

BMJ Open Protocol for the prospective observational clinical study: estimation of fetal weight by MRI 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 (≥ 95 th centile) may play an important role in guiding obstetric interventions, such as induction of labour or caesarean section. Traditionally, identification of fetuses suspected of macrosomia has been based on biometric measurements using two-dimensional (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 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 with 2D US, can improve the identification of LGA neonates ≥ 95 th centile.

Methods and analysis All eligible women attending the 36-week clinic will be invited to participate in the screening study for LGA fetuses ≥ 95 th 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 with the centile of birth weight used as the gold standard. Besides birth weight, other pregnancy and neonatal outcomes will be collected and analysed. 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.

Ethics and dissemination The study will be conducted in accordance with the International Conference on Harmonisation for good clinical practice and the appropriate regulatory requirement(s). A favourable ethical opinion was obtained from the Ethics Committee

Strengths and limitations of this study

- This is the first prospective head-to-head comparison of ultrasound (US) estimation of fetal weight (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 ≥ 95 th 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-centre study and the extrapolation of our findings to other perinatal centres needs further evaluation.

of the University Hospital Brugmann, reference number CE2016/44. Results will be published in peer-reviewed journals and disseminated at international conferences.

Trial registration number NCT02713568.

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 (LGA). 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 labour or caesarean 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 haemorrhage in the mother.¹ A recent multicentre randomised controlled trial appears to confirm the advantages of a policy of induction of labour for suspected macrosomia, demonstrating a clear reduction in the rates of shoulder dystocia and composite perinatal morbidity.⁸ A meta-analysis 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 caesarean and instrumental delivery, without reducing perinatal morbidity.

Despite these conflicting data and a lack of evidence to support routine third-trimester US,¹⁰ the absence of specific guidance, coupled with concerns regarding perinatal outcomes, obstetricians still request an US 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 US-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 labour and caesarean section to those fetuses at greatest risk of suspected macrosomia. Some publications have already demonstrated that MRI-derived EFW close to delivery is more accurate than US, with a precision superior to that of US using birth weight as a golden standard,^{14–23} and a recent meta-analysis has confirmed this promising accuracy.²⁴

HYPOTHESIS

We hypothesise that MRI-EFW at 36+0–36+6 weeks of gestation is significantly more accurate than US-EFW in the prediction of LGA neonates (≥ 95 th 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 the 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 (≥ 95 th 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:

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

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

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

- ▶ ≤ 10 th centile for gestational age.
- ▶ ≤ 5 th centile for gestational age.
- ▶ ≤ 3 rd 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 haemorrhage 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 caesarean section, operative vaginal delivery (vacuum or forceps), postpartum haemorrhage (1000 mL or more), blood transfusion and anal sphincter tear.

CENTRES

This is a single-centre study conducted at the department of obstetrics 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 MRI-EFW versus US-EFW for the prediction of LGA neonates. Randomisation 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 delivery at our maternity at the University Hospital Brugmann, in Brussels, Belgium.
 French-speaking 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 the 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 an 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 paediatric 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 PREdict neonatal MACROsomia (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 counselling about the study is provided and women who agree to participate, after obtaining a written informed consent, will undergo 15 min 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, two US 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 trans-abdominal sonography by one of four 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 (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 precession (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 380×309 mm², matrix 166×256, TR (repetition time)/TE (echo time)=4.65 ms/2.33 ms, resulting voxel resolution of 1.9×1.5×4.0 mm³ and a bandwidth of 399 Hz/pixel.

For further research, other sequences will 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 min.

MRI will be performed using one of two MRI magnets: Siemens Magnetom Avanto with a bore diameter of 60 cm or area 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 the five 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 $0.12+1.031\times\text{FBV}=\text{MRI-EFW}$ (kg) developed by Baker *et al.*¹⁴ where FBV is entered in litres. 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 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 MRI-EFW will not be disclosed to them or their healthcare 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 ≥ 95 th 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).
- ▶ 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 (eg, 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 Serious adverse event (SAEs) and suspected unexpected adverse reactions

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 PREMACHRO 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 ≥ 95 th centile (available data from 5920 deliveries between 2011 and 2016), we determined that a sample size of 90 cases of macrosomic fetuses ($\geq P95$) 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 fulfil 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 3500 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 with 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 test²⁹ for paired comparisons will be used in sensitivity and specificity and will use the generalised score statistic³⁰ to analyse 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, SD, 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 two 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). Results will be published in peer-reviewed journals and disseminated at international conferences.

DISCUSSION

Macrosomia is a risk factor for unfavourable delivery outcomes, including operative vaginal or caesarean 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 caesarean 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 labour between 37⁰ and 38⁰ weeks, which effectively arrests the problem of continued fetal overgrowth, thereby reducing the associated risks of fetal and maternal morbidity.⁸ Induction of labour 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 labour, including neonatal respiratory morbidity⁸ 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 US is also imprecise in the 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 caesarean section, in cases of suspected macrosomia in both diabetic and non-diabetic pregnancies.

Contributors 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.

Patient consent for publication Not required.

Ethics 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.

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