delivery;

Pregnancies ending with a stillborn;

Women who deliver outside our network of hospitals in Brussels where a full pediatric report is not available and where there is uncertainty whether the neonate's weight is measured within 6 hours after birth.

METHODS

We will recruit women attending their routine third-trimester scan in pregnancy at 30-35 weeks of gestation as well as women attending our antenatal clinic after 30 weeks of gestation at the university hospital Brugmann, in Brussels, Belgium. The patient information sheet concerning the PREMACRO study will be given to them and they will be invited to attend the 36-week clinic.

If women attend the 36-week clinic, detailed counseling about the study is provided and women who agree to participate, after obtaining a written informed consent, will undergo 15 minutes apart a US scan for fetal biometric measurement and MRI for fetal body volume (FBV) measurement. There is no prespecified order for these examinations, which are performed according to which machine is available first. For the purpose of the study, 2 ultrasound machines have been installed in the Radiology Department on the same floor as the MRI machine.

US examination and US-EFW:

Prenatal US examinations will be carried out using transabdominal sonography by one of 4 experienced consultants in Maternal Fetal Medicine Department. US-EFW will be obtained between 36.0-36+6 weeks of gestation, according to Hadlock *et al.* (25,26), based on measurements of biparietal diameter, head circumference, abdominal circumference and femoral length. Two Voluson E8 machines will be used for the purpose of the study (GE Medical Systems, Zipf, Austria). A percentile for the US-EFW will be obtained after plotting the weight estimation on the curves as described by Yudkin *et al.* (27). All data will be entered in ASTRAIA software gmbh (Munich, Germany). The participants, general practitioners, obstetricians and midwives of the patients will be aware of the results of US-EFW which will be used for clinical management.

MRI examination

MRI will be performed using a clinical 1.5 T whole-body unit with a gradient field strength of 45 mT/m. Patients will be scanned in the supine position, with a combination of a six-channel phased-array body and six elements of the spine coil positioned over the lower pelvic area. The MRI protocol consists of a 'scout' scan in order to gather information about the orientation of the fetus. Subsequently, we will perform T2-weighted imaging (WI) using fast imaging with steady-state free procession (True FISP) sequences in the fetal sagittal plane: 9-15 adjacent slices average-adjusted according to fetal size with a 4 mm slice thickness, an intersection gap of 20, a field-of-view of 380 x 309 mm^2, matrix 166 x 256, TR (repetition time)/TE (echo time) = 4.65 ms/2.33 ms, resulting voxel resolution of 1.9 x 1.5 x 4.0 mm^3 and a bandwidth of 399 Hz/pixel.

For further research, other sequences with be acquired in the following order: True FISP sequences in the fetal sagittal plane with a 4 mm slice thickness and an intersection gap of 4

mm, followed by sequences for pelvimetric measurements. Sequences degraded by fetal motion or following maternal movements will be repeated with the same parameters. For the PREMACRO study, total examination time will be kept under 5 minutes.

MRI will be performed using one of 2 MRI magnets: Siemens Magnetom Avanto with a bore diameter of 60 cm or Aera with a bore diameter of 70 cm (Erlangen, Germany).

MRI planimetric measurements and MRI-EFW:

Total FBV planimetric measurements will be performed by one of 5 trainees in the Maternal Fetal Medicine Department or the Radiology Department. Prior to the PREMACRO study, all trainees will receive extensive training in planimetric measurements by an expert (CK or MMC) with at least 100 FBV measured per trainee. All but one of the trainees performing the FBV measurements are different from those performing the US-EFW. However, for the only trainee performing both US-EFW and FBV measurements, we made sure that the trainee never evaluated the same woman using both imaging modalities. FBV will be measured on the day of MRI or on the following 2 days by the available trainee without a specific order. FBV will be measured using semi-automatic software on a picture archiving and communication system (PACS) (Impax, Agfa-Gevaert, Mortsel, Belgium) as previously described (18). This semi-automatic software was designed for volumetric measurements, but was validated by our research team in collaboration with Agfa HealthCare.

Operators performing FBV measurements will be blinded to the US-EFW results. If the total FBV cannot be measured on MRI, this will be noted. The time required to perform the FBV measurements with 4 mm slice thickness and an intersection gap of 20 mm will also be recorded. FBV measurements will be entered in the ASTRAIA database. MRI-EFW will be calculated using the equation 0.12+1.031*FBV = MRI-EFW (kg) developed by Baker *et al.* (14), where FBV is entered in liters. MRI-EFW will not be entered in the ASTRAIA database, but will be kept in a secure database by the principal investigator. Data will be transmitted to the Independent Data Monitoring Committee (IDMC) on a monthly basis.

In contrast to the US-EFW, the participants, general practitioners, obstetricians and midwives of the patients will be blinded to the results of the MRI-EFW.

A percentile for the MRI-EFW will be obtained after plotting the weight estimation on the curves as described by Yudkin *et al.* (27).

MRI-EFW will be defined as successful if all the following conditions are met:

- Patient did not feel any discomfort during the MRI or felt discomfort but the acquisition of the main sequence was successful.
- MRI acquisition of the main sequence: True FISP sequence with a 4 mm slice thickness, an intersection gap of 20 mm, could be performed.
- FBV acquisition was complete and allowed MRI planimetric measurement.

MRI-EFW will be defined as a failure if any of these conditions are met:

- Women could not be accommodated in the magnet because of a high body mass index.
- Women did not undergo MRI due to claustrophobia, discomfort resulting in interruption of the examination before the main sequence of the True FISP with a 4 mm slice thickness and an intersection gap of 20 mm could be performed.
- Women presenting with a contraindication to MRI.

- The examination could not be started or continued because of an incident with the magnet.

The characteristics of women in both groups will be detailed and compared.

Measurement of neonatal weight at birth:

We will aim to measure neonatal weight immediately after birth or within 6 hours of delivery. A percentile for the birth weight will be obtained after plotting the actual weight on the curves as described by Yudkin *et al.* (27) and this will be considered as the gold standard for the US-EFW and MRI-EFW-derived percentile at 36.0-36+6 weeks of gestation.

Data collection:

Data on study participants will be entered in an electronic case report form (CRF) in the ASTRAIA database. Data on pregnancy and neonatal outcomes will be collected from our obstetrical electronic database MOSOS (BMA B.V., Houten, The Netherlands) and hospital maternity records. If neonates are admitted to NICU, additional neonatal outcomes will be collected from the discharge summary.

Patient and Public Involvement:

Patients and or public were not involved in the design, recruitment or conduct of the study. However, while all study participants were informed that MREFW will not be disclosed to them or their health care providers before delivery and during the study period, study participants were informed that after completion of the study and publication of the data, they were free to contact us and we would inform them about their MRI-EFW.

OUTCOMES

Primary outcome

LGA neonate ≥ 95th centile for gestational age, based on the curves as described by Yudkin *et al.* (27).

Secondary outcomes

As defined above in the Secondary objectives section.

SIDE EFFECTS AND ADVERSE EVENT REPORTING

This study is considered a minimal risk study. However, investigators are required to report any suspected or actual Unexpected Adverse Events (UAEs) that patients have while they are participating. Subject study participation begins at the time of consent and ends when the results of the neonatal weight are received. A UAE is defined as any event that meets the following conditions:

- The event is **not** a known or reasonably foreseeable risk associated with the study procedures (includes risks related to breaches of confidential information specified in the informed consent), and

- The event, in the investigator's opinion, is or could be directly related to the subject's participation in this research protocol/protocol procedure. Please note that the only procedures in this protocol are US and MRI and measuring neonatal weight at birth. Any other care delivered as part of a subject's regular plan of care are not study-related activities.
- Clinical outcomes (e.g. adverse birth outcome, pregnancy complications) experienced by patients other than those associated with the study procedures will not be considered as UAEs.

Events that are the result of a natural progression of an underlying disease, disorder, condition, or a predisposing risk factor profile for the patient do not qualify as UAEs. UAEs should be reported to the study sponsor within 24 hours of discovery. The study site at the University Hospital Brugmann, Brussels, Belgium is responsible for complying with local IRB requirements for the reporting of UAEs.

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Procedure for reporting SAEs and SUSARs

If an adverse event is considered to be serious, it must be documented and reported to the trial coordinator, whether attributed to the treatment or not. SAEs will be reported to the IDMC and all events will be followed up until resolution.

All suspected adverse reactions that are both unexpected and serious are subject to expedited reporting. If the trial coordinator is notified of an SAE which qualifies as a suspected unexpected adverse reaction (SUSAR), then details will immediately be passed to the sponsor. The sponsor will report all SUSARs that are fatal or life-threatening to the Ethics Committee not later than 7 days after the sponsor is first made aware of the reaction.

An annual safety report for the study will be submitted to the Ethics Committee, including listings of all suspected serious adverse reactions.

STATISTICAL ANALYSIS PLAN INCLUDING SAMPLE SIZE AND POWER CALCULATION

On the basis of results of a pilot study conducted in our department before the PREMACRO study and assumptions with respect to the performance of MRI-EFW (AUROC 0.981) and US-EFW (AUROC 0.921) in the prediction of neonatal macrosomia as well as on the basis of the prevalence of neonates born in our department ≥ 95th centile (available data from 5920 deliveries between 2011 and 2016), we determined that a sample size of 90 cases of macrosomic fetuses (≥ P95) and 2250 negative controls would provide a power of 90% to determine the primary outcome of detecting a difference between the AUROC of MRI-EFW and US-EFW (of 0.06) at significance level of 5%.

Assuming that 70% of women with singleton pregnancies who fulfill the entry criteria agree to participate in the study and provide follow-up data and also allow for loss to follow-up (~ 5%), we would need to approach about 3,500 such women to meet our primary outcome.

The first enrolment for the study was in May 2016. As of September 2018, 2004 women have been screened and recruited to the study. So far, the rate of women refusing the study at the 36-week clinic is only 8.5% rather than 30%. Yet, this is an underestimation of the proportion of women refusing the study from those that were approached during the third-trimester scan and/or

the antenatal clinic when the patient information sheet was given to them. Thus, the proportion of women receiving the patient information sheet and not attending our 36-week clinic is probably even higher than 30%.

Type of analysis and statistical tests

MRI-EFW and US-EFW each produce a measured value and classify the fetus as macrosomic or not. The ROC curve is generated by computing sensitivity and specificity for each technique (US and MRI) as compared to the actual classification of a neonate being macrosomic or not at birth. The differences between the ROC curves will be calculated as the primary outcome, taking into account the paired nature of the data. AUC values will be compared with the use of a z-test according to the method of DeLong *et al.* (28). A *p* value of less than 0.05 will be considered to indicate statistical significance.

Confidence intervals will be computed with the use of the Clopper-Pearson method. The exact binomial test (29) for paired comparisons will be used in sensitivity and specificity and will use the generalized score statistic (30) to analyze positive and negative predictive values. We will compare the sensitivity, specificity, positive and negative predictive values, and likelihood ratios of MRI-EFW and US-EFW for the detection of neonatal macrosomia for a fixed false-positive rate of 5 and 10%.

Descriptive statistics

For categorical variables, summary tabulations of the number and percentage of patients in each category (with a category for missing data) of the parameter will be presented. For continuous variables, the number of patients, mean, median, standard deviation, minimum, and maximum values or interquartile ranges will be presented. Graphical displays will be produced as appropriate.

The SPIRIT reporting guidelines were used (31).

COMMITTEE OVERSIGHTS

The IDMC is independent of the trial and is responsible for monitoring the progress of the trial, including recruitment, protocol adherence, SAEs as well as the result of the comparison between the 2 estimations to the primary outcome measure. The IDMC is the only oversight body that has access to unblinded data. The IDMC is responsible for safeguarding the interests of trial participants, monitoring the accumulating data and making recommendations to the Trial Steering Committee (TSC) on whether the trial should continue as planned.

The TSC is the independent group responsible for oversight of the trial in order to safeguard the interests of trial participants. The TSC provides advice to the chief investigator, Brugmann CTU, the funder and sponsor on all aspects of the trial through its independent chair.

ETHICS AND DISSEMINATION

The study will be conducted in accordance with the International Conference on Harmonization (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). A favorable ethical opinion was obtained from the Ethics Committee of the University Hospital Brugmann, reference number CE2016/44. Results will be published in peer-reviewed journals and disseminated at international conferences.

DISCUSSION

Macrosomia is a risk factor for unfavorable delivery outcomes, including operative vaginal or cesarean delivery and shoulder dystocia (1,32). Shoulder dystocia can cause neonatal morbidity, including fracture of the clavicle, brachial plexus injury, or asphyxia and maternal complications such as vaginal tears and postpartum haemorrhage. The traditional approach to screening for macrosomia is based on clinical measurement of fundal height or US-EFW using the Hadlock formula, but such an approach identifies only 73% of LGA neonates > 95th centile, for a fixed 10% false-positive rate (33).

Findings from a decision analysis suggested that the number of elective cesarean sections needed to avoid one permanent brachial plexus injury is quite high (12). This strategy is thus recommended only when fetal weight is estimated to exceed 4500 g for women with diabetes and 5000 g for those without diabetes (34). Another approach would be to induce labor between 37^{0} and 38^{6} weeks, which effectively arrests the problem of continued fetal overgrowth, thereby reducing the associated risks of fetal and maternal morbidity (8). Induction of labor for suspected LGA fetuses above the 95th percentile was shown to be associated with a reduced risk of shoulder dystocia and associated morbidity compared with expectant management (8,9). However, these benefits should be balanced against the effects of early-term induction of labor, including neonatal respiratory morbidity (8) therefore this proposed strategy remains the subject of much ongoing debate .

The problem is that any strategy to detect macrosomic fetuses is limited by the imprecision of the methods for estimation of fetal weight (35). Fundal height is imprecise, subject to measurement errors, and dependent on the thickness of the maternal abdominal wall and the amount of amniotic fluid (36). Ultrasound is also imprecise in estimation of fetal weight, especially for LGA fetuses (37).

There is evidence that MRI-EFW is more precise than US-EFW. So far, published data comparing the two techniques have been collected from a limited number of cases, mainly by comparing their ability to predict absolute weight estimation, rather than LGA neonates. Also, the data are retrospective, the evaluation has been done within hours of delivery rather than remote from delivery, and in most cases a time-consuming method has been used for planimetric FBV measurement. The present study is a large prospective study, using a simplified method for planimetric FBV evaluation, designed to streamline the process, thus making it more practical in the clinical setting. Furthermore, the study was also designed to evaluate women several weeks prior to the expected date of confinement, which would give more time to make further evaluations if necessary and implement clinical decisions, should this method be adopted into routine clinical practice in the future.

This study will assess whether MRI-EFW is more accurate than US-EFW in prediction of LGA and small-for-gestational-age neonates, and if our hypothesis is correct, by how much is the performance improved. The latter will determine if the introduction of MRI for the prediction of macrosomia or small-for-gestational-age neonates is cost-effective and may form the basis for the design of future interventional studies based on a more accurate method of fetal weight estimation. The results of the study could also be used to develop new recommendations for elective cesarean section, in cases of suspected macrosomia in both diabetic and non-diabetic pregnancies.

Author Contributions: CK, MMC, AC and JCJ conceived and designed the study, drafted the original grant proposal and trial protocol. JCJ provided methodological and statistical expertise. CK provide expertise in the pregnancy clinical outcomes. CK and JCJ drafted the original protocol and the manuscript. All authors have responsibilities for day-to-day running of the trial including participant recruitment and data collection. All authors critically reviewed and approved the final version of the manuscript.

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Disclaimer: The views expressed in this publication are those of the authors and not necessarily those of the FMFB, Brugmann Foundation, healthcare systems or competent authorities.

Competing interests: None declared.

Acknowledgements: None.

Ethical approval: This study will be conducted in accordance with the principles of Good Clinical Practice. This protocol was submitted to the University Hospital Brugmann Research Ethics Committee, in Brussels, Belgium and a favorable opinion was granted. The reference number is CE2016/44.

Provenance and peer review: Not commissioned; externally peer-reviewed.

Data statement section: Technical appendix, statistical code, and dataset available from the Dryad repository, DOI: [will be available soon].

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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	13
Protocol version	#3	Date and version identifier	2
		Initially V.2.0, date 26-Feb-2016 followed by V.2.1, date 19-May 2016, which is the last version where we asked a minor amendment adding among the secondary outcomes prediction by ultrasound and MRI of the neonates above the 97th centile for gestational age.	
Funding	#4	Sources and types of financial, material, and other support	13
		Support was mainly for financing the MRI examinations.	

Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 13
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	10
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	11
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4,5
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained.	6

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7,8
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	11
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	N/A
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
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	5,9
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)	7
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	10
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	10
Allocation: sequence	#16a	Method of generating the allocation sequence (eg,	N/A

generation		computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7,8
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial No unblinding for MRI results are permissible, or needed.	8
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	9
Data collection plan: retention	#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	9
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	8

		found, if not in the protocol	
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	10,11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10,11
Statistics: analysis population and missing data	#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)	N/A
Data monitoring: formal committee	#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 found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9,10
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor The Trial Steering Committee meets every 6 months.	
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	2
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7

Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers All authors should have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.	
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code The full protocol will be published with article on Journal site	
Informed consent	#32	Model consent form and other related documentation given	

materials		to participants and authorised surrogates Given in annexes	
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A