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# BMJ Open

## 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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3 1 **Predicting intrapartum fetal compromise at term using the cerebroplacental ratio and placental**  
4 **growth factor levels (PROMISE) study: randomised controlled trial protocol**  
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27 participate in report of the data. SK is the principal investigator (PI) for the study.  
28  
29

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34 17 **Title (short version):** The PROMISE study protocol.  
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## 33 **ABSTRACT**

### 34 **Introduction**

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

### 45 **Methods and analysis**

46 This is a single-site, non-blinded, individual patient randomised controlled trial of a screening test  
47 performed at term, combining the fetal CPR and maternal serum PIGF. Women with a singleton,  
48 non-anomalous pregnancy will be recruited after 34 weeks gestation and randomised to either  
49 receive the screening test or not. Screened pregnancies determined to be at risk will be  
50 recommended induction of labour. Demographic, obstetric history and antenatal data will be  
51 collected at enrolment and perinatal outcomes will be recorded after delivery. Relative risks and  
52 95% confidence intervals will be reported for the primary outcome. Regression techniques will be  
53 used to examine the influence of prognostic factors on the primary and secondary outcomes.

### 54 **Ethics and dissemination**

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

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2  
3 59 **Keywords:** Intrapartum fetal compromise, cerebroplacental ratio, placental growth factor, perinatal  
4  
5 60 outcome, screening test  
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7 61  
8

9 62 **Strengths and limitations of this study**

- 11 63 • Will provide the first high-level evidence of the impact of a screening test combining the  
12 fetal cerebroplacental ratio and maternal placental growth factor on intrapartum fetal  
13 64 compromise and adverse neonatal outcomes.  
14  
15 65  
16  
17 66 • Single-site, randomised controlled trial in a high-income setting.  
18  
19  
20 67 • Unable to blind participants or clinicians to randomisation due to nature of intervention.  
21  
22 68 • Sample-size powered to detect a 40% reduction in a composite outcome indicative of  
23 significant perinatal asphyxia.  
24 69  
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## 72 INTRODUCTION

### 73 Background

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

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

1  
2  
3 98 uterine contractions with acute cerebral redistribution, evidenced by a reduced middle cerebral  
4  
5 99 artery Pulsatility Index (MCA PI). This centralisation of blood flow is identical to that observed  
6  
7 100 chronically in growth restricted fetuses. Some studies suggest that intrauterine pressures of just  
8  
9 101 35mmHg are enough to obliterate uterine artery end diastolic velocities,<sup>8</sup> resulting in reduced  
10  
11 102 placental perfusion. Impaired placental transfer of oxygen and other substrates during labour is  
12  
13 103 likely to be responsible for the “fetal distress” that develops as a consequence of regular uterine  
14  
15 104 contractions. However, up to 63% of babies who become distressed and suffer oxygen deprivation in  
16  
17 105 labour have no apparent prior risk factors.<sup>7</sup>

19  
20 106 The fetal cerebroplacental ratio (CPR) is the ratio of the MCA PI to the Umbilical Artery  
21  
22 107 Pulsatility Index (UA PI). The CPR gradually rises until around the 34<sup>th</sup> week, and subsequently slowly  
23  
24 108 declines until term.<sup>9</sup> In some term small-for-gestational-age (SGA) fetuses, the MCA PI is reduced  
25  
26 109 despite normal UA Doppler indices (i.e. a low CPR) and this is associated with poorer perinatal  
27  
28 110 outcomes<sup>10 11</sup> and adverse neuro-behaviour sequelae.<sup>12</sup> We<sup>13-15</sup> and others<sup>16-18</sup> have established that  
29  
30 111 the CPR is an independent predictor of intrapartum fetal compromise, poor acid base status at birth  
31  
32 112 and of neonatal unit admission at term. In addition, a low CPR may also reflect a failure of a fetus to  
33  
34 113 reach its genetic growth potential at term,<sup>19 20</sup> despite having a normal birth weight. Furthermore, a  
35  
36 114 low CPR has been shown to be associated with an increased risk of stillbirth regardless of the  
37  
38 115 gestation or size of the baby.<sup>21</sup> An ongoing randomised controlled trial (RATIO37),<sup>22</sup> currently in the  
39  
40 116 recruitment phase, aims to determine whether the addition of the CPR to standard ultrasound  
41  
42 117 biometry measured at term can identify fetal growth restriction (FGR) due to placental insufficiency.

44  
45 118 Circulating maternal levels of angiogenic factors such as placental growth factor (PlGF) are  
46  
47 119 lower in pregnancies complicated by placental dysfunction.<sup>23-25</sup> PlGF is a member of the vascular  
48  
49 120 endothelial growth factor (VEGF) family and is predominantly expressed by the placenta. PlGF has a  
50  
51 121 pivotal role in placental angiogenesis and induces vasodilation of uterine and myometrial vessels.<sup>26</sup>  
52  
53 122 This effect is particularly pronounced in uterine arteries during pregnancy, suggesting that PlGF  
54  
55 123 contributes to vascular remodelling during gestation. During the first and second trimesters of

1  
2  
3 124 pregnancy, low maternal levels of PIGF are linked to impaired placental development and  
4  
5 125 angiogenesis, leading to multiple pregnancy complications including miscarriage, stillbirth,  
6  
7 126 preeclampsia, small for gestational age (SGA) infants and FGR.<sup>25 27</sup> Low maternal PIGF levels are also  
8  
9 127 predictive of preeclampsia and FGR when measured in late pregnancy.<sup>24 28 29</sup> PIGF may also help  
10  
11 128 determine whether a fetus is constitutionally small or growth restricted with low PIGF levels  
12  
13 129 associated with histopathological signs of placental underperfusion.<sup>23 30</sup> Furthermore, in women with  
14  
15 130 SGA fetuses, a low PIGF measured in the third trimester is associated with adverse perinatal  
16  
17 131 outcome (emergency caesarean for fetal distress and/or neonatal acidosis).<sup>31</sup> More recently, it has  
18  
19 132 been reported that pre-labour PIGF levels are significantly lower in women that developed  
20  
21 133 intrapartum fetal compromise and have adverse neonatal outcome, even after excluding SGA  
22  
23 134 fetuses.<sup>32</sup>

24  
25  
26 135 We have previously shown that a CPR threshold of <10<sup>th</sup> centile appears to be a good  
27  
28 136 discriminator for identifying fetuses at risk of intrapartum compromise.<sup>33</sup> Our recent publication<sup>34</sup>  
29  
30 137 assessing the utility of a screening test for intrapartum fetal compromise at term incorporating the  
31  
32 138 CPR and maternal PIGF levels showed that the sensitivities, specificities and positive likelihood ratios  
33  
34 139 for cesarean section for intrapartum fetal compromise were 100%, 86%, and 7.14. Combining both  
35  
36 140 measures in the predictive model substantially improved the results of either element alone, raising  
37  
38 141 the possibility that this might be a reasonable way to screen for this complication at term.

#### 142 **Justification for study and hypothesis**

143  
144 In most women although placental function is sufficient to allow appropriate fetal growth  
145  
146 throughout pregnancy, in some it may not be adequate to meet the additional demands required in  
147  
148 the last few weeks of pregnancy or during labour thereby predisposing these vulnerable fetuses to  
149  
150 intrapartum compromise and subsequent risk of serious morbidity and mortality. A strategy to  
151  
152 identify these infants is thus urgently needed. A screening test incorporating the CPR and maternal  
153  
154 PIGF levels could identify these at risk babies. Furthermore, if this screening strategy is combined  
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1  
2  
3 149 with induction of labour for women that screen positive it may reduce the risk of emergency  
4  
5 150 operative birth and serious adverse neonatal outcomes.

## 6 7 151 **OBJECTIVES**

### 8 9 152 **Primary objective**

10  
11 153 To determine if the introduction of a pre-labour screening test at 37-38 weeks of gestation  
12  
13 154 for intrapartum fetal compromise combining the CPR and maternal PIGF level results in a reduction  
14  
15 155 in a composite measure of adverse perinatal outcomes (emergency caesarean for fetal compromise  
16  
17 156 or severe acidosis at birth or five minute Apgar score  $\leq 5$  or death).

### 18 19 157 **Secondary objective**

20  
21 158 To determine if introduction of this screening test results in a reduction in overall operative  
22  
23 159 delivery rates (instrumental and caesarean section) for fetal compromise and neonatal morbidity  
24  
25 160 [defined as admission to the neonatal intensive care unit (NICU) for >48 hours or severe respiratory  
26  
27 161 distress (respiratory support >4 hours)].

## 28 29 162 **METHODS**

### 30 31 163 **Study design**

32  
33 164 This is a single-site (Mater Mothers' Hospital, Brisbane, Australia), non-blinded, individual  
34  
35 165 patient RCT of a screening test performed at term, combining the fetal CPR and maternal serum  
36  
37 166 PIGF. Our study protocol follows the recommendations of the SPIRIT guidance for clinical trials.<sup>35</sup>

### 38 39 167 **Inclusion criteria**

- 40  
41  
42 168
- 43 169 • Women aged between 18-45 years who are able to give informed consent
  - 44 170 • Singleton pregnancy between 34+0 – 37+6 weeks gestation
  - 45 171 • Cephalic presentation
  - 46 172 • Planning a vaginal delivery

### 47 48 173 **Exclusion criteria**

- 49  
50  
51 174
- 52 175 • Multiple pregnancy
  - 53 176 • Maternal body mass index (BMI) >40kg/m<sup>2</sup>

- 1  
2  
3 175 • Previous caesarean section  
4  
5 176 • Known fetal anomaly or aneuploidy  
6  
7 177 • Known fetal growth restriction (defined as estimated fetal weight <10<sup>th</sup> centile and abnormal  
8  
9 178 umbilical artery Dopplers)  
10  
11 179 • Known rupture of membranes  
12

13 180 **Intervention**

14  
15 181 Once recruited study participants will be randomised to either receive the screening test  
16  
17 182 (intervention group) or not (control group). Figure 1 outlines the management for participants in  
18  
19 183 both groups. Women in the control group will receive standard antenatal care as per the hospital's  
20  
21 184 policies and guidelines. The screening test will be a combination of two elements - an ultrasound  
22  
23 185 scan measuring fetal CPR and blood test measuring maternal serum PIGF levels performed between  
24  
25 186 37+0 to 38+0 weeks gestation.  
26  
27

28 187 Ultrasound parameters measured will include fetal biometry, UA PI and MCA PI. The  
29  
30 188 pulsatility indices will be measured from an automated trace of at least three consecutive  
31  
32 189 waveforms of the relevant vessel in the absence of fetal breathing movements or uterine  
33  
34 190 contractions. The angle of insonation will be as close to zero degrees as possible. The UA PI will be  
35  
36 191 recorded from a free-floating section of cord and the MCA PI will be obtained from the proximal  
37  
38 192 third of the vessel, taking care to avoid excessive transducer compression of the fetal head. Each  
39  
40 193 parameter will be recorded three times and a mean of these values used for data analysis. Maternal  
41  
42 194 serum PIGF levels will be quantified using the DELFIA Xpress immunoassay (PerkinElmer, Turku,  
43  
44 195 Finland). The DELFIA platform requires a 40- $\mu$ L SST plasma sample and reports a concentration in the  
45  
46 196 range of 7–4,000 pg/mL with an overall coefficient of variation of 10.1–5.1% (at 27.6 and 74.2  
47  
48 197 pg/mL, respectively).  
49  
50

51 198 Based on pilot data, a screen positive result (identifying an at risk fetus) is defined as a CPR  
52  
53 199 of  $\leq 10^{\text{th}}$  centile AND maternal PIGF level  $\leq 40^{\text{th}}$  centile. Any other combination is considered a screen  
54  
55 200 negative result. Women who screen positive will be advised of the increased risk of intrapartum fetal  
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201 compromise and induction of labour within seven days of the test result will be recommended. If she  
202 chooses not to be delivered, then weekly fetal surveillance at the discretion of the treating obstetric  
203 team will be offered until birth occurs. Women who screen negative will receive standard obstetric  
204 care. Intrapartum care (including induction of labour if applicable) for all participants will be as per  
205 the hospital's policies and guidelines, however all women who screen positive will receive  
206 continuous electronic fetal heart rate monitoring in labour. The only results that will be released to  
207 obstetric caregivers is the designation - "screen positive" or "screen negative". However, if the  
208 ultrasound scan detects a malpresentation, estimated fetal weight (EFW) <5th or >95th centile or  
209 pathological umbilical artery Dopplers (absent or reversed end diastolic flow) the obstetric team  
210 caring for the woman will be informed of these findings.

#### 211 **Data collection**

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

#### 219 **Primary outcome**

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

#### 225 **Secondary outcomes**

226 Secondary outcomes include overall operative delivery rates (instrumental and caesarean  
227 section) for fetal compromise, and maternal and neonatal morbidity [defined as admission to the  
228 neonatal intensive care unit (NICU) for >48 hours or severe respiratory distress (respiratory support  
229 >4 hours)].

### 230 **Sample size calculation**

231 The proposed sample size is based on previous pilot data from our group which found 17.6%  
232 of women experienced the primary composite outcome measure. Anticipating a 40% reduction in  
233 the proportion of adverse events to 10.6% in the screening test intervention group, a sample size of  
234 382 women is required in each group (type 1 error of 5% and power of 80%). Assuming a 10% drop  
235 out rate, we plan to recruit a total of 840 women. There are >5500 publically-funded births at the  
236 Mater Mother's Hospital each year. With an estimated 70% of women being eligible to participate it  
237 is expected that the required sample size can be recruited within 2 years.

### 238 **Study review and data monitoring**

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

### 250 **Randomisation**

1  
2  
3 251 Randomisation will be performed using the *STATA 13* (StataCorp, College Station, Texas)  
4  
5 252 program and will be undertaken by an Epidemiologist within the Mater Research Institute.  
6  
7 253 Participants will be randomised to either screening test or no screening test in equal numbers (1:1)  
8  
9 254 in block sizes of four and six to yield the appropriate sample size. Allocations will be concealed in  
10  
11 255 opaque envelopes until individual randomisation occurs.

### 13 256 **Statistical analysis**

15 257 Outcome comparisons for women and infants will be analysed for the primary and  
16  
17 258 secondary outcomes on an “intention to treat” basis, according to treatment allocation at  
18  
19 259 randomisation. The relative risks and 95% confidence intervals will be reported for the primary  
20  
21 260 outcome (composite adverse outcome), and the number needed to treat to prevent one adverse  
22  
23 261 outcome will be calculated. Subgroup analysis comparing either proportions or means, as  
24  
25 262 appropriate, will be undertaken for elements of the primary composite outcome and secondary  
26  
27 263 outcomes. Regression techniques will be used to examine the influence of prognostic factors on the  
28  
29 264 major primary outcome and secondary outcomes.

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### 36 267 **Figure Legend**

38 268 Figure 1. Flow chart of study intervention and participant management. CPR – cerebroplacental  
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40 269 ratio; PIGF – placental growth factor.

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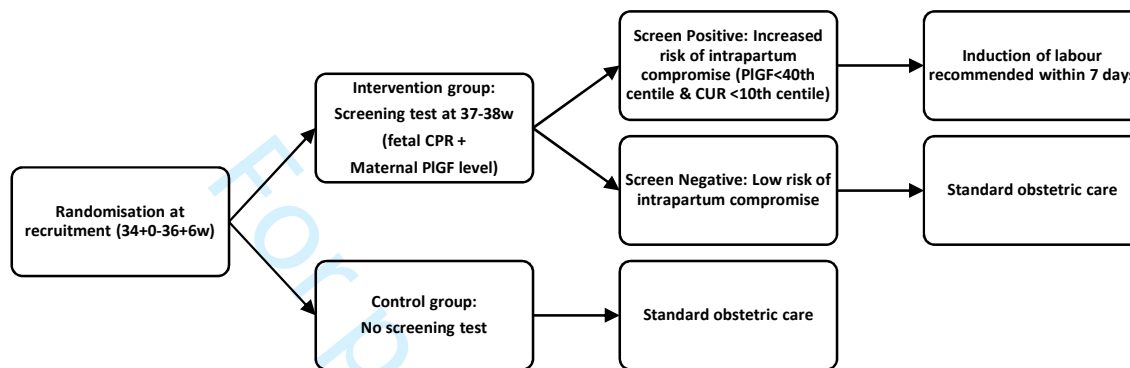
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Figure 1. Flow chart of study intervention and participant management. CPR – cerebroplacental ratio; PIGF – placental growth factor.





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

Section/item	Item No	Description	Addressed on page number
<b>Administrative information</b>			
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

1  
2  
3 Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including 7-11  
4 clinical and statistical assumptions supporting any sample size calculations

5  
6 Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size 7-11  
7

8 **Methods: Assignment of interventions (for controlled trials)**  
9

10 Allocation:

11  
12 Sequence generation 16a Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any 10  
13 factors for stratification. To reduce predictability of a random sequence, details of any planned restriction  
14 (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants  
15 or assign interventions  
16

17 Allocation concealment mechanism 16b Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, 10  
18 opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned  
19  
20

21 Implementation 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to 10  
22 interventions  
23

24 Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome 7-11  
25 assessors, data analysts), and how  
26

27 17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's n/a  
28 allocated intervention during the trial  
29  
30

31 **Methods: Data collection, management, and analysis**  
32

33 Data collection methods 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related 7-11  
34 processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of  
35 study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.  
36 Reference to where data collection forms can be found, if not in the protocol  
37

38 18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be 7-11  
39 collected for participants who discontinue or deviate from intervention protocols  
40  
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44

1				
2				
3	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
4				
5				
6				
7	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
8				
9				
10		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
11				
12		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
13				
14				

### 15 **Methods: Monitoring**

16				
17	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
18				
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21				
22		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
23				
24				
25	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
26				
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28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	10
29				
30				
31				

### 32 **Ethics and dissemination**

33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	10
35				
36				
37	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
38				
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3	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
4				
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6		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	10
7				
8	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
9				
10				
11	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	n/a
12				
13				
14	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
15				
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17	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
18				
19				
20	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
21				
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23				
24				
25		31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
26				
27		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
28				
29	<b>Appendices</b>			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Ethics approved
32				
33				
34	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
35				
36				

37 \*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.  
 38 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons  
 39 "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.  
 40

# BMJ Open

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

Journal:	<i>BMJ Open</i>
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<b>Primary Subject Heading</b>:	Obstetrics and gynaecology
Secondary Subject Heading:	Obstetrics and gynaecology
Keywords:	Intrapartum fetal compromise, cerebroplacental ratio, placental growth factor, perinatal outcome, screening test

SCHOLARONE™  
Manuscripts



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3 1 **Predicting intrapartum fetal compromise at term using the cerebroplacental ratio and placental**  
4 **growth factor levels (PROMISE) study: randomised controlled trial protocol**  
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7 3  
8  
9 4 **Helen Sherrell<sup>1</sup>, Vicki Clifton<sup>1</sup>, Sailesh Kumar<sup>1,2,3</sup>**

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17 Queensland, Brisbane, Australia.  
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20  
21

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24

25  
26 **Authors' contributions:** HS is the study coordinator, contributed to study planning, will collect and  
27 analyse the data and will participate in reporting the data. VC contributed to study planning and will  
28 participate in report of the data. SK is the principal investigator (PI) for the study.  
29  
30

31 The authors report **no conflicts of interest.**  
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38 **Title (short version):** The PROMISE study protocol.  
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## 33 **ABSTRACT**

### 34 **Introduction**

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

### 45 **Methods and analysis**

46 This is a single-site, non-blinded, individual patient randomised controlled trial of a screening test  
47 performed at term, combining the fetal CPR and maternal serum PlGF. Women with a singleton,  
48 non-anomalous pregnancy will be recruited after 34 weeks gestation and randomised to either  
49 receive the screening test or not. Screened pregnancies determined to be at risk will be  
50 recommended induction of labour. Demographic, obstetric history and antenatal data will be  
51 collected at enrolment and perinatal outcomes will be recorded after delivery. Relative risks and  
52 95% confidence intervals will be reported for the primary outcome. Regression techniques will be  
53 used to examine the influence of prognostic factors on the primary and secondary outcomes.

### 54 **Ethics and dissemination**

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

1  
2  
3 59 **Keywords:** Intrapartum fetal compromise, cerebroplacental ratio, placental growth factor, perinatal  
4  
5 60 outcome, screening test  
6  
7 61  
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9 62

10 **Strengths and limitations of this study**

- 11 • Will provide the first high-level evidence of the impact of a screening test combining the  
12 fetal cerebroplacental ratio and maternal placental growth factor on intrapartum fetal  
13 64 compromise and adverse neonatal outcomes.  
14  
15 65  
16  
17 66 • Single-site, randomised controlled trial in a high-income setting.  
18  
19 67 • Unable to blind participants or clinicians to randomisation due to nature of intervention.  
20  
21 68 • Sample-size powered to detect a 40% reduction in a composite outcome indicative of  
22 69 significant perinatal asphyxia.  
23  
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## 72 INTRODUCTION

### 73 Background

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

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

1  
2  
3 98 to oxygenate the fetus as labour progresses. The fetus responds to uterine contractions with acute  
4  
5 99 cerebral redistribution, evidenced by a reduced middle cerebral artery Pulsatility Index (MCA PI).  
6  
7 100 This centralisation of blood flow is identical to that observed chronically in growth restricted fetuses.  
8  
9 101 Some studies suggest that intrauterine pressures of just 35mmHg are enough to obliterate uterine  
10  
11 102 artery end diastolic velocities,<sup>8</sup> resulting in reduced placental perfusion. Impaired placental transfer  
12  
13 103 of oxygen and other substrates during labour is likely to be responsible for the “fetal distress” that  
14  
15 104 develops as a consequence of regular uterine contractions. However, up to 63% of babies who  
16  
17 105 become distressed and suffer oxygen deprivation in labour have no apparent prior risk factors.<sup>7</sup>

18  
19  
20 106 The fetal cerebroplacental ratio (CPR) is the ratio of the MCA PI to the Umbilical Artery  
21  
22 107 Pulsatility Index (UA PI). The CPR gradually rises until around the 34<sup>th</sup> week, and subsequently slowly  
23  
24 108 declines until term.<sup>9</sup> In some term small-for-gestational-age (SGA) fetuses, the MCA PI is reduced  
25  
26 109 despite normal UA Doppler indices (i.e. a low CPR) and this is associated with poorer perinatal  
27  
28 110 outcomes<sup>10 11</sup> and adverse neuro-behaviour sequelae.<sup>12</sup> We<sup>13-15</sup> and others<sup>16-18</sup> have established that  
29  
30 111 the CPR is an independent predictor of intrapartum fetal compromise, poor acid base status at birth  
31  
32 112 and of neonatal unit admission at term. In addition, a low CPR may also reflect a failure of a fetus to  
33  
34 113 reach its genetic growth potential at term,<sup>19 20</sup> despite having a normal birth weight. Furthermore, a  
35  
36 114 low CPR has been shown to be associated with an increased risk of stillbirth regardless of the  
37  
38 115 gestation or size of the baby.<sup>21</sup> An ongoing randomised controlled trial (RATIO37),<sup>22</sup> currently in the  
39  
40 116 recruitment phase, aims to determine whether the addition of the CPR to standard ultrasound  
41  
42 117 biometry measured at term can identify fetal growth restriction (FGR) due to placental insufficiency.

43  
44  
45 118 Circulating maternal levels of angiogenic factors such as placental growth factor (PlGF) are  
46  
47 119 lower in pregnancies complicated by placental dysfunction.<sup>23-25</sup> PlGF belongs to the vascular  
48  
49 120 endothelial growth factor (VEGF) family and is primarily produced by the placenta. It plays a key role  
50  
51 121 in placental angiogenesis and vascular remodelling and is known to stimulate dilation of myometrial  
52  
53 122 and uterine vessels.<sup>26</sup> This effect is particularly pronounced in uterine arteries during pregnancy,  
54  
55 123 suggesting that PlGF contributes to vascular remodelling during gestation. During the first and

1  
2  
3 124 second trimesters of pregnancy, low maternal levels of PIGF are linked to impaired placental  
4  
5 125 development and angiogenesis, leading to multiple pregnancy complications including miscarriage,  
6  
7 126 stillbirth, preeclampsia, small for gestational age (SGA) infants and FGR.<sup>25 27</sup> Low maternal PIGF levels  
8  
9 127 are also predictive of preeclampsia and FGR when measured in late pregnancy.<sup>24 28 29</sup> PIGF may also  
10  
11 128 help determine whether a fetus is constitutionally small or growth restricted with low PIGF levels  
12  
13 129 associated with histopathological signs of placental underperfusion.<sup>23 30</sup> Furthermore, in women with  
14  
15 130 SGA fetuses, a low PIGF measured in the third trimester is associated with adverse perinatal  
16  
17 131 outcome (emergency caesarean for fetal distress and/or neonatal acidosis).<sup>31</sup> More recently, it has  
18  
19 132 been reported that pre-labour PIGF levels are significantly lower in women that developed  
20  
21 133 intrapartum fetal compromise and have adverse neonatal outcome, even after excluding SGA  
22  
23 134 fetuses.<sup>32</sup>

24  
25  
26 135 We have previously shown that a CPR threshold of <10<sup>th</sup> centile appears to be a good  
27  
28 136 discriminator for identifying fetuses at risk of intrapartum compromise.<sup>33</sup> Our recent publication<sup>34</sup>  
29  
30 137 assessing the utility of a screening test for intrapartum fetal compromise at term incorporating the  
31  
32 138 CPR and maternal PIGF levels showed that the sensitivities, specificities and positive likelihood ratios  
33  
34 139 for cesarean section for intrapartum fetal compromise were 100%, 86%, and 7.14. Combining both  
35  
36 140 measures in the predictive model substantially improved the results of either element alone, raising  
37  
38 141 the possibility that this might be a reasonable way to screen for this complication at term.

#### 142 **Justification for study and hypothesis**

143  
144 In most women although placental function is sufficient to allow appropriate fetal growth  
145  
146 throughout pregnancy, in some it may not be adequate to meet the additional demands required in  
147  
148 the last few weeks of pregnancy or during labour thereby predisposing these vulnerable fetuses to  
149  
150 intrapartum compromise and subsequent risk of serious morbidity and mortality. A strategy to  
151  
152 identify these infants is thus urgently needed. A screening test incorporating the CPR and maternal  
153  
154 PIGF levels could identify these at risk babies. Furthermore, if this screening strategy is combined  
155  
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1  
2  
3 149 with induction of labour for women that screen positive it may reduce the risk of emergency  
4  
5 150 operative birth and serious adverse neonatal outcomes.

## 6 7 151 **OBJECTIVES**

### 8 9 152 **Primary objective**

10  
11 153 To determine if the introduction of a pre-labour screening test at 37-38 weeks of gestation  
12  
13 154 for intrapartum fetal compromise combining the CPR and maternal PIGF level results in a reduction  
14  
15 155 in a composite measure of adverse perinatal outcomes (emergency caesarean for fetal compromise  
16  
17 156 or severe acidosis at birth or five minute Apgar score  $\leq 5$  or death).

### 18 19 157 **Secondary objective**

20  
21 158 To determine if introduction of this screening test results in a reduction in overall operative  
22  
23 159 delivery rates (instrumental and caesarean section) for fetal compromise and neonatal morbidity  
24  
25 160 [defined as admission to the neonatal intensive care unit (NICU) for >48 hours or severe respiratory  
26  
27 161 distress (respiratory support >4 hours)].

## 28 29 162 **METHODS**

### 30 31 163 **Study design**

32  
33 164 This is a single-site (Mater Mothers' Hospital, Brisbane, Australia), non-blinded, individual  
34  
35 165 patient RCT of a screening test performed at term, combining the fetal CPR and maternal serum  
36  
37 166 PIGF. Our study protocol follows the recommendations of the SPIRIT guidance for clinical trials.<sup>35</sup>

### 38 39 167 **Inclusion criteria**

- 40  
41  
42 168
- 43 169 • Women aged between 18-45 years who are able to give informed consent
  - 44 170 • Singleton pregnancy between 34+0 – 37+6 weeks gestation
  - 45 171 • Cephalic presentation
  - 46 172 • Planning a vaginal delivery

### 47 48 172 **Exclusion criteria**

- 49  
50  
51 173
- 52 174 • Multiple pregnancy
  - 53 175 • Maternal body mass index (BMI) >40kg/m<sup>2</sup>

- 1  
2  
3 175 • Previous caesarean section  
4  
5 176 • Known fetal anomaly or aneuploidy  
6  
7 177 • Known fetal growth restriction (defined as estimated fetal weight <10<sup>th</sup> centile and abnormal  
8  
9 178 umbilical artery Dopplers)  
10  
11 179 • Known rupture of membranes  
12

### 13 180 **Intervention**

14  
15 181 Once recruited study participants will be randomised to either receive the screening test  
16  
17 182 (intervention group) or not (control group). Figure 1 outlines the management for participants in  
18  
19 183 both groups. Women in the control group will receive standard antenatal care (appropriate to her  
20  
21 184 pregnancy) as per the hospital's policies and guidelines. The screening test will be a combination of  
22  
23 185 two elements - an ultrasound scan measuring fetal CPR and blood test measuring maternal serum  
24  
25 186 PIGF levels performed between 37+0 to 38+0 weeks gestation.  
26  
27

28 187 Ultrasound parameters measured will include fetal biometry, UA PI and MCA PI. The  
29  
30 188 pulsatility indices will be measured from an automated trace of at least three consecutive  
31  
32 189 waveforms of the relevant vessel in the absence of fetal breathing movements or uterine  
33  
34 190 contractions. The angle of insonation will be as close to zero degrees as possible. The UA PI will be  
35  
36 191 recorded from a free-floating section of cord and the MCA PI will be obtained from the proximal  
37  
38 192 third of the vessel, taking care to avoid excessive transducer compression of the fetal head. Each  
39  
40 193 parameter will be recorded three times and a mean of these values used for data analysis. Maternal  
41  
42 194 serum PIGF levels will be quantified using the DELFIA Xpress immunoassay (PerkinElmer, Turku,  
43  
44 195 Finland). The DELFIA platform requires a 40- $\mu$ L SST plasma sample and reports a concentration in the  
45  
46 196 range of 7–4,000 pg/mL with an overall coefficient of variation of 10.1–5.1% (at 27.6 and 74.2  
47  
48 197 pg/mL, respectively).  
49  
50

51 198 Based on published data from our group<sup>34</sup>, a screen positive result (identifying an at risk  
52  
53 199 fetus) is defined as a CPR of  $\leq 20^{\text{th}}$  centile AND maternal PIGF level  $\leq 33^{\text{rd}}$  centile. Any other  
54  
55 200 combination is considered a screen negative result. Women who screen positive will be advised of  
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1  
2  
3 201 the increased risk of intrapartum fetal compromise and induction of labour within seven days of the  
4  
5 202 test result will be recommended. If she chooses not to be delivered, then weekly fetal surveillance at  
6  
7 203 the discretion of the treating obstetric team will be offered until birth occurs. Women who screen  
8  
9 204 negative will receive standard obstetric care, appropriate to her pregnancy. Intrapartum care  
10  
11 205 (including induction of labour if applicable) for all participants will be as per the hospital's policies  
12  
13 206 and guidelines, however all women who screen positive will receive continuous electronic fetal heart  
14  
15 207 rate monitoring in labour. The only results that will be released to obstetric caregivers is the  
16  
17 208 designation - "screen positive" or "screen negative". However, if the ultrasound scan detects a  
18  
19 209 malpresentation, estimated fetal weight (EFW) <5th or >95th centile or pathological umbilical artery  
20  
21 210 Dopplers (absent or reversed end diastolic flow) the obstetric team caring for the woman will be  
22  
23 211 informed of these findings.

#### 212 **Data collection**

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

#### 220 **Primary outcome**

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

#### 226 **Secondary outcomes**

227 Secondary outcomes include overall operative delivery rates (instrumental and caesarean  
228 section) for fetal compromise, and maternal and neonatal morbidity [defined as admission to the  
229 neonatal intensive care unit (NICU) for >48 hours or severe respiratory distress (respiratory support  
230 >4 hours)].

### 231 **Sample size calculation**

232 The proposed sample size is based on previous pilot data from our group which found 17.6%  
233 of women experienced the primary composite outcome measure. Anticipating a 40% reduction in  
234 the proportion of adverse events to 10.6% in the screening test intervention group, a sample size of  
235 382 women is required in each group (type 1 error of 5% and power of 80%). Assuming a 10% drop  
236 out rate, we plan to recruit a total of 840 women. There are >5500 publically-funded births at the  
237 Mater Mother's Hospital each year. With an estimated 70% of women being eligible to participate it  
238 is expected that the required sample size can be recruited within 2 years.

### 239 **Study review and data monitoring**

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

### 251 **Randomisation**

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

### 257 **Statistical analysis**

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

### 266 **Patient and public involvement**

267 100 women from a tertiary antenatal outpatient setting were invited to complete an  
268 anonymised patient acceptability questionnaire to elicit their views in regards to participating in a  
269 RCT of a screening test for intrapartum fetal compromise. The results of this survey were used to  
270 inform the study design. All study participants will be invited to nominate if they would like to  
271 receive an email outlining the results of the study after completion.

### 273 **Figure Legend**

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

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

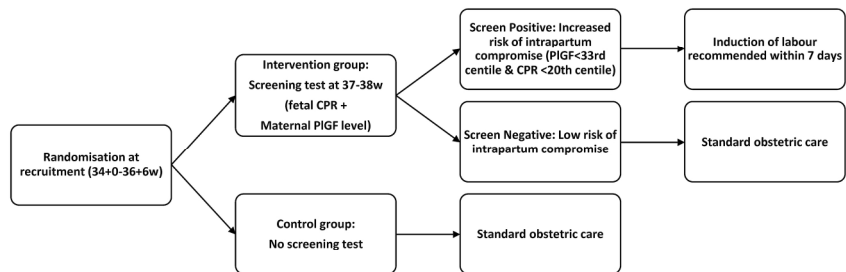


Figure 1. Flow chart of study intervention and participant management. CPR – cerebroplacental ratio; PIGF – placental growth factor.

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
<b>Administrative information</b>			
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

1  
2  
3 Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including 7-11  
4 clinical and statistical assumptions supporting any sample size calculations

5  
6 Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size 7-11  
7

8 **Methods: Assignment of interventions (for controlled trials)**  
9

10 Allocation:

11  
12 Sequence generation 16a Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any 10  
13 factors for stratification. To reduce predictability of a random sequence, details of any planned restriction  
14 (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants  
15 or assign interventions

16  
17 Allocation concealment mechanism 16b Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, 10  
18 opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned  
19

20  
21 Implementation 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to 10  
22 interventions

23  
24 Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome 7-11  
25 assessors, data analysts), and how

26  
27 17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's n/a  
28 allocated intervention during the trial  
29  
30

31 **Methods: Data collection, management, and analysis**  
32

33 Data collection methods 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related 7-11  
34 processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of  
35 study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.  
36 Reference to where data collection forms can be found, if not in the protocol

37  
38 18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be 7-11  
39 collected for participants who discontinue or deviate from intervention protocols  
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3	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
4				
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6				
7	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
8				
9				
10		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
11				
12		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
13				
14				

### 15 **Methods: Monitoring**

16				
17	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
18				
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22		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
23				
24				
25	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
26				
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28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	10
29				
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31				

### 32 **Ethics and dissemination**

33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	10
35				
36				
37	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
38				
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3	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
4				
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6		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	10
7				
8	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
9				
10				
11	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	n/a
12				
13				
14	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
15				
16				
17	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
18				
19				
20	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
21				
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25		31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
26				
27		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
28				
29	<b>Appendices</b>			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Ethics approved
32				
33				
34	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
35				
36				

37 \*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.  
 38 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons  
 39 "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.  
 40