BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-022567
Article Type:	Protocol
Date Submitted by the Author:	23-Feb-2018
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Keywords:	Intrapartum fetal compromise, cerebroplacental ratio, placental growth factor, perinatal outcome, screening test

Predicting intrapartum fetal compromise at term using the cerebroplacental ratio and placental growth factor levels (PROMISE) study: randomised controlled trial protocol

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Funding statement: HS is a recipient of a NHMRC Scholarship and stipend through Mater Medical Research Institute (Mater Perinatal Scholarship).

Authors' contributions: HS is the study coordinator, contributed to study planning, will collect and analyse the data and will participate in reporting the data. VC contributed to study planning and will participate in report of the data. SK is the principal investigator (PI) for the study.

The authors report **no conflicts of interest**.

Title (short version): The PROMISE study protocol.

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Word count: 2317

ABSTRACT

Introduction

Intrapartum complications are a major contributor to adverse perinatal outcomes, including stillbirth, hypoxic-ischaemic brain injury and subsequent longer term disability. In many cases hypoxia develops as a gradual process due to the inability of the fetus to tolerate the stress of parturition suggesting reduced feto-placental reserve before labour commences. The fetal cerebroplacental (CPR) ratio is an independent predictor of intrapartum fetal compromise, poor acid base status at birth and of neonatal unit admission at term. Similarly, circulating maternal levels of placental growth factor (PlGF) are lower in pregnancies complicated by placental dysfunction. This paper outlines the protocol for the PROMISE Study which aims to determine if the introduction of a pre-labour screening test for intrapartum fetal compromise combining the CPR and maternal PlGF level results in a reduction of adverse perinatal outcomes.

Methods and analysis

This is a single-site, non-blinded, individual patient randomised controlled trial of a screening test performed at term, combining the fetal CPR and maternal serum PlGF. Women with a singleton, non-anomalous pregnancy will be recruited after 34 weeks gestation and randomised to either receive the screening test or not. Screened pregnancies determined to be at risk will be recommended induction of labour. Demographic, obstetric history and antenatal data will be collected at enrolment and perinatal outcomes will be recorded after delivery. Relative risks and 95% confidence intervals will be reported for the primary outcome. Regression techniques will be used to examine the influence of prognostic factors on the primary and secondary outcomes.

Ethics and dissemination

This study has been reviewed and approved by the Mater Human Research Ethics Committee (Reference: HREC EC00332) and will follow the principles of Good Clinical Practice. The study results will be disseminated at national and international conferences and published in peer-reviewed journals. Australian New Zealand Clinical Trial Registry: ACTRN12616001009404.

Keywords: Intrapartum fetal compromise, cerebroplacental ratio, placental growth factor, perinatal outcome, screening test

Strengths and limitations of this study

- Will provide the first high-level evidence of the impact of a screening test combining the fetal cerebroplacental ratio and maternal placental growth factor on intrapartum fetal compromise and adverse neonatal outcomes.
- Single-site, randomised controlled trial in a high-income setting.
- Unable to blind participants or clinicians to randomisation due to nature of intervention.
- Sample-size powered to detect a 40% reduction in a composite outcome indicative of significant perinatal asphyxia.

INTRODUCTION

Background

Globally, intrapartum complications are a major contributor to adverse perinatal outcomes, including stillbirth, hypoxic-ischaemic brain injury and subsequent longer term disability. Worldwide, of the 7.6 million deaths under 5 years of age, almost 9.4% are as a consequence of intrapartum related complications mainly in low and middle income countries (LMIC) and it is estimated that globally almost 45% of stillbirths (approximately 1.3 million per annum) occur during the intrapartum period.[1] In Australia, hypoxic peripartum death is one of the top three causes of mortality in singletons ≥37 weeks.[2] Additionally, there is significant neonatal morbidity (neonatal encephalopathy, respiratory distress, acidosis and admission to the neonatal intensive care unit) associated with intrapartum hypoxia. These compromised babies frequently require rapid delivery by emergency operative delivery which carries considerably more maternal risk than less urgent procedures. In Australia, emergency caesarean rates for intrapartum fetal compromise (fetal distress) range from 11% of all caesareans in Queensland to 16.3% in Tasmania.[2] Neonatal outcomes are also significantly poorer following emergency caesarean for fetal distress.[3]

Whilst some cases of intrapartum fetal hypoxia at term arise because of acute catastrophic events such as cord prolapse, placental abruption or uterine rupture, the majority do not, and hypoxia in these cases develops as a gradual process due to the inability of the fetus to tolerate the stress of parturition suggesting reduced feto-placental reserve before labour commences. Why some term babies are more prone to intrapartum compromise is not entirely clear although growth restriction is implicated in many cases.[4 5] If not delivered rapidly enough, these babies are at risk of hypoxic brain injury and subsequent disability with hypoxic ischaemic encephalopathy being the strongest and most consistent risk factor for cerebral palsy in term infants.[6] Labour is an asphyxial process, with contractions reducing blood flow in the uterine arteries and thus decreasing oxygen availability to the placenta and fetus.[7] This results in a gradual deterioration of the fetal condition reflecting a steady decline in the ability of the placenta as labour progresses. The fetus responds to

uterine contractions with acute cerebral redistribution, evidenced by a reduced middle cerebral artery Pulsatility Index (MCA PI). This centralisation of blood flow is identical to that observed chronically in growth restricted fetuses. Some studies suggest that intrauterine pressures of just 35mmHg are enough to obliterate uterine artery end diastolic velocities,[8] resulting in reduced placental perfusion. Impaired placental transfer of oxygen and other substrates during labour is likely to be responsible for the "fetal distress" that develops as a consequence of regular uterine contractions. However, up to 63% of babies who become distressed and suffer oxygen deprivation in labour have no apparent prior risk factors.[7]

The fetal cerebroplacental ratio (CPR) is the ratio of the MCA PI to the Umbilical Artery Pulsatility Index (UA PI). The CPR gradually rises until around the 34th week, and subsequently slowly declines until term.[9] In some term small-for-gestational-age (SGA) fetuses, the MCA PI is reduced despite normal UA Doppler indices (i.e. a low CPR) and this is associated with poorer perinatal outcomes[10 11] and adverse neuro-behaviour sequelae.[12] We[13-15] and others[16-18] have established that the CPR is an independent predictor of intrapartum fetal compromise, poor acid base status at birth and of neonatal unit admission at term. In addition, a low CPR may also reflect a failure of a fetus to reach its genetic growth potential at term, [19 20] despite having a normal birth weight. Furthermore, a low CPR has been shown to be associated with an increased risk of stillbirth regardless of the gestation or size of the baby.[21] An ongoing randomised controlled trial (RATIO37),[22] currently in the recruitment phase, aims to determine whether the addition of the CPR to standard ultrasound biometry measured at term can identify fetal growth restriction (FGR) due to placental insufficiency.

Circulating maternal levels of angiogenic factors such as placental growth factor (PlGF) are lower in pregnancies complicated by placental dysfunction.[23-25] PlGF is a member of the vascular endothelial growth factor (VEGF) family and is predominantly expressed by the placenta. PlGF has a pivotal role in placental angiogenesis and induces vasodilation of uterine and myometrial vessels.[26] This effect is particularly pronounced in uterine arteries during pregnancy, suggesting that PlGF contributes to vascular remodelling during gestation. During the first and second trimesters of

pregnancy, low maternal levels of PlGF are linked to impaired placental development and angiogenesis, leading to multiple pregnancy complications including miscarriage, stillbirth, preeclampsia, small for gestational age (SGA) infants and FGR.[25 27] Low maternal PlGF levels are also predictive of preeclampsia and FGR when measured in late pregnancy.[24 28 29] PlGF may also help determine whether a fetus is constitutionally small or growth restricted with low PlGF levels associated with histopathological signs of placental underperfusion.[23 30] Furthermore, in women with SGA fetuses, a low PlGF measured in the third trimester is associated with adverse perinatal outcome (emergency caesarean for fetal distress and/or neonatal acidosis).[31] More recently, it has been reported that pre-labour PlGF levels are significantly lower in women that developed intrapartum fetal compromise and have adverse neonatal outcome, even after excluding SGA fetuses.[32]

We have previously shown that a CPR threshold of <10th centile appears to be a good discriminator for identifying fetuses at risk of intrapartum compromise.[33] Our recent publication[34] assessing the utility of a screening test for intrapartum fetal compromise at term incorporating the CPR and maternal PlGF levels showed that the sensitivities, specificities and positive likelihood ratios for cesarean section for intrapartum fetal compromise were 100%, 86%, and 7.14. Combining both measures in the predictive model substantially improved the results of either element alone, raising the possibility that this might be a reasonable way to screen for this complication at term.

Justification for study and hypothesis

In most women although placental function is sufficient to allow appropriate fetal growth throughout pregnancy, in some it may not be adequate to meet the additional demands required in the last few weeks of pregnancy or during labour thereby predisposing these vulnerable fetuses to intrapartum compromise and subsequent risk of serious morbidity and mortality. A strategy to identify these infants is thus urgently needed. A screening test incorporating the CPR and maternal PlGF levels could identify these at risk babies. Furthermore, if this screening strategy is combined

with induction of labour for women that screen positive it may reduce the risk of emergency operative birth and serious adverse neonatal outcomes.

OBJECTIVES

Primary objective

To determine if the introduction of a pre-labour screening test at 37-38 weeks of gestation for intrapartum fetal compromise combining the CPR and maternal PlGF level results in a reduction in a composite measure of adverse perinatal outcomes (emergency caesarean for fetal compromise or severe acidosis at birth or five minute Apgar score ≤5 or death).

Secondary objective

To determine if introduction of this screening test results in a reduction in overall operative delivery rates (instrumental and caesarean section) for fetal compromise and neonatal morbidity [defined as admission to the neonatal intensive care unit (NICU) for >48 hours or severe respiratory distress (respiratory support >4 hours)].

METHODS

Study design

This is a single-site (Mater Mothers' Hospital, Brisbane, Australia), non-blinded, individual patient RCT of a screening test performed at term, combining the fetal CPR and maternal serum PlGF. Our study protocol follows the recommendations of the SPIRIT guidance for clinical trials.[35]

Inclusion criteria

- Women aged between 18-45 years who are able to give informed consent
- Singleton pregnancy between 34+0 – 37+6 weeks gestation
- Cephalic presentation
- Planning a vaginal delivery

Exclusion criteria

- Multiple pregnancy
- Maternal body mass index (BMI) >40kg/m^2

- Previous caesarean section
- Known fetal anomaly or aneuploidy
- Known fetal growth restriction (defined as estimated fetal weight <10th centile and abnormal umbilical artery Dopplers)
- Known rupture of membranes

Intervention

Once recruited study participants will be randomised to either receive the screening test (intervention group) or not (control group). Figure 1 outlines the management for participants in both groups. Women in the control group will receive standard antenatal care as per the hospital's policies and guidelines. The screening test will be a combination of two elements - an ultrasound scan measuring fetal CPR and blood test measuring maternal serum PlGF levels performed between 37+0 to 38+0 weeks gestation.

Ultrasound parameters measured will include fetal biometry, UA PI and MCA PI. The pulsatility indices will be measured from an automated trace of at least three consecutive waveforms of the relevant vessel in the absence of fetal breathing movements or uterine contractions. The angle of insonation will be as close to zero degrees as possible. The UA PI will be recorded from a free-floating section of cord and the MCA PI will be obtained from the proximal third of the vessel, taking care to avoid excessive transducer compression of the fetal head. Each parameter will be recorded three times and a mean of these values used for data analysis. Maternal serum PlGF levels will be quantified using the DELFIA Xpress immunoassay (PerkinElmer, Turku, Finland). The DELFIA platform requires a 40-µL SST plasma sample and reports a concentration in the range of 7–4,000 pg/mL with an overall coefficient of variation of 10.1–5.1% (at 27.6 and 74.2 pg/mL, respectively).

Based on pilot data, a screen positive result (identifying an at risk fetus) is defined as a CPR of ≤10th centile AND maternal PlGF level ≤40th centile. Any other combination is considered a screen negative result. Women who screen positive will be advised of the increased risk of intrapartum fetal

compromise and induction of labour within seven days of the test result will be recommended. If she chooses not to be delivered, then weekly fetal surveillance at the discretion of the treating obstetric team will be offered until birth occurs. Women who screen negative will receive standard obstetric care. Intrapartum care (including induction of labour if applicable) for all participants will be as per the hospital's policies and guidelines, however all women who screen positive will receive continuous electronic fetal heart rate monitoring in labour. The only results that will be released to obstetric caregivers is the designation - "screen positive" or "screen negative". However, if the ultrasound scan detects a malpresentation, estimated fetal weight (EFW) <5th or >95th centile or pathological umbilical artery Dopplers (absent or reversed end diastolic flow) the obstetric team caring for the woman will be informed of these findings.

Data collection

Demographic and antenatal data will be collected for all participants from the maternity database and stored in an anonymised and secure format. Collected data will include maternal age, ethnicity, socioeconomic status, body mass index (BMI), history of smoking, previous pregnancy outcomes including mode of delivery and any complications. For the current pregnancy, data collected will include mode of conception, blood pressure at booking, first trimester screening results, presence of hypertensive disorders of pregnancy, diabetes mellitus, thyroid dysfunction, antepartum haemorrhage and maternal medications.

Primary outcome

The primary outcome is a composite measure of adverse outcomes: emergency caesarean section for intrapartum fetal compromise **or** neonatal acidosis (defined as cord arterial pH <7.1 or lactate >6 mmol/L or base excess ≤-12mmol/L) **or** Apgar score ≤5 at 5 minutes **or** stillbirth **or** neonatal death within 28 days. These specific outcomes have been chosen as they indicate significant perinatal asphyxia.

Secondary outcomes

Secondary outcomes include overall operative delivery rates (instrumental and caesarean section) for fetal compromise, and maternal and neonatal morbidity [defined as admission to the neonatal intensive care unit (NICU) for >48 hours or severe respiratory distress (respiratory support >4 hours)].

Sample size calculation

The proposed sample size is based on previous pilot data from our group which found 17.6% of women experienced the primary composite outcome measure. Anticipating a 40% reduction in the proportion of adverse events to 10.6% in the screening test intervention group, a sample size of 382 women is required in each group (type 1 error of 5% and power of 80%). Assuming a 10% drop out rate, we plan to recruit a total of 840 women. There are >5500 publically-funded births at the Mater Mother's Hospital each year. With an estimated 70% of women being eligible to participate it is expected that the required sample size can be recruited within 2 years.

Study review and data monitoring

The study protocol, patient information and consent form and other accompanying material that will be provided to participants have been reviewed and approved by the Mater Human Research Ethics Committee (Reference No: HREC EC00332). The study will be conducted in accordance with the principles of Good Clinical Practice. A Data Safety and Monitoring Committee (DSMC) will be established to oversee any adverse events arising from this study. Members of the DMSC will be external to and independent of the research group and will include an obstetrician, neonatologist and statistician. The study results will be disseminated at national and international conferences and published in peer-reviewed journals. This study has been registered as a clinical trial with the Australian New Zealand Clinical Trials Registry (ANZCTR Trial ID: ACTRN12616001009404 and WHO UTN: U1111-1181-3852). Recruitment for the study commenced in April 2017 and the study is planned to continue until May 2019.

Randomisation

Randomisation will be performed using the *STATA 13* (StataCorp, College Station, Texas) program and will be undertaken by an Epidemiologist within the Mater Research Institute. Participants will be randomised to either screening test or no screening test in equal numbers (1:1) in block sizes of four and six to yield the appropriate sample size. Allocations will be concealed in opaque envelopes until individual randomisation occurs.

Statistical analysis

Outcome comparisons for women and infants will be analysed for the primary and secondary outcomes on an "intention to treat" basis, according to treatment allocation at randomisation. The relative risks and 95% confidence intervals will be reported for the primary outcome (composite adverse outcome), and the number needed to treat to prevent one adverse outcome will be calculated. Subgroup analysis comparing either proportions or means, as appropriate, will be undertaken for elements of the primary composite outcome and secondary outcomes. Regression techniques will be used to examine the influence of prognostic factors on the major primary outcome and secondary outcomes.

Figure Legend

Figure 1. Flow chart of study intervention and participant management. CPR – cerebroplacental ratio; PlGF – placental growth factor.

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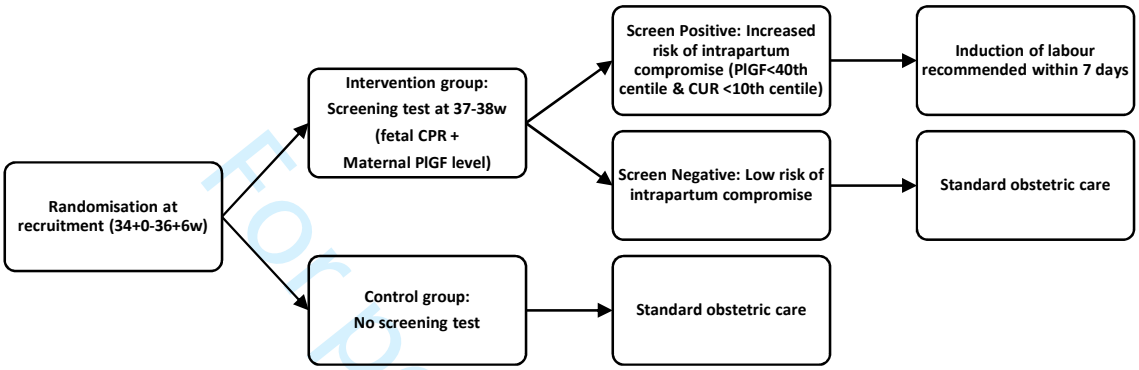
Figure 1. Flow chart of study intervention and participant management. CPR – cerebroplacental ratio; PlGF – placental growth factor.



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
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	10
	2b	All items from the World Health Organization Trial Registration Data Set	10
Protocol version	3	Date and version identifier	n/a
Funding	4	Sources and types of financial, material, and other support	1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	n/a
	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	n/a
	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)	1 & 10

Introduction			
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	6
	6b	Explanation for choice of comparators	8
Objectives	7	Specific objectives or hypotheses	7
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, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
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	7-11
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)	7-11
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-11
	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)	7-11
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7-11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7-11
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	7-11
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)	7-11

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	7-11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7-11
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, 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	10
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	10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7-11
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection methods	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	7-11
	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	7-11

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9
Statistical methods	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	11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
	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)	11
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10
	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	10
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	10
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	10
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)	10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	10
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	10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	n/a
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10
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	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	10
	31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Ethics approved
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	Ethics approved

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Predicting intrapartum fetal compromise at term using the cerebroplacental ratio and placental growth factor levels (PROMISE) study: randomised controlled trial protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-022567.R1
Article Type:	Protocol
Date Submitted by the Author:	30-May-2018
Complete List of Authors:	Sherrell, Helen ; Mater Research Institute-University of Queensland Clifton, Vicky; Mater Research Institute-University of Queensland Kumar, Sailesh; Mater Research Institute-University of Queensland; Mater Mothers' Hospital, Maternal Fetal Medicine
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Obstetrics and gynaecology
Keywords:	Intrapartum fetal compromise, cerebroplacental ratio, placental growth factor, perinatal outcome, screening test

Predicting intrapartum fetal compromise at term using the cerebroplacental ratio and placental growth factor levels (PROMISE) study: randomised controlled trial protocol

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Funding statement: HS is a recipient of a NHMRC Scholarship and stipend through Mater Medical Research Institute (Mater Perinatal Scholarship).

Authors' contributions: HS is the study coordinator, contributed to study planning, will collect and analyse the data and will participate in reporting the data. VC contributed to study planning and will participate in report of the data. SK is the principal investigator (PI) for the study.

The authors report **no conflicts of interest**.

Title (short version): The PROMISE study protocol.

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Word count: 2317

ABSTRACT

Introduction

Intrapartum complications are a major contributor to adverse perinatal outcomes, including stillbirth, hypoxic-ischaemic brain injury and subsequent longer term disability. In many cases hypoxia develops as a gradual process due to the inability of the fetus to tolerate the stress of parturition suggesting reduced feto-placental reserve before labour commences. The fetal cerebroplacental (CPR) ratio is an independent predictor of intrapartum fetal compromise, poor acid base status at birth and of neonatal unit admission at term. Similarly, circulating maternal levels of placental growth factor (PlGF) are lower in pregnancies complicated by placental dysfunction. This paper outlines the protocol for the PROMISE Study which aims to determine if the introduction of a pre-labour screening test for intrapartum fetal compromise combining the CPR and maternal PlGF level results in a reduction of adverse perinatal outcomes.

Methods and analysis

This is a single-site, non-blinded, individual patient randomised controlled trial of a screening test performed at term, combining the fetal CPR and maternal serum PlGF. Women with a singleton, non-anomalous pregnancy will be recruited after 34 weeks gestation and randomised to either receive the screening test or not. Screened pregnancies determined to be at risk will be recommended induction of labour. Demographic, obstetric history and antenatal data will be collected at enrolment and perinatal outcomes will be recorded after delivery. Relative risks and 95% confidence intervals will be reported for the primary outcome. Regression techniques will be used to examine the influence of prognostic factors on the primary and secondary outcomes.

Ethics and dissemination

This study has been reviewed and approved by the Mater Human Research Ethics Committee (Reference: HREC EC00332) and will follow the principles of Good Clinical Practice. The study results will be disseminated at national and international conferences and published in peer-reviewed journals. Australian New Zealand Clinical Trial Registry: ACTRN12616001009404.

Keywords: Intrapartum fetal compromise, cerebroplacental ratio, placental growth factor, perinatal outcome, screening test

Strengths and limitations of this study

- Will provide the first high-level evidence of the impact of a screening test combining the fetal cerebroplacental ratio and maternal placental growth factor on intrapartum fetal compromise and adverse neonatal outcomes.
- Single-site, randomised controlled trial in a high-income setting.
- Unable to blind participants or clinicians to randomisation due to nature of intervention.
- Sample-size powered to detect a 40% reduction in a composite outcome indicative of significant perinatal asphyxia.

INTRODUCTION

Background

Globally, intrapartum complications are a major contributor to adverse perinatal outcomes, including stillbirth, hypoxic-ischaemic brain injury and subsequent longer term disability. Worldwide, of the 7.6 million deaths under 5 years of age, almost 9.4% are as a consequence of intrapartum related complications mainly in low and middle income countries (LMIC) and it is estimated that globally almost 45% of stillbirths (approximately 1.3 million per annum) occur during the intrapartum period.[1] In Australia, hypoxic peripartum death is one of the top three causes of mortality in singletons ≥37 weeks.[2] Additionally, there is significant neonatal morbidity (neonatal encephalopathy, respiratory distress, acidosis and admission to the neonatal intensive care unit) associated with intrapartum hypoxia. These compromised babies frequently require rapid delivery by emergency operative delivery which carries considerably more maternal risk than less urgent procedures. In Australia, emergency caesarean rates for intrapartum fetal compromise (fetal distress) range from 11% of all caesareans in Queensland to 16.3% in Tasmania.[2] Neonatal outcomes are also significantly poorer following emergency caesarean for fetal distress.[3]

In some term babies, intrapartum fetal compromise or hypoxia occurs as a result of unpredictable acute events such as uterine rupture, cord prolapse or placental abruption. However, most cases of asphyxia during labour occur due to a gradual decline in the ability of the fetus to tolerate the process of parturition. It is likely that these infants have decreased feto-placental reserve prior to the onset uterine contractions. The underlying process causing this placental dysfunction is not completely understood but likely to be related to sub-optimal fetal growth.[4 5] If delivery is not expedited these infants are at serious risk of brain injury and subsequent permanent disability with hypoxic ischaemic encephalopathy a key risk factor for the development of cerebral palsy in term infants.[6] Labour is an asphyxial process, with contractions reducing blood flow in the uterine arteries and thus decreasing oxygen availability to the placenta and fetus.[7] This results in a gradual deterioration of the fetal condition reflecting a steady decline in the ability of the placenta

to oxygenate the fetus as labour progresses. The fetus responds to uterine contractions with acute cerebral redistribution, evidenced by a reduced middle cerebral artery Pulsatility Index (MCA PI). This centralisation of blood flow is identical to that observed chronically in growth restricted fetuses. Some studies suggest that intrauterine pressures of just 35mmHg are enough to obliterate uterine artery end diastolic velocities,[8] resulting in reduced placental perfusion. Impaired placental transfer of oxygen and other substrates during labour is likely to be responsible for the "fetal distress" that develops as a consequence of regular uterine contractions. However, up to 63% of babies who become distressed and suffer oxygen deprivation in labour have no apparent prior risk factors.[7]

The fetal cerebroplacental ratio (CPR) is the ratio of the MCA PI to the Umbilical Artery Pulsatility Index (UA PI). The CPR gradually rises until around the 34th week, and subsequently slowly declines until term.[9] In some term small-for-gestational-age (SGA) fetuses, the MCA PI is reduced despite normal UA Doppler indices (i.e. a low CPR) and this is associated with poorer perinatal outcomes[10 11] and adverse neuro-behaviour sequelae.[12] We[13-15] and others[16-18] have established that the CPR is an independent predictor of intrapartum fetal compromise, poor acid base status at birth and of neonatal unit admission at term. In addition, a low CPR may also reflect a failure of a fetus to reach its genetic growth potential at term, [19 20] despite having a normal birth weight. Furthermore, a low CPR has been shown to be associated with an increased risk of stillbirth regardless of the gestation or size of the baby.[21] An ongoing randomised controlled trial (RATIO37),[22] currently in the recruitment phase, aims to determine whether the addition of the CPR to standard ultrasound biometry measured at term can identify fetal growth restriction (FGR) due to placental insufficiency.

Circulating maternal levels of angiogenic factors such as placental growth factor (PlGF) are lower in pregnancies complicated by placental dysfunction.[23-25] PlGF belongs to the vascular endothelial growth factor (VEGF) family and is primarily produced by the placenta. It plays a key role in placental angiogenesis and vascular remodelling and is known to stimulate dilation of myometrial and uterine vessels.[26] This effect is particularly pronounced in uterine arteries during pregnancy, suggesting that PlGF contributes to vascular remodelling during gestation. During the first and

second trimesters of pregnancy, low maternal levels of PlGF are linked to impaired placental development and angiogenesis, leading to multiple pregnancy complications including miscarriage, stillbirth, preeclampsia, small for gestational age (SGA) infants and FGR.[25 27] Low maternal PlGF levels are also predictive of preeclampsia and FGR when measured in late pregnancy.[24 28 29] PlGF may also help determine whether a fetus is constitutionally small or growth restricted with low PlGF levels associated with histopathological signs of placental underperfusion.[23 30] Furthermore, in women with SGA fetuses, a low PlGF measured in the third trimester is associated with adverse perinatal outcome (emergency caesarean for fetal distress and/or neonatal acidosis).[31] More recently, it has been reported that pre-labour PlGF levels are significantly lower in women that developed intrapartum fetal compromise and have adverse neonatal outcome, even after excluding SGA fetuses.[32]

We have previously shown that a CPR threshold of <10th centile appears to be a good discriminator for identifying fetuses at risk of intrapartum compromise.[33] Our recent publication[34] assessing the utility of a screening test for intrapartum fetal compromise at term incorporating the CPR and maternal PlGF levels showed that the sensitivities, specificities and positive likelihood ratios for cesarean section for intrapartum fetal compromise were 100%, 86%, and 7.14. Combining both measures in the predictive model substantially improved the results of either element alone, raising the possibility that this might be a reasonable way to screen for this complication at term.

Justification for study and hypothesis

In most women although placental function is sufficient to allow appropriate fetal growth throughout pregnancy, in some it may not be adequate to meet the additional demands required in the last few weeks of pregnancy or during labour thereby predisposing these vulnerable fetuses to intrapartum compromise and subsequent risk of serious morbidity and mortality. A strategy to identify these infants is thus urgently needed. A screening test incorporating the CPR and maternal PlGF levels could identify these at risk babies. Furthermore, if this screening strategy is combined

with induction of labour for women that screen positive it may reduce the risk of emergency operative birth and serious adverse neonatal outcomes.

OBJECTIVES

Primary objective

To determine if the introduction of a pre-labour screening test at 37-38 weeks of gestation for intrapartum fetal compromise combining the CPR and maternal PlGF level results in a reduction in a composite measure of adverse perinatal outcomes (emergency caesarean for fetal compromise or severe acidosis at birth or five minute Apgar score ≤5 or death).

Secondary objective

To determine if introduction of this screening test results in a reduction in overall operative delivery rates (instrumental and caesarean section) for fetal compromise and neonatal morbidity [defined as admission to the neonatal intensive care unit (NICU) for >48 hours or severe respiratory distress (respiratory support >4 hours)].

METHODS

Study design

This is a single-site (Mater Mothers' Hospital, Brisbane, Australia), non-blinded, individual patient RCT of a screening test performed at term, combining the fetal CPR and maternal serum PlGF. Our study protocol follows the recommendations of the SPIRIT guidance for clinical trials.[35]

Inclusion criteria

- Women aged between 18-45 years who are able to give informed consent
- Singleton pregnancy between 34+0 – 37+6 weeks gestation
- Cephalic presentation
- Planning a vaginal delivery

Exclusion criteria

- Multiple pregnancy
- Maternal body mass index (BMI) >40kg/m^2

- Previous caesarean section
- Known fetal anomaly or aneuploidy
- Known fetal growth restriction (defined as estimated fetal weight <10th centile and abnormal umbilical artery Dopplers)
- Known rupture of membranes

Intervention

Once recruited study participants will be randomised to either receive the screening test (intervention group) or not (control group). Figure 1 outlines the management for participants in both groups. Women in the control group will receive standard antenatal care (appropriate to her pregnancy) as per the hospital's policies and guidelines. The screening test will be a combination of two elements - an ultrasound scan measuring fetal CPR and blood test measuring maternal serum PlGF levels performed between 37+0 to 38+0 weeks gestation.

Ultrasound parameters measured will include fetal biometry, UA PI and MCA PI. The pulsatility indices will be measured from an automated trace of at least three consecutive waveforms of the relevant vessel in the absence of fetal breathing movements or uterine contractions. The angle of insonation will be as close to zero degrees as possible. The UA PI will be recorded from a free-floating section of cord and the MCA PI will be obtained from the proximal third of the vessel, taking care to avoid excessive transducer compression of the fetal head. Each parameter will be recorded three times and a mean of these values used for data analysis. Maternal serum PlGF levels will be quantified using the DELFIA Xpress immunoassay (PerkinElmer, Turku, Finland). The DELFIA platform requires a 40-µL SST plasma sample and reports a concentration in the range of 7–4,000 pg/mL with an overall coefficient of variation of 10.1–5.1% (at 27.6 and 74.2 pg/mL, respectively).

Based on published data from our group[34], a screen positive result (identifying an at risk fetus) is defined as a CPR of $\leq$20th centile AND maternal PlGF level $\leq$33rd centile. Any other combination is considered a screen negative result. Women who screen positive will be advised of

the increased risk of intrapartum fetal compromise and induction of labour within seven days of the test result will be recommended. If she chooses not to be delivered, then weekly fetal surveillance at the discretion of the treating obstetric team will be offered until birth occurs. Women who screen negative will receive standard obstetric care, appropriate to her pregnancy. Intrapartum care (including induction of labour if applicable) for all participants will be as per the hospital's policies and guidelines, however all women who screen positive will receive continuous electronic fetal heart rate monitoring in labour. The only results that will be released to obstetric caregivers is the designation - "screen positive" or "screen negative". However, if the ultrasound scan detects a malpresentation, estimated fetal weight (EFW) <5th or >95th centile or pathological umbilical artery Dopplers (absent or reversed end diastolic flow) the obstetric team caring for the woman will be informed of these findings.

Data collection

Demographic and antenatal data will be collected for all participants from the maternity database and stored in an anonymised and secure format. Collected data will include maternal age, ethnicity, socioeconomic status, body mass index (BMI), history of smoking, previous pregnancy outcomes including mode of delivery and any complications. For the current pregnancy, data collected will include mode of conception, blood pressure at booking, first trimester screening results, presence of hypertensive disorders of pregnancy, diabetes mellitus, thyroid dysfunction, antepartum haemorrhage and maternal medications.

Primary outcome

The primary outcome is a composite measure of adverse outcomes: emergency caesarean section for intrapartum fetal compromise **or** neonatal acidosis (defined as cord arterial pH <7.1 or lactate >6 mmol/L or base excess ≤-12mmol/L) **or** Apgar score ≤5 at 5 minutes **or** stillbirth **or** neonatal death within 28 days. These specific outcomes have been chosen as they indicate significant perinatal asphyxia.

Secondary outcomes

Secondary outcomes include overall operative delivery rates (instrumental and caesarean section) for fetal compromise, and maternal and neonatal morbidity [defined as admission to the neonatal intensive care unit (NICU) for >48 hours or severe respiratory distress (respiratory support >4 hours)].

Sample size calculation

The proposed sample size is based on previous pilot data from our group which found 17.6% of women experienced the primary composite outcome measure. Anticipating a 40% reduction in the proportion of adverse events to 10.6% in the screening test intervention group, a sample size of 382 women is required in each group (type 1 error of 5% and power of 80%). Assuming a 10% drop out rate, we plan to recruit a total of 840 women. There are >5500 publically-funded births at the Mater Mother's Hospital each year. With an estimated 70% of women being eligible to participate it is expected that the required sample size can be recruited within 2 years.

Study review and data monitoring

The study protocol, patient information and consent form and other accompanying material that will be provided to participants have been reviewed and approved by the Mater Human Research Ethics Committee (Reference No: HREC EC00332). The study will be conducted in accordance with the principles of Good Clinical Practice. A Data Safety and Monitoring Committee (DSMC) will be established to oversee any adverse events arising from this study. Members of the DMSC will be external to and independent of the research group and will include an obstetrician, neonatologist and statistician. The study results will be disseminated at national and international conferences and published in peer-reviewed journals. This study has been registered as a clinical trial with the Australian New Zealand Clinical Trials Registry (ANZCTR Trial ID: ACTRN12616001009404 and WHO UTN: U1111-1181-3852). Recruitment for the study commenced in April 2017 and the study is planned to continue until May 2019.

Randomisation

Randomisation will be performed using the *STATA 13* (StataCorp, College Station, Texas) program and will be undertaken by an Epidemiologist within the Mater Research Institute. Participants will be randomised to either screening test or no screening test in equal numbers (1:1) in block sizes of four and six to yield the appropriate sample size. Allocations will be concealed in opaque envelopes until individual randomisation occurs.

Statistical analysis

Outcome comparisons for women and infants will be analysed for the primary and secondary outcomes on an "intention to treat" basis, according to treatment allocation at randomisation. The relative risks and 95% confidence intervals will be reported for the primary outcome (composite adverse outcome), and the number needed to treat to prevent one adverse outcome will be calculated. Subgroup analysis comparing either proportions or means, as appropriate, will be undertaken for elements of the primary composite outcome and secondary outcomes. Regression techniques will be used to examine the influence of prognostic factors on the major primary outcome and secondary outcomes.

Patient and public involvement

100 women from a tertiary antenatal outpatient setting were invited to complete an anonymised patient acceptability questionnaire to elicit their views in regards to participating in a RCT of a screening test for intrapartum fetal compromise. The results of this survey were used to inform the study design. All study participants will be invited to nominate if they would like to receive an email outlining the results of the study after completion.

Figure Legend

Figure 1. Flow chart of study intervention and participant management. CPR – cerebroplacental ratio; PlGF – placental growth factor.

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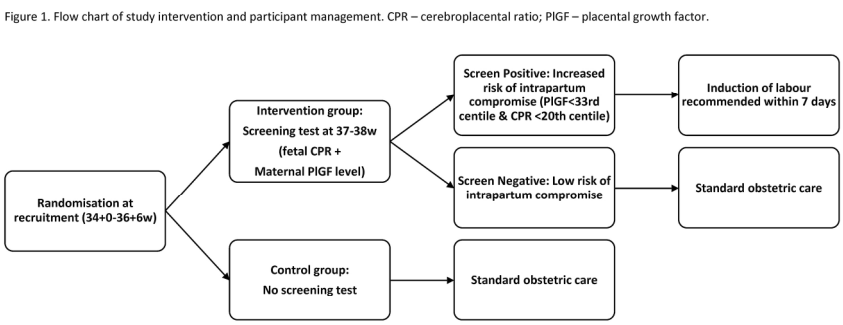

Figure 1. Flow chart of study intervention and participant management. CPR – cerebroplacental ratio; PlGF – placental growth factor.

209x148mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
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	10
	2b	All items from the World Health Organization Trial Registration Data Set	10
Protocol version	3	Date and version identifier	n/a
Funding	4	Sources and types of financial, material, and other support	1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	n/a
	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	n/a
	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)	1 & 10

Introduction			
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	6
	6b	Explanation for choice of comparators	8
Objectives	7	Specific objectives or hypotheses	7
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, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
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	7-11
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)	7-11
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-11
	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)	7-11
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7-11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7-11
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	7-11
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)	7-11

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	7-11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7-11
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, 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	10
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	10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7-11
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection methods	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	7-11
	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	7-11

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9
Statistical methods	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	11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
	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)	11
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10
	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	10
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	10
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	10
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)	10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	10
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	10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	n/a
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10
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	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	10
	31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Ethics approved
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	Ethics approved

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.