PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Predicting intrapartum fetal compromise at term using the cerebroplacental ratio and placental growth factor levels (PROMISE) study: randomised controlled trial protocol
AUTHORS	Sherrell, Helen; Clifton, Vicky; Kumar, Sailesh

VERSION 1 – REVIEW

REVIEWER	Francesc Figueras University of Barcelona
REVIEW RETURNED	27-Mar-2018

GENERAL COMMENTS	The research question is relevant, the background for it is sound and the researchers have an excellent track on it. The design is appropriate. Altogether, the study has the potential to bring good evidence on the impact of a pre-labor screening. Minor issues I missed the expected rate for screened +: they say that based on a pilot study women will qualify for positive if PLGF<40th centile and CPR<10th. However, from a previous publication of the same group the best prediction was achieved by a combination of the CPR< 20th and placental growth factor <33rd. Please clarify it. I missed a paragraph on the study potential limitations. What would be the management of a woman with risk factors (for instance a previous PE) in the control group? According to figure 1, a “no-screening” will be followed. According the text, she would receive “standard obstetrical care”. Are there no indications for serial US scanning in their local guidelines? Major issue My main concern has to do with the sample size. Their aimed reduction of 40% of adverse outcomes seems to me over-optimistic, and has the risk of resulting in underpowered findings. An aimed reduction of 30% would require 716 patients per arm, and a 20% reduction of 1688. I would strongly recommend increasing the sample size to avoid such risk.

REVIEWER	Sue Walker University of Melbourne, Mercy Health
REVIEW RETURNED	30-Mar-2018

GENERAL COMMENTS	Many thanks for asking me to review this protocol. The paper is well written and the case for the trial is cogently argued. This is an important area of contemporary research and the trial proposed is well supported by their preliminary data. My only concern relates to the anticipated magnitude of effect, although more supportive data

	from their previous studies may clarify this and support the proposed sample size. What proportion of the population are expected to be screen positive? In their previous paper using this combined strategy, very different thresholds were chosen to generate 100% sensitivity with 20% PPV (ie 20th centile CPR and 33rd for PlGF). This combined test had a FPR of 14%. We don't have the data to know what the screen positive rate will be of this combination, but if it was similar, approx 54 out of 382 in the intervention arm would be screen positive. Is the hospital able to support the increased surveillance/ induction rate of 14%? To expect that the adverse outcome (CS for non reassuring fetal status) of 17.6% will reduce to 10% means that there will be approx 68 in the observation group compared to 38 in the intervention group (reduction of n=30). I guess it is assumed that this will occur through earlier induction (presumably before worsening of placental function) in the screen positive group, but would mean this would have to almost halve the CS rate in this group (54 goes down to 30). It's impossible to know, of course, but this seems optimistic. Also, can you confirm intention to treat, ie those with ARED or EFW<5th stay in the intervention group? They will have a higher CS for NFS, but shouldn't be excluded as this would bias toward effect. There are limitations in using non reassuring CTG as an indicator of intrapartum fetal compromise contributing to primary outcome. This outcome isn't particularly specific as 'indicating significant perinatal asphyxia'. I accept it is pragmatic endpoint but suggest it would be preferable to get objective measures (cord pH or scalp lactate) in as many as possible (even though it will reduce the numbers experiencing the primary outcome) My only minor comment is in second paragraph introduction where an additional few words are required: 'This results in a gradual deterioration of the fetal condition reflecting a steady decline in the ability of the placenta (to what? 'oxygenate the fetus' for example) as labour progresses'

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

"I missed the expected rate for screened +: they say that based on a pilot study women will qualify for positive if PLGF<40th centile and CPR<10th. However, from a previous publication of the same group the best prediction was achieved by a combination of the CPR< 20th and placental growth factor <33rd. Please clarify it."
The initial CPR and PlGF centile thresholds for the screening test were based on unpublished preliminary pilot data from a low risk population at the study site hospital generated by our research group in late 2015. Since then our research group has expanded this sample population, reanalysed the data and recently published this new data in late 2017 (Bligh et al (2017), reference #34 in the protocol. As you note, the best prediction was achieved using the combination of CPR <20th centile AND maternal PlGF level <33rd centile. Since submitting our original manuscript we have subsequently had an Ethics amendment approved to change the screening test thresholds to reflect our most current published data. The methods section of the manuscript has been updated accordingly.

"I missed a paragraph on the study potential limitations."

The potential limitations (and strengths) of the study are outlined in bullet points in a section immediately following the abstract.

"What would be the management of a woman with risk factors (for instance a previous PE) in the control group? According to figure 1, a “no-screening” will be followed. According the text, she would receive “standard obstetrical care”. Are there no indications for serial US scanning in their local guidelines?"
To clarify, “standard obstetric care” will be tailored to the individual women’s pregnancy and risk factors (independent of the study). For example if a woman recruited to the control group developed pre-eclampsia she would be managed as per the hospital’s policy for pre-eclampsia which includes initial admission, US scan for fetal wellbeing, etc. We have amended the manuscript to include the comment “appropriate to her pregnancy” after the mention of “standard obstetric care”.

"My main concern has to do with the sample size. Their aimed reduction of 40% of adverse outcomes seems to me over-optimistic, and has the risk of resulting in underpowered findings. An aimed reduction of 30% would require 716 patients per arm, and a 20% reduction of 1688. I would strongly recommend increasing the sample size to avoid such risk."
We plan to conduct an interim analysis once 200 participants have been recruited to assess the proportion of participants in the control group experiencing the primary composite outcome and the magnitude of the difference when comparing the two groups. We are certainly open to the possibility of increasing the sample size (and lowering the treatment effect) following the interim analysis.

Reviewer 2

"My only concern relates to the anticipated magnitude of effect, although more supportive data from their previous studies may clarify this and support the proposed sample size."
Please see response to similar query from Reviewer 1.

"What proportion of the population are expected to be screen positive?"
It is estimated that approximately 10% of the screening group will have a positive result.

"In their previous paper using this combined strategy, very different thresholds were chosen to generate 100% sensitivity with 20% PPV (ie 20th centile CPR and 33rd for PlGF). This combined test had a FPR of 14%. We don't have the data to know what the screen positive rate will be of this combination, but if it was similar, approx 54 out of 382 in the intervention arm would be screen positive. Is the hospital able to support the increased surveillance/ induction rate of 14%?"
Given our expected screen positive rate of 10%, we anticipate approximately 42 additional women will require induction over the 2 year recruiting period. As a part of the Research Governance process, approval and support for the study were obtained from the Heads of Obstetrics and Midwifery, including acknowledging the capability of the birth suite to manage the small increase in inductions.

"To expect that the adverse outcome (CS for non reassuring fetal status) of 17.6% will reduce to 10% means that there will be approx 68 in the observation group compared to 38 in the intervention group (reduction of n=30). I guess it is assumed that this will occur through earlier induction (presumably before worsening of placental function) in the screen positive group, but would mean this would have to almost halve the CS rate in this group (54 goes down to 30). It's impossible to know, of course, but this seems optimistic."
The primary outcome is a composite that includes any one of CS for intrapartum fetal compromise, neonatal acidosis, 5-minute Apgar ≤5 or perinatal death. As such, the emergency CS rate would not necessarily need to halve in order to achieve this difference. To achieve our desired 40% reduction in the composite outcome we expect approximately 67 women in the control group to have the

composite outcome compared to approximately 40 women in the intervention group (reduction of n=27).

"Also, can you confirm intention to treat, ie those with ARED or EFW<5th stay in the intervention group? They will have a higher CS for NFS, but shouldn't be excluded as this would bias toward effect."
Yes, any participant randomised to the screening test group will be included in the outcome analyses regardless of any abnormalities that develop or are identified after randomisation. However, known FGR or ARED are exclusion criteria and women with these conditions already diagnosed would not be recruited initially.

"There are limitations in using non reassuring CTG as an indicator of intrapartum fetal compromise contributing to primary outcome. This outcome isn't particularly specific as 'indicating significant perinatal asphyxia'. I accept it is pragmatic endpoint but suggest it would be preferable to get objective measures (cord pH or scalp lactate) in as many as possible (even though it will reduce the numbers experiencing the primary outcome)."
Determining whether an emergency CS is performed for presumed intrapartum fetal compromise will be at the discretion of the obstetric team managing the woman's labour. The primary indication for the CS delivery is recorded in the operation notes and hospital's maternity database. This decision is often made on the basis of intrapartum CTG abnormalities but a proportion of women will also have fetal scalp lactate measurements during their labour (if these occur they will also be recorded). We agree that more objective measures of perinatal asphyxia are ideal and all women in the study (both control and intervention groups) will be consented to have cord blood analysis at delivery regardless of the mode of birth.

"My only minor comment is in second paragraph introduction where an additional few words are required: 'This results in a gradual deterioration of the fetal condition reflecting a steady decline in the ability of the placenta (to what? 'oxygenate the fetus' for example) as labour progresses'."
The suggested additional words have been added to this paragraph in the introduction.

Formatting Amendments

"Kindly re-upload FIGURE in either TIFF or JPG format with at least 300 dpi resolution."
The figure has been re-formatted and re-uploaded.

"Authors must include a statement in the methods section of the manuscript under the sub-heading 'Patient and Public Involvement'."
This statement has been included in the methods section.

VERSION 2 – REVIEW

REVIEWER	Sue Walker Mercy Hospital for Women, University of Melbourne
REVIEW RETURNED	22-Jun-2018

GENERAL COMMENTS	Thank you for undertaking these revisions. I thank the authors for the additional clarification in particular regarding screen positive thresholds and expected screen positive rate. Although I have residual concerns regarding power of the study, I am reassured by the proposed interim analysis which will identify whether the composite adverse outcome is occurring as expected in the control and intervention group.