BMJ Open

PARROT Ireland: (Placental growth factor in Assessment of women with suspected pre-eclampsia to Reduce maternal morbidity: a Stepped Wedge Cluster Randomised Control Trial) Research Study Protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-023562
Article Type:	Protocol
Date Submitted by the Author:	12-Apr-2018
Complete List of Authors:	Hayes Ryan, Deirdre; The Irish Centre for Fetal and Neonatal Translational Research (INFANT), UCC, Cork; Dept. of Obstetrics and Gynaecology, University College Cork Hemming, Karla; University of Birmingham, Public Health Brethnach, FIONNUALA; Rotunda Hospital, Royal College of Surgeons in Ireland, Dublin Cotter, Amanda; Department of Obstetrics and Gynaecology, Graduate Entry Medical School, University of Limerick Devane, Declan; HRB Trials Methodology Research Network; National Univeristy of Ireland, Galway Hunter, Alyson; Royal Maternity Hospital, Grosvenor Road, BT12 6BB McAuliffe, Fionnuala; Perinatal Research Centre, Obstetrics & Gynaecology, School of Medicine, University College Dublin, National Maternity Hospital, Dublin, Ireland Morrison, John; National University of Ireland Galway, Obstetrics and Gynaecology Murphy, Deirdre; Trinity College Dublin & Coombe Women & Infants University Hospital Dublin 8, Republic of Ireland Khashan, Ali; University College Cork, Department of Epidemiology and Public Health; The Irish Centre for Fetal and Neonatal Translational Research (INFANT), University College Cork, Ireland McElroy, Brendan; Economics Department, University College Cork, Cork, Ireland Murphy , A; University College Cork, Economics Department Dempsey, E; University College Cork, Department of Paediatrics and Child Health; The Irish Centre for Fetal and Neonatal Translational Research (INFANT), University College Cork, Ireland O'Donoghue, Keelin; Dept. of Obstetrics and Gynaecology, University College Cork; The Irish Centre for Fetal and Neonatal Translational Research (INFANT), University College Cork, Ireland Kenny, Louise; University of Liverpool School of Life Sciences, Department of Women's and Children's Health; The Irish Centre for Fetal and Neonatal Translational Research (INFANT), University College Cork, Ireland
Keywords:	Pre-eclampsia, placental growth factor, stepped wedge cluster randomised trial, point of care diagnostic test

PARROT Ireland: (Placental growth factor in Assessment of women with suspected pre-eclampsia to Reduce maternal morbidity: a Stepped Wedge Cluster Randomised Control Trial) Research Study Protocol

*Corresponding author
Deirdre Hayes-Ryan[1,2*]
Email: deirdre.hayesryan@ucc.ie

Karla Hemming[3]
Email: k.hemming@bham.ac.uk

Fionnaula Breathnaeach[4]
Email: fbreathnach@rcsi.ie

Amanda Cotter[5]
Email: amanda.cotter@ul.ie`

Declan Devane[1,6,7]
Email: declan.devane@nuigalway.ie

Ali Hunter[8]
Email: alyson.hunter@belfasttrust.hscni.net

Fionnaula M McAuliffe[9]
Email: fionnuala.mcauliffe@ucd.ie

John Morrisson[7]
Email: john.morrison@nuigalway.ie

Deirdre J Murphy[10]
Email: MURPHYD4@tcd.ie

Ali Kashan[1,11]
Email: a.khashan@ucc.ie

Brendan McElroy[12]
Email: b.mcelroy@ucc.ie

Aileen Murphy[12]
Email: aileen.murphy@ucc.ie

Eugene Dempsey[1,2]
Email: G.Dempsey@ucc.ie

Keelin O'Donoghue[1,2]
Email: k.odonoghue@ucc.ie

Louise C Kenny[1,13]
Email: L.Kenny@ucc.ie

[1]The Irish Centre for Fetal and Neonatal Translational Research (INFANT), University College Cork, Ireland
[2]Cork University Maternity Hospital, Cork, Ireland
[3]University of Birmingham, United Kingdom
[4]Rotunda Hospital, Parnell Square W, Dublin 1, Ireland
[5]University Maternity Hospital Limerick
[6]HRB Trials Methodology Research Network
[7]National University of Ireland, Galway, Ireland
[8]Royal Jubilee Maternity Hospital, Belfast, Northern Ireland
[9]Perinatal Research Centre, Obstetrics & Gynaecology, School of Medicine, University College Dublin, National Maternity Hospital, Dublin, Ireland
[10]Trinity College Dublin & Coombe Women & Infants University Hospital Dublin 8, Republic of Ireland
[11] School of Public Health, University College Cork, Cork, Ireland
[12]Economics Department, University College Cork, Cork, Ireland
[13] Department of Women's and Children's Health, Liverpool Women's Hospital, University of Liverpool, UK

Abstract

Background

Women presenting with suspected pre-eclampsia are currently triaged on the basis of hypertension and dipstick proteinuria. This may result in significant false positive and negative diagnoses resulting in increased morbidity or unnecessary intervention. Recent data suggests that placental growth factor testing may be a useful adjunct in the management of women presenting with preterm pre-eclampsia. The primary objective of this trial is to determine if the addition of placental growth factor testing to the current clinical assessment of women with suspected preterm pre-eclampsia, is beneficial for both mothers and babies.

Methods

This is a multicentre, stepped wedge cluster, randomised trial aiming to recruit 4000 women presenting with symptoms suggestive of preterm pre-eclampsia between 20 and 36+6 weeks' gestation. The intervention of an unblinded point of care test, performed at enrolment, will quantify maternal levels of circulating plasma placental growth factor. The intervention will be rolled out sequentially, based on randomisation, in the seven largest maternity units on the island of Ireland. Primary outcome is a composite outcome of maternal morbidity (derived from the modified fullPIERS model). To ensure we are not reducing maternal morbidity at the expense of earlier delivery and worse neonatal outcomes, we have established a co-primary outcome which will examine the effect of the intervention on neonatal morbidity, assessed using a composite neonatal score. Secondary outcomes include mode of delivery, antenatal detection of growth restriction and use of antihypertensive agents as well as the health economic impact of incorporation of placental growth factor testing into routine care.

Discussion

This trial will assess the impact of incorporating placental growth factor measurement to the current clinical assessment of women with suspected pre-eclampsia prior to 37 weeks' gestation on maternal, neonatal and health economic outcomes. We hypothesise the addition of placental growth factor measurement will reduce associated maternal morbidity and neonatal morbidity, through improved risk stratification, earlier diagnosis and therefore targeted management of women with the disease and their neonates. If this trial demonstrates a beneficial impact on maternal morbidity and/or neonatal morbidity there will be a strong case for incorporating placental growth factor into routine diagnostic testing and management for women presenting with suspected pre-eclampsia before 37 weeks' gestation.

Strengths and limitations of this study

- Randomised Trial
- Multiple sites with wide geographic distribution
- Stepped wedge design

Trial registration

Clinical Trials NCT02881073 (26th August 2016)

Keywords

Pre-eclampsia, placental growth factor, PlGF, diagnostic test, point of care, stepped wedge cluster randomised controlled trial

Background

Pre-eclampsia (PET) is characterised by hypertension and proteinuria, complicates 2-8% of pregnancies, and is associated with significant maternal and neonatal morbidity and mortality (1). Currently women who present with suspected pre-eclampsia are triaged on the basis of hypertension and dipstick proteinuria. Both of these clinical endpoints are subject to observer error and poor test accuracy, with false positive and negative diagnoses of pre-eclampsia occurring in clinical practice (2-5). Current biochemical tests are imperfect at stratifying women for more intensive surveillance as they only identify advanced disease where there is already marked end-organ damage (6). While biomarkers and imaging techniques have been evaluated for improving detection, none have adequate sensitivity and/or specificity for the diagnosis of pre-eclampsia (7).

Placental growth factor (PlGF) belongs to the vascular endothelial growth factor (VEGF) family and represents a key regulator of angiogenic events in pathological conditions. PlGF exerts its biological function through the binding and activation of the receptor Flt-1. In pre-eclampsia, it is thought that endothelial dysfunction leads to an increased level of a circulating decoy receptor, known as soluble Flt-1, (sFlt-1), a soluble receptor for both VEGF-A and PlGF (8). Circulating levels of sFlt-1 are increased in pre-eclampsia and particularly in the early onset form of the disease, resulting in reduced levels of free VEGF-A and PlGF in the maternal circulation. Thus, the endothelial dysfunction observed in pre-eclampsia may be due to excess neutralisation of VEGF-A and PlGF by circulating sFlt-1. Levine et al. showed that in normal pregnancy, PlGF levels track the development of the

placenta, peaking at about 32 weeks' gestation when the placenta is developed fully and then declining until delivery (9). However, in pre-eclampsia, this rise and fall is considerably lower throughout pregnancy, and levels are strikingly lower when the condition presents clinically.

The PELICAN study was the first and largest prospective evaluation of PlGF in women presenting with suspected pre-eclampsia (10). This blinded observational cohort study was conducted in seven consultant-led maternity units in the UK and Ireland between January 2011 and February 2012. It enrolled women being investigated for suspected pre-eclampsia, quantified their plasma PlGF using a point of care device, the Alere Triage PlGF test ®, but did not reveal the result to their clinician. The study found that a PlGF value <100 pg/ml, in women presenting prior to 35 completed weeks' gestation had a negative predictive value of 98% (95% CI, 93 to 99.5) and a positive predictive value of 44% (95% CI, 36 to 52) in determining those that would require delivery for a confirmed diagnosis of pre-eclampsia within the next 14 days. The study reported a PlGF <100 pg/ml to be a better predictor than all other current commonly used predictive tests of pre-eclampsia, either singly or in combination (blood pressure, urinalysis or biochemical markers) with an area under the ROC curve for low PlGF of 0.87 compared to 0.76 for the next best predictor.

The PROGNOSIS study was a prospective, multicentre, blinded, observational study conducted in 14 countries from 2011 to 2014 (11). Its aim was to derive and validate a ratio of serum sFlt-1 to PlGF that would be predictive of the absence or presence of pre-eclampsia in the short term. It included women with singleton pregnancies from 24 weeks to 36+6 weeks' gestation in whom a clinical suspicion of pre-eclampsia existed. The Elecsys immunoassay was used to quantify levels of PlGF and sFlt-1. The development cohort of over 500 participants identified a sFlt-1:PlGF ratio of 38 as having an important predictive value. The subsequent validation cohort, again with over 500 participants, reported a negative predictive value of 99.3% (95% CI 97.9–99.9) for ruling out pre-eclampsia within one week. Interestingly, the same cut off of 38 was predictive of the absence of fetal adverse

outcomes within 1 week; negative predictive value of 99.3% [95% CI, 97.9 to 99.9]. The study showed that an sFlt-1: PlGF ratio of 38 or lower can be used to predict the short-term absence of pre-eclampsia and adverse fetal events in women in whom the syndrome is suspected clinically (12). The positive predictive value; a diagnosis of preeclampsia, eclampsia, or the HELLP syndrome within 4 weeks, was 36.7% (95% CI, 28.4 to 45.7) using the same sFlt-1: PlGF ratio of 38. Post hoc analysis however showed this was still an improvement in prediction compared to the use of clinical variables such as blood pressure and urinalysis alone.

NICE (The National Institute for Health and Clinical Excellence, UK) has recently published guidance on incorporation of PlGF testing, in addition to clinical assessment, in women presenting with suspected pre-eclampsia from 20-34^{+6} weeks' gestation. It advises that the Triage PlGF test or Elecsys immunoassay sFlt□1/PlGF ratio test may be used, in combination with clinical assessment, to "rule-out" pre-eclampsia in this group of women. However, it advises that these tests should not yet be used to diagnose pre-eclampsia until further research is available, specifically on how an abnormal PlGF result would affect management decisions regarding timing and gestation of delivery and the outcomes associated with this (13).

The objective of this randomised trial is to evaluate the impact of knowledge of PlGF measurement on clinically relevant outcomes. We hypothesise that adding PlGF measurement to current clinical assessment of women with suspected pre-eclampsia prior to 37 weeks' gestation will reduce associated maternal morbidity through improved risk stratification, earlier diagnosis and targeted management of women with the disease. Any intervention in late pregnancy may have an impact on the fetus. On the one hand, earlier diagnosis of pre-eclampsia may precipitate earlier delivery and lead to an increase in neonatal morbidity and mortality secondary to iatrogenic prematurity. Conversely, improved identification of those neonates at highest risk of imminent placental dysfunction may reduce

neonatal morbidity by allowing for timely intervention. It is therefore imperative that full evaluation of both potential benefit and harm is conducted before PlGF testing is implemented routinely into clinical practice. If this trial demonstrates a beneficial impact on maternal morbidity and/or neonatal morbidity, alongside a favourable health economic assessment, then there would be a strong case for incorporating PlGF testing into routine clinical investigations for women presenting with suspected pre-eclampsia before 37 weeks' gestation in a wide variety of healthcare settings.

Methods and Design

Study Design

PARROT Ireland is a multi-centre, stepped wedge cluster-controlled trial of PlGF measurement in women presenting with suspected pre-eclampsia prior to 37 weeks' gestation. As implementation of a diagnostic test may alter physician management, a cluster design was chosen rather than individual randomisation. This allows for a change in management to occur at a hospital rather than at an individual woman level, which is preferable in trials involving a diagnostic test and allows the clinical influence of the additional test to be evaluated in a pragmatic fashion (14). Each maternity hospital acts as a cluster. All clusters commenced the trial in the control arm and in turn, each cluster transitions at random from the control to the intervention at pre-specified time points. Once a cluster has changed over to the intervention, it continues as such for the remainder of the trial so that by the end of the trial all clusters will be in the intervention arm (Figure.1). A stepped wedge design was chosen so as to increase the social acceptability of the trial to the 7 hospitals (the stake holders / decision makers in all of the hospitals expressed a desire to participate in a trial in which they were guaranteed to get the intervention); and because a trial with just 7 clusters risks baseline imbalance in a parallel design.

The trial will continue for a period of twenty-two months, and with seven clusters the interval between transitions is approximately three months in duration. A restricted method of randomisation was used to provide a balance in total (expected) number of observations across intervention and control periods (details below) (15-17). There is a short transition period of one week whenever a new cluster transitions from control to the intervention. Data collected during this transition period will not be included in any analysis of outcomes. Recruitment will stop on a pre-specified fixed date in late April 2019 and the study will end when the last recruited participant and neonate are discharged and all outcome data collected.

Setting & Participants

The trial is being conducted within the Health Research Board Mother and Baby Clinical Trial Network Collaborative. The Coombe Women and Infants University Hospital Dublin, Cork University Maternity Hospital, University Maternity Hospital Limerick, The Royal Jubilee Maternity Hospital Belfast, University College Hospital Galway, The National Maternity Hospital Dublin and The Rotunda Maternity Hospital Dublin are the seven largest consultant-led maternity units on the island of Ireland. Combined, they have an annual birth rate of over 44,000, representing over half of the country's total annual births. Women attending these maternity units who present with suspected pre-term pre-eclampsia are eligible for inclusion in this trial. Detailed inclusion and exclusion criteria are described (Table 1 & 2).

Randomisation

The trial statisticians for the study developed a randomisation sequence for site transition from control to intervention; however, the order of site transitioning is concealed from sites and principal investigators until 12 weeks prior to the sites transition date. An allocation sequence was randomly selected (i.e. a cross-over order for the 7 clusters) from a set of random sequences constrained so that the sum of the total cluster sizes in the intervention status was similar to the total sum of the cluster sizes in the control status. Similar was

defined to be a difference in the total sums exposed to intervention and control statuses being no different than the expected middle 25th percentile range of differences. To implement this, 10,000 simulations of possible (unique) allocation sequences were performed. From this, the difference in number exposed to intervention and control for each sequence was determined. An allocation sequence was then selected at random from those falling within the middle 25th percentile range of differences (14-16).

Control

Eligible women are approached and provided with detailed information about the trial, both verbally and written, by a trained researcher. Eligibility is determined by review of symptoms and signs at the time of presentation to the maternity hospital by the local researcher. Participants are not aware of their maternity hospitals current randomisation prior to their enrolment on the trial. Informed consent is obtained in accordance with ICH - GCP guidelines (18). Once an eligible woman has given written informed consent for inclusion in the study, her maternity hospitals current group allocation is revealed (Figure 2). Participants enrolled in the control arm receive usual hospital care as per National guidelines; these are Health Service Executive/Institute of Obstetrics and Gynaecology Irish guidelines for those in the Republic or the NICE guidelines for those in Northern Ireland (Figure 3a and 3b) (19, 20).

Intervention

Participants enrolled in the intervention arm have their plasma PlGF quantified in addition to routine hospital investigations. The PlGF result is made immediately available to the participants clinical team and documented clearly in the participant's medical notes. A suggested further management algorithm is provided to the clinician based on both the degree of hypertension present and the PlGF result. (Figure 4). This algorithm advocates increased frequency of review for those participants identified as having an abnormal PlGF result. The final decision regarding frequency of review remains with the treating clinician. If

4 weeks or more pass and the participant re-presents with symptoms suggestive of pre-eclampsia, a repeat PlGF quantification may be performed as long as the inclusion/exclusion criteria are still satisfied.

PlGF Quantification

Maternal plasma PlGF quantification is performed on an ethylenediaminetetraacetic acid (EDTA) venous blood sample obtained in the standard fashion. Plasma is obtained through centrifugation and the sample is then processed immediately using a CE marked validated point of care platform; the automated Triage® Meterpro (ALERE San Diego, CA). Each hospital has the necessary equipment in situ and appropriately trained researchers in place, to perform this test as per manufacturer's guidelines. The PlGF measurement is reported as the absolute value in pg/ml within 30 minutes of sampling.

Outcome Measure

Primary Outcome Measure

To evaluate if the intervention is beneficial to both women and their babies and more importantly to ensure it is not harmful to either, the study has two equally important co-primary outcome measures. These are maternal morbidity and neonatal morbidity. For maternal morbidity assessment, the fullPIERS score is used with the addition of severe hypertension (Table 3). Severe systolic hypertension is an independent risk factor for stroke in pregnancy and in high resource settings uncontrolled hypertension is the main cause of death in women with pre-eclampsia. (21-23) For neonatal morbidity assessment, babies are dichotomised into having or not having objectively identified neonatal morbidity by means of a composite neonatal score (Table 4). The interval from diagnosis of pre-eclampsia to delivery is not a suitable outcome measure to use, as we are aware that knowledge of PlGF result may alter clinician management and expedite delivery (24).

Secondary outcome measure

Secondary outcomes include each component of the primary outcome reported individually as well as further maternal and neonatal assessments such as mode of delivery, antenatal detection of growth restriction and use of antihypertensive agents (Table 5 & 6)

A separate health economic evaluation is assessing the intervention's economic impact. This is achieved through the use of participant quality of life (QoL) questionnaires (EQ-5D & SF-36), (25, 26) a specially designed study specific participant costing questionnaire and by assessment of costs to the health service of community based/ inpatient/day case care, through chart review at discharge (27-29).

Data collection

Trial data captured locally at site by researchers are transmitted securely using an electronic clinical record form (eCRF) to a specific database developed by MedSciNet. Baseline demographic data, QoL questionnaires and the PlGF result are entered live to the eCRF at point of recruitment. The full eCRF is completed after discharge from the maternity hospital post-delivery, and includes neonatal and maternal medical outcome, costing questionnaire & repeat QoL questionnaires. All data entered to the eCRF is pseudo-anonymised with each participant identified by a unique study number. The identifier key is kept separately locally at site in a secure location. The data system is built to the same security and confidentiality standards as those of hospital electronic health records. The data at each participating centre are handled in accordance with local regulatory legislation and Ethics Committee approval. A detailed description of schedule and timing of data collection is provided (Figure 5).

Sample Size

The sample size was fixed by the number of sites and the study duration. It is anticipated that the total sample size will be in the region of 4000 participants; split across 7 clusters and the 8 time periods in the design (equivalent to a cluster-period size of about 71). With a sample size of 4000 and using a two-sided type I error rate of 0.025 (to allow for two co-

primary outcomes), we determined the power to detect a 7% reduction in maternal morbidity (relative risk reduction of 20%) from 35% to 28% in the intervention i.e. 'active' group. This is assuming an ICC in the region of 0.01; but also consider Sensitivity to a range of ICC values between 0.005 and 0.05. The second co-primary outcome is adverse neonatal outcomes. Due to scarcity of information on the ICC, the same ICC as for the maternal outcome is assumed. Current rates of adverse events are around 10%. We determine power to detect an absolute change in neonatal adverse outcomes of 6%.

To allow for the longitudinal nature of the trial, where correlations may differ between observations in the same cluster-period; and those measured in different cluster periods, we incorporate cluster-auto correlations (CAC). There is little information to support likely values for the CAC, so we are guided by values in the literature and explore sensitivity across a range of values (0.64, 0.80 and 0.96) (30, 31).

The power has been estimated using an online RShiny App. (32, 33) We have not included transition periods in the calculation but given the transition periods are just one week in length, this is not expected to significantly affect power. There has been no allowance for varying cluster sizes as this is currently not something which is technically possible in a stepped wedge study. Sample size calculations were performed assuming linear mixed models with categorical effects for time; random cluster and random cluster by period effects. (34) Under these assumptions, we constructed power curves, which reveal that under most anticipated scenarios the trial will have in the region of 80% power (Figures 6 & 7). (31, 35)

Data Analysis

Clinical Outcome

The primary aim of the study is to evaluate whether there is a difference in the two composite outcomes before and after exposure to the intervention. Mixed effects regression models will be used to allow for the clustering within sites. Calendar time will also be adjusted for since the intervention is sequentially rolled-out both by including fixed categorical time effects and random cluster by categorical time effects (36).

The primary estimate of the treatment effects will therefore be cluster and time adjusted. Time adjustment is essential, as it is a stepped wedge trial. Log Poisson regression models with robust variance estimation (to allow for misspecification of binomial errors) will be used so as to allow estimates of relative risks (37); to estimate risk differences corresponding Binomial models with log links will be fitted. Secondary analysis will adjust for individual and cluster level covariates. Both individual and cluster level covariates to be included in the adjustment will be pre- specified. Null hypotheses and analyses for secondary outcomes take a similar form to that for the primary outcome, and where outcomes are not binary, analysis will be using the generalized linear mixed model. Transformations will be performed where data are markedly not normally distributed. For the analysis adjusted for covariates and for the secondary outcomes (unadjusted) multiple imputation methods will be used if the proportion of missing data is more than about 5%, and this multiple imputation will also allow for the clustered and temporal nature of the trial. It is not expected that there will be any missing data in the primary outcome; as it will be assumed that if the outcome is present then it will be recorded and if it is not recorded we will assume it is absent. This is a standard and realistic assumption. Results will be presented as adjusted risk ratios with confidence intervals (CI) and risk differences to allow full appreciation of clinical effect. To allow for the two primary outcomes, we will follow good practice and adjust for this multiplicity using a Bonferroni correction and so report 97.5% confidence intervals.

For secondary continuous outcomes mean differences will be reported and 99% confidence intervals for secondary outcomes. We will report latent intra-cluster correlations for all outcomes, along with 95% confidence intervals. Pre-specified subgroup analysis will be

undertaken on the primary outcome based on women presenting <35 weeks' gestation versus >35 weeks' gestation; size of unit and final confirmed diagnosis. The stepped wedge trial design will also allow investigation of treatment effect heterogeneity across clusters and time. These exploratory analyses will be reported using 99% confidence intervals. Analysis will be conducted by intention to treat and sites will be considered exposed to the intervention post randomised cross-over date.

Health Economic Outcome

The economic evaluation will be informed by a decision analytical model, which will be designed and constructed for the study to reflect the maternal and fetal pathway and health states. Employing a decision analytical model allows for the extrapolation of existing data and the opportunity to systematically synthesise evidence from various sources. Primary data on maternal health outcomes will be available from the study with the distribution of EQ-5D-5L & SF-3F6 questionnaires which will inform the estimation of Quality Adjusted Life Years (QALYs). Fetal outcomes will be informed by secondary sources. A systematic literature review will be conducted, the results of which will be used to inform a meta-analysis so as to estimate fetal quality of life outcomes for the estimation of QALYs. Primary data on resource utilisation will be collected using the costing questionnaire. The costs and effects of the intervention and comparator will be compared to estimate an incremental cost effectiveness ratio in a Cost Utility Analysis. To address parameter and structural uncertainties, a probabilistic sensitivity analysis (PSA) will be performed.

Discussion

Based on previous experience during the PELICAN study, an analysis of success criteria and barriers to our proposed study was conducted. Potential barriers include the overestimation of (i) identification of eligible women by the research team, (ii) primary

outcome event rate (iii) and retention / attrition i.e. gaining outcomes data on all women included.

A recruitment feasibility audit conducted in Cork University Maternity Hospital (CUMH) over the course of a typical week in July 2016 identified 21 women who would be eligible for inclusion in the PARROT Ireland study. This would equate to almost 1100 women per annum in CUMH, approximately 13% of its annual delivery rate. This is in keeping with the quoted 10% incidence of hypertensive disorders of pregnancy (HDP) in the population (38). It is anticipated that over the 24 month duration of the study across the 7 hospitals approximately 11,500 women will meet the study inclusion criteria (13% of the combined annual delivery rate), and of these 4,000 will be recruited into this trial (33% of those eligible). As inclusion in the trial will be optional and require informed consent from participants, not all eligible women in each unit will be included. Projected inclusion rates will be apparent via a dedicated MedSciNet database pre-programmed, available online and contemporaneously updated, allowing prompt action to intervene when not optimal. A conservative requirement of <50% of all eligible women to be recruited in order to reach targets has deliberately been chosen and successful recruitment of the same population in the PELICAN study is reassuring.

As participation in the trial does not require any extra attendances/input from the participant for the remainder of the pregnancy, it is likely that retention of participants will not be an issue. Similarly, the data outcome to assess for maternal and neonatal morbidity can be readily obtained post-delivery following discharge of the participant from their stored medical records locally at each unit. However, in order to fully examine the health economic outcomes there exists a reliance on the return of completed questionnaires by the participant post-delivery. To minimise attrition rates, the researcher at each site will endeavour to meet with each participant post-delivery prior to their discharge and encourage them to complete the health economic questionnaires.

The primary aim of the PARROT Ireland trial is to establish the effectiveness of revealed plasma PlGF measurement in reducing maternal morbidity (with assessment of neonatal safety in parallel) in women presenting with suspected pre-eclampsia prior to 37 weeks' gestation. Should the trial show a reduction in maternal morbidity without an increase in neonatal morbidity, or indeed a reduction in neonatal morbidity with no change in maternal morbidity, it would provide a strong argument for its incorporation into routine obstetric practice. The long-term aim of the trial is to demonstrate if PlGF measurement enables appropriate antenatal stratification of women presenting with suspected pre-eclampsia.

Avoiding unnecessary hospital admission would be both clinically and economically beneficial. In contrast, those at increased risk of imminent adverse events, identified by an abnormal PlGF result, would have hospital resources re-directed to them. We anticipate that this trial will provide a definitive result on the benefits of PlGF testing which will act to influence international clinical practice.

Abbreviations

ALT: Alanine Aminotransferase
AST: Aspartate Aminotransferase
CAC: cluster-auto correlations
CI: Confidence Interval
CNS: Central Nervous System
CSF: Cerebrospinal Fluid
DBP: Diastolic Blood Pressure
EC: Ethics Committee
eCRF: Electronic Clinical Report Form
Flt-1: fms-like tyrosine kinase 1
GCS: Glasgow Coma Scale
HDP: Hypertensive Disorder of Pregnancy
HSE: Health Service Executive
ICC: Intraclass Correlation Coefficient
INFANT: The Irish Centre for Fetal and Neonatal Translational Research
NICE: National Institute for Clinical Excellence
NICU: Neonatal Intensive Care Unit
NNU: Neonatal Unit
PARROT: Placental growth factor in Assessment of women with suspected pre-eclampsia to Reduce maternal morbidity: a Stepped Wedge Cluster Randomised Control Trial
PET: Pre-eclampsia
PIL: Patient Information Leaflet
PlGF: Placental Growth Factor
PSA: Probabilistic Sensitivity Analysis
QALY: Quality Adjusted life year
QoL: Quality of Life
RCT: Randomised Controlled Trial
SBP: Systolic Blood Pressure
sFlt-1: soluble fms-like tyrosine kinase 1
VEGF: Vascular endothelial growth factor

Declarations

Ethics approval and consent to participate

The trial is being conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with Good Clinical Practice and applicable regulatory requirements. The local ethics committee at each participating site has reviewed the trial protocol, including the patient information and informed consent form, and full ethical approval granted. Each eligible woman identified is required to give written informed consent prior to her inclusion in the trial. A GCP trained researcher at the local site obtains this consent.

Clinical Research Ethics Committee Cork: ECM 3 (h) 08/11/16

University College Hospital Galway EC: Ref 50/12

Coombe Womens & Infants University Hospital EC: Study No 20-2016

National Maternity Hospital EC: EC 20.2016

University Hospital Limerick EC: Ref: 68/16

Health Research Authority (Belfast): 16/WM/0484

Rotunda Hospital EC: REC-2016-020..

Consent for publication

Not Applicable

Availability of data and material

The dataset generated from this study is saved onto a secure electronic database and after close of the study will be archived in line with GCP regulations. The anonymised completed dataset will be available from the chief investigator of the trial upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

The PARROT Ireland trial is funded by the Health Research Board Mother and Baby Clinical Trial Network Ireland (HRB CTN-2014-010) and by the INFANT research centre. Researchers from INFANT had a role in the design of the study and in writing the protocol.

Authors' contributions

All authors contributed to the overall study design and specific methodologies. LK conceived and designed the study with DD. LK and DHR produced the detailed protocol, with input from all authors. DHR drafted the manuscript with assistance from KH, KOD and LK. All authors have critically read, contributed with inputs and revisions and approved the final manuscript.

Acknowledgements

The authors would like to thank PARROT Ireland participants and the associated maternity units and staff for their support and involvement in this study.

References

1. Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. Lancet. 2005;365(9461):785-99.
2. Meyer NL, Mercer BM, Friedman SA, Sibai BM. Urinary dipstick protein: a poor predictor of absent or severe proteinuria. American journal of obstetrics and gynecology. 1994;170(1 Pt 1):137-41.
3. Waugh JJ, Bell SC, Kilby MD, Blackwell CN, Seed P, Shennan AH, et al. Optimal bedside urinalysis for the detection of proteinuria in hypertensive pregnancy: a study of diagnostic accuracy. BJOG : an international journal of obstetrics and gynaecology. 2005;112(4):412-7.
4. Kuo VS, Koumantakis G, Gallery ED. Proteinuria and its assessment in normal and hypertensive pregnancy. American journal of obstetrics and gynecology. 1992;167(3):723-8.
5. Villar J, Repke J, Markush L, Calvert W, Rhoads G. The measuring of blood pressure during pregnancy. American journal of obstetrics and gynecology. 1989;161(4):1019-24.
6. ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. Obstetrics and gynecology. 2002;99(1):159-67.
7. Meads CA, Cnossen JS, Meher S, Juarez-Garcia A, ter Riet G, Duley L, et al. Methods of prediction and prevention of pre-eclampsia: systematic reviews of accuracy and effectiveness literature with economic modelling. Health Technology Assessment. 2008;12(6):1-+.
8. Hayman R, Brockelsby J, Kenny L, Baker P. Preeclampsia: The endothelium, circulating factor(s) and vascular endothelial growth factor. Journal of the Society for Gynecologic Investigation. 1999;6(1):3-10.
9. Levine RJ, Maynard SE, Qian C, Lim KH, England LJ, Yu KF, et al. Circulating Angiogenic Factors and the Risk of Preeclampsia. New England Journal of Medicine. 2004;350(7):672-83.
10. Chappell LC, Duckworth S, Seed PT, Griffin M, Myers J, Mackillop L, et al. Diagnostic Accuracy of Placental Growth Factor in Women With Suspected Preeclampsia A Prospective Multicenter Study. Circulation. 2013;128(19):2121-31.
11. Zeisler H, Llurba E, Chantraine F, Vatish M, Staff AC, Sennström M, et al. Predictive Value of the sFlt-1:PlGF Ratio in Women with Suspected Preeclampsia. New England Journal of Medicine. 2016;374(1):13-22.
12. Zeisler H, Llurba E, Chantraine F, Vatish M, Staff AC, Sennstrom M, et al. Predictive Value of the sFlt-1:PlGF Ratio in Women with Suspected Preeclampsia. New England Journal of Medicine. 2016;374(1):13-22.
13. PlGF-based testing to help diagnose suspected pre-eclampsia (Triage PlGF test, Elecsys immunoassay sFlt-1/PlGF ratio, DELFIA Xpress PlGF 1-2-3 test, and BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ra [cited May 2016]. Diagnostics guidance [DG23] Published date: May 2016:[Available from: https://www.nice.org.uk/guidance/dg23/chapter/1-Recommendations.
14. Hemming K, Haines TP, Chilton PJ, Girling AJ, Lilford RJ. The stepped wedge cluster randomised trial: rationale, design, analysis, and reporting. BMJ : British Medical Journal. 2015;350.
15. Bland JM. Cluster randomised trials in the medical literature: two bibliometric surveys. BMC medical research methodology. 2004;4:21-.
16. Brown CA, Lilford RJ. The stepped wedge trial design: a systematic review. BMC medical research methodology. 2006;6:54-.
17. Stolberg HO, Norman G, Trop I. Randomized controlled trials. American Journal of Roentgenology. 2004;183(6):1539-44.
18. GCP. ICH HARMONISED TRIPARTITE GUIDELINE, GUIDELINE FOR GOOD CLINICAL PRACTICE E6(R1) 1996. Available from: https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf.
19. HSE. THE MANANGEMENT OF HYPERTENSION IN PREGNANCY. 2016. p. 1-32.
20. NICE. Hypertension in Pregnancy 2010. Available from: https://www.nice.org.uk/guidance/cg107.

21. Cantwell R, Clutton-Brock T, Cooper G, Dawson A, Drife J, Garrod D, et al. Saving Mothers' Lives: Reviewing maternal deaths to make motherhood safer: 2006-2008. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. BJOG : an international journal of obstetrics and gynaecology. 2011;118 Suppl 1:1-203.
22. Schutte JM, Schuitemaker NWE, Van Roosmalen J, Steegers EAP, Dutch Maternal Mortality C. Substandard care in maternal mortality due to hypertensive disease in pregnancy in the Netherlands. BJOG: An International Journal of Obstetrics & Gynaecology. 2008;115(6):732-6.
23. Martin Jr JN, Thigpen BD, Moore RC, Rose CH, Cushman J, May W. Stroke and severe preeclampsia and eclampsia: A paradigm shift focusing on systolic blood pressure. Obstetrics and gynecology. 2005;105(2):246-54.
24. Sharp A, Chappell L, Dekker G, Pelletier S, Garnier Y, Zeren O, et al. OP 2 Placental growth factor informed management of suspected pre-eclampsia and/or fetal growth restriction – The MAPPLE cohort study. Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health. 2017;9(Supplement C):9-10.
25. EQ-5D. Available from: www.euroqol.org
26. SF 6D. Available from: https://www.sheffield.ac.uk/scharr/sections/heds/mvh/sf-6d
27. EuroQol--a new facility for the measurement of health-related quality of life. Health policy (Amsterdam, Netherlands). 1990;16(3):199-208.
28. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Medical care. 1992;30(6):473-83.
29. Brazier J, Usherwood T, Harper R, Thomas K. Deriving a preference-based single index from the UK SF-36 Health Survey. Journal of clinical epidemiology. 1998;51(11):1115-28.
30. Martin J, Girling A, Nirantharakumar K, Ryan R, Marshall T, Hemming K. Intra-cluster and inter-period correlation coefficients for cross-sectional cluster randomised controlled trials for type-2 diabetes in UK primary care. Trials. 2016;17:402.
31. Hooper R, Bourke L. Cluster randomised trials with repeated cross sections: alternatives to parallel group designs. BMJ : British Medical Journal. 2015;350.
32. Hemming K. Available from: https://clusterrcts.shinyapps.io/rshinyapp/.
33. Campbell MK, Fayers PM, Grimshaw JM. Determinants of the intracluster correlation coefficient in cluster randomized trials: the case of implementation research. Clinical trials (London, England). 2005;2(2):99-107.
34. Hemming K, Taljaard M. Sample size calculations for stepped wedge and cluster randomised trials: a unified approach. Journal of clinical epidemiology. 2016;69:137-46.
35. Hemming K, Eldridge S, Forbes G, Weijer C, Taljaard M. How to design efficient cluster randomised trials. Bmj. 2017;358:j3064.
36. Hemming K, Taljaard M, Forbes A. Analysis of cluster randomised stepped wedge trials with repeated cross-sectional samples. Trials. 2017;18:101.
37. Zou GY. A modified Poisson regression approach to prospective studies with binary data. American Journal of Epidemiology. 2004;159(7):702-6.
38. Duley L. The Global Impact of Pre-eclampsia and Eclampsia. Seminars in Perinatology. 2009;33(3):130-7.

Appendices;

Table 1: Inclusion Criteria

Pregnant women between 20+0 and 36+6 weeks of gestation (inclusive) with a;

- Singleton pregnancy
- Aged 18 years or over
- Able to give informed consent
- Presenting with suspected pre-eclampsia: (one or more of the following)
  - Hypertension
  - Dipstick proteinuria
  - Headache
  - Visual disturbances
  - Epigastric or right upper quadrant pain
  - Increasing oedema
  - Suspected fetal growth restriction
  - If the healthcare provider deems that the woman requires further evaluation for possible pre-eclampsia

Table 2: Exclusion Criteria

- Confirmed pre-eclampsia at point of enrolment;
  "sustained hypertension with systolic BP ≥ 140 or diastolic BP ≥ 90 on at least two occasions at least 4hrs apart) with significant quantified proteinuria (>300mg protein on 24hr collection or urine protein creatinine ratio >30mg/mmol) or abnormal pre-eclampsia bloods"
- ≥37 weeks gestation
- Multiple pregnancy
- Abnormal pre-eclampsia bloods (new onset reduced number of platelets or deranged liver function/renal function tests, identified during routine care prior to enrolment and not attributable to anything other than pre-eclampsia).
- Decision regarding imminent delivery already made
- Lethal fetal abnormality present
- Previous participation in PELICAN trial in a prior pregnancy
- Participation in a conflicting trial at the same time as PARROT Ireland
- Plan to use off protocol PIGF testing

Table 3: Components of the Maternal Morbidity Composite Score

- Confirmed placental abruption
- Intensive Care Admission
- CNS compromise;
  Generalized tonic clonic seizure due to eclampsia, GCS <13, cerebral haemorrhage/ infarct, cortical blindness, retinal detachment, Transient ischaemic attack, reversible ischaemic neurological deficit
- Cardiorespiratory compromise;
  myocardial ischaemia/ infarction, SpO2 <90%, >50% FiO2 for >1hr, intubation (other than for Caesarean section), pulmonary oedema, need for positive inotrope support
- Haematological compromise;
  transfusion of any blood product, platelet count <100 x 109/l;
- Liver compromise;
  hepatic dysfunction (ALT or AST >70 IU/L, haematoma, rupture;
- Kidney compromise;
  acute renal insufficiency (creatinine >150 micromol/l); hemodialysis
- Severe hypertension
  (systolic BP ≥ 160 mmHg on at least one occasion)

Table 4: Components of the Neonatal Morbidity Composite Score

- Perinatal death or death before hospital discharge
- NICU admission for ≥48 hrs.
- Birthweight ≤ 5th customised centile
- Apgar score <7 at 5 minutes
- Umbilical artery acidosis at birth (cord pH <7.2)
- Admission to neonatal unit
- Respiratory distress syndrome
- Interventricular haemorrhage
- Retinopathy of prematurity
- Confirmed infection
- Necrotising enterocolitis
- Fetal growth restriction identified on antenatal ultrasound
- Gestation at delivery

Table 5: Secondary Outcomes -Maternal

- Final diagnosis of hypertensive disorder of pregnancy (*Chronic HTN, Gestational HTN or pre-eclampsia*)
- Gestation at diagnosis of pre-eclampsia
- use of 1 or more antihypertensive drugs
- Instrumental Delivery (V*entouse or Forceps*)
- Severe hypertension (systolic BP ≥ 160 mmHg on at least one occasion)
- Maternal morbidity by fullPIERS model
    - *Confirmed placental abruption*
    - *Intensive care admission*
    - *Central Nervous System Compromise*
    - *Cardiorespiratory Compromise*
    - *Haematological Compromise*
    - *Liver Compromise*
    - *Kidney Compromise*
- Progression to severe pre-eclampsia as defined by ACOG practice bulletin
    - *Systolic BP ≥ 160mmHG or diastolic BP ≥ 110mmHG on 2 occasions at least 4 hours apart while the patient is on bed rest (unless antihypertensive therapy is initiated before this time)*
    - *Thrombocytopenia (Platelet count <100 x 109/L)*
    - *Impaired liver function as indicated by abnormally elevated blood concentrations of liver enzymes (to twice normal concentration), severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by an alternative diagnoses, or both*
    - *Progressive renal insufficiency (serum creatinine concentration greater than 1.1mg/dL (150 µmol/L) or a doubling of the serum creatinine concentration in the absence of other renal disease)*
    - *Pulmonary oedema*
    - *New onset cerebral or visual disturbances*
- Elective delivery: induction of labour or Caesarean section
- Caesarean section: emergency and elective

Table 6: Secondary Outcomes -Neonatal

- Fetal growth restriction identified on antenatal ultrasound *(Estimated Fetal Weight and/or abdominal circumference <10th customised centile, abnormality in umbilical artery doppler velocity or reduced level of amniotic fluid)*
- Gestation at delivery
- Perinatal death or death before hospital discharge
- Admission to NICU
- NICU admission for ≥48 hours
- Birthweight ≤ 5th customised centile
- Apgar score <7 at 5 minutes
- Umbilical artery acidosis at birth (*arterial cord pH <7.2*)
- Respiratory distress syndrome
- Interventricular haemorrhage
- Retinopathy of prematurity

- Confirmed infection (*confirmed on blood or CSF cultures*)
- Necrotising enterocolitis

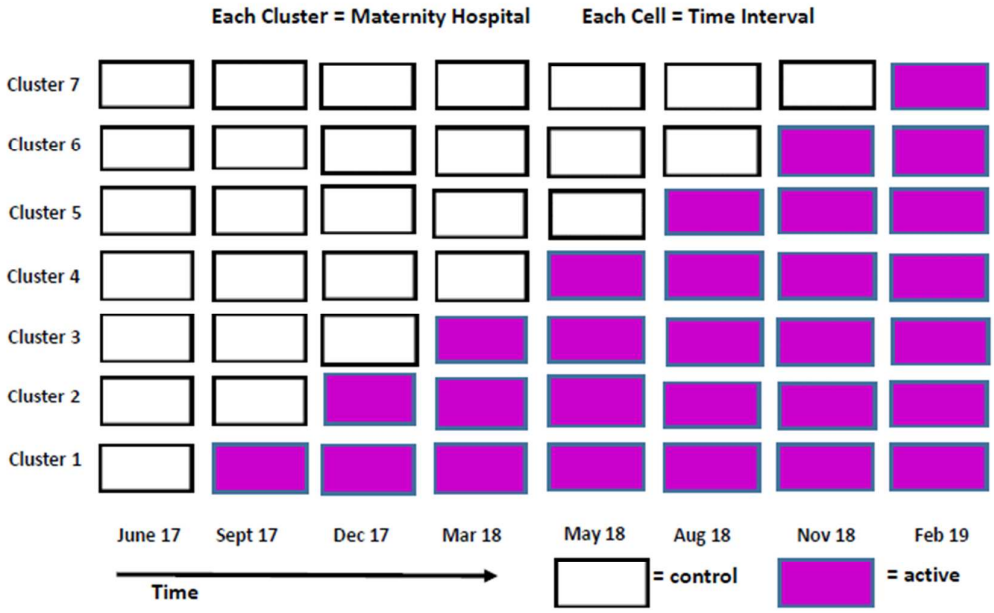

Figure 1; Stepped Wedge Cluster Randomised Design for PARROT Ireland

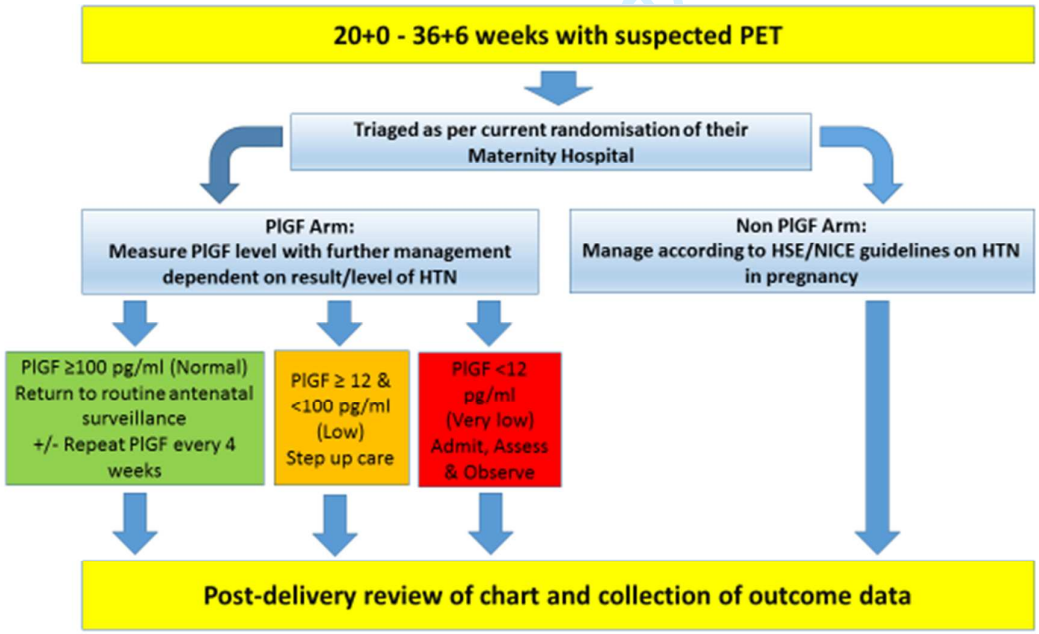

Figure 2; Trial Schematic for PARROT Ireland

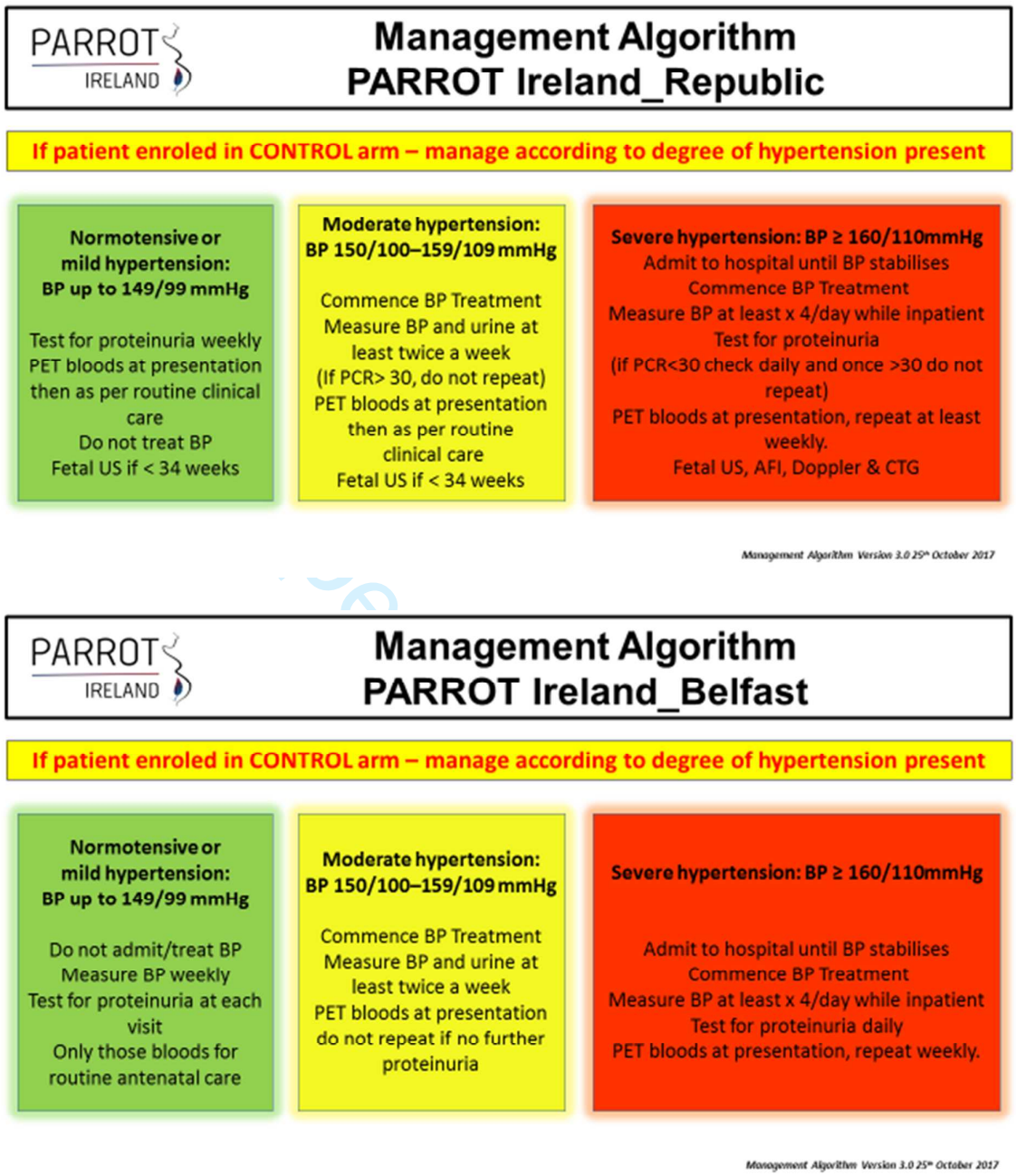

Figure 3; Management Algorithm for Control arm based on HSE/NICE guidelines for PARROT Ireland

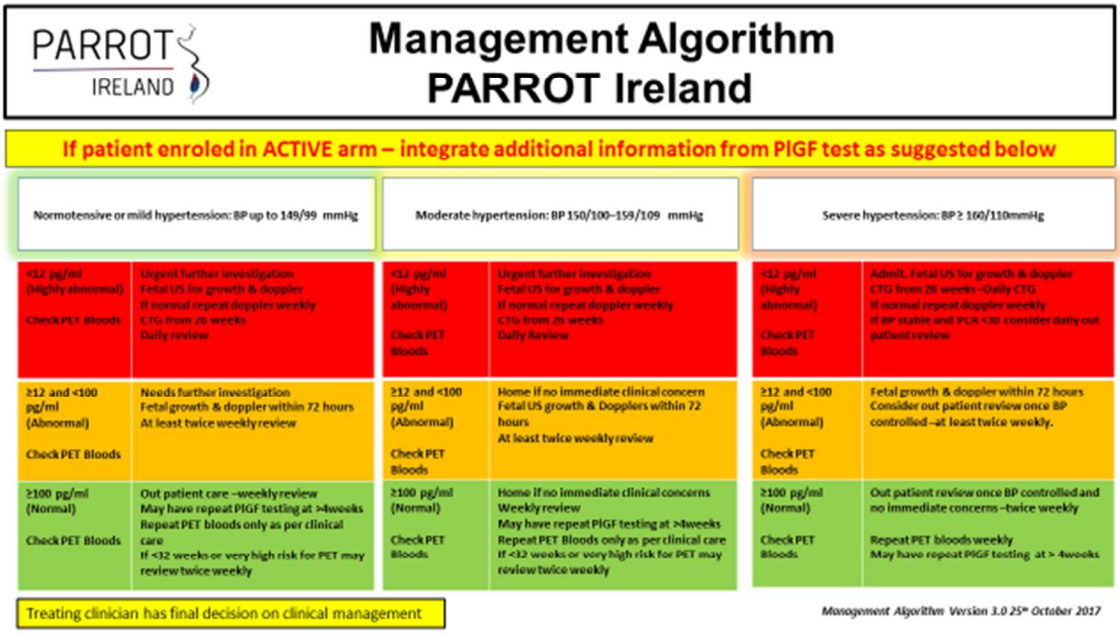

Figure 4; Suggested Management Algorithm for Intervention for PARROT Ireland

	On presentation with suspected PET Between 20+0 and 36+6 weeks	From enrollment to discharge post delivery		Discharge post delivery	
	In-person visit	Chart	In-person visit	Chart	In-person completed
Randomisation-Institutional level	X				
Inclusion/Exclusion	X				
Informed Consent	X				
Demographics		X[a]			
History, Comorbidities		X[a]			
Con Medications		X[a]		X	
Physical Measurements		X[a]			
Clinical readings		X[a]			
PIGF[b] measurement	X		X[c]		
Biobank sample[d]	X				
Fetal assessments				X	
Prenatal admissions				X	
Maternal PET bloods				X	
Newborn data				X	
Neonatal outcome				X	
Maternal outcome				X	
Complications				X	
Postnatal admissions				X	
Clinical Management				X	
Final Outcomes				X	
EQ-5D, SF-36	X				X
Costing questionnaire					X
In person visits	X		X[c]		

Figure 5; SPIRIT Flow Diagram for Schedule of events in PARROT Ireland

[a] May be captured in chart review or in consultation with participant at any time following enrolment.

[b] PIGF testing depends on Institutional randomisation allocation.

[c] PIGF testing will be repeated if readmission for suspected preeclampsia. May be repeated more than once. No more often than 4 weekly.

[d] Only at biobanking sites

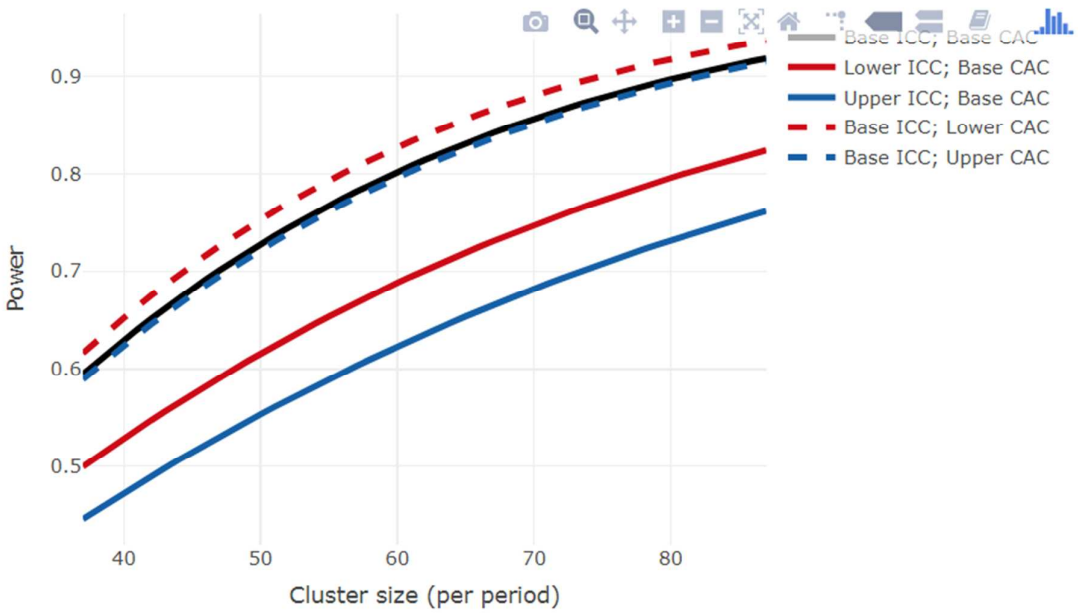

Figure 6; Power Curve for PARROT Ireland for Maternal Adverse Outcomes

Caption: Calculation assumes a stepped wedge design with 7 clusters randomised to 7 sequences (8 cluster-periods); a cross-sectional design; Base-case ICC is 0.001; lower ICC is 0.005; upper ICC is 0.01; base-case CAC is 0.8; lower CAC is 0.64; upper CAC is 0.96. Proportion under the control condition is 0.35 and under the intervention condition is 0.28; significance level is 0.025 (see text for justification) and test is two sided. Assumes large sample normal approximations.

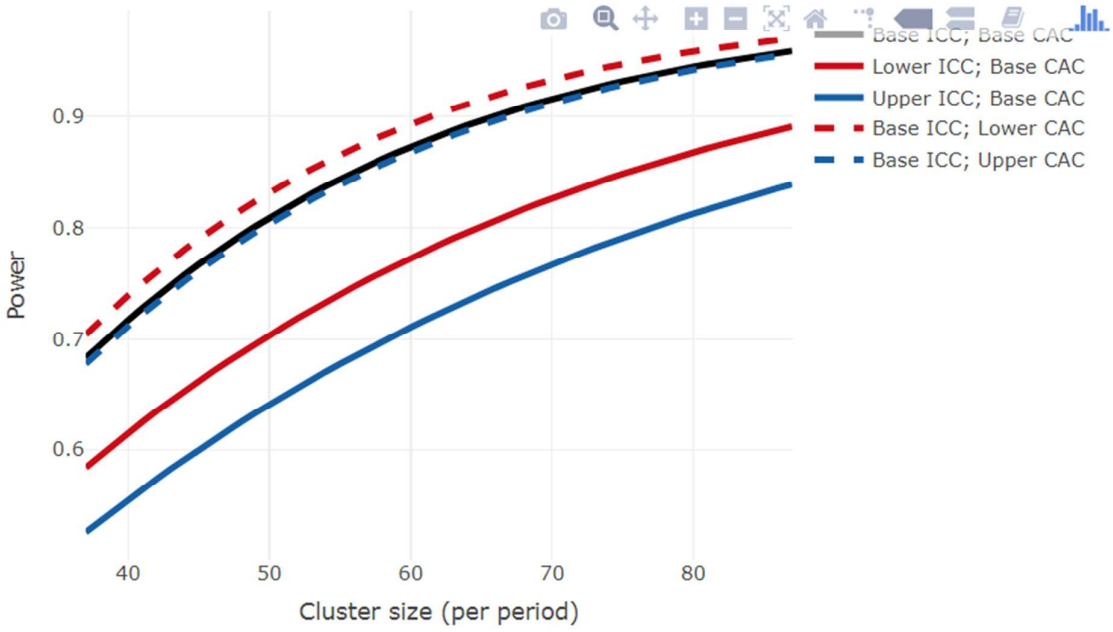

Figure 7: Power Curve for PARROT Ireland for Neonatal Adverse Outcomes

Caption: Calculation assumes a stepped wedge design with 7 clusters randomised to 7 sequences (8 cluster-periods); a cross-sectional design; Base-case ICC is 0.001; lower ICC is 0.005; upper ICC is 0.01; base-case CAC is 0.8; lower CAC is 0.64; upper CAC is 0.96. Proportion under the control condition is 0.1 and under the intervention condition is 0.155; significance level is 0.025 (see text for justification) and test is two sided. Assumes large sample normal approximations.

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	2
	2b	All items from the World Health Organization Trial Registration Data Set	9-11
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	4-5
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	4
	5b	Name and contact information for the trial sponsor	4
	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	33
	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)	34

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	14-16
	6b	Explanation for choice of comparators	14-16
Objectives	7	Specific objectives or hypotheses	16
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)	21-22
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	21
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)	22-23
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	23-24
	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)	23-24
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	25
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	23-24
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	17-20
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)	11/23-24

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	30
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	30
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	25
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	25
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	25
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	25
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	25
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	27-29
	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	27-29

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	27-29
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	31
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	32
	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)	31-32
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	29
	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	33
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	29
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	32
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	34
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)	36

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	25
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	27
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	27-29
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	35
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	27-29
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	35
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	36
	31b	Authorship eligibility guidelines and any intended use of professional writers	36
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	36
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	41-46
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	27

*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

PARROT Ireland: (Placental growth factor in Assessment of women with suspected pre-eclampsia to Reduce maternal morbidity: a Stepped Wedge Cluster Randomised Control Trial) Research Study Protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-023562.R1
Article Type:	Protocol
Date Submitted by the Author:	02-Oct-2018
Complete List of Authors:	Hayes Ryan, Deirdre; The Irish Centre for Fetal and Neonatal Translational Research (INFANT), UCC, Cork; Dept. of Obstetrics and Gynaecology, University College Cork Hemming, Karla; University of Birmingham, Public Health Brethnach, FIONNUALA; Rotunda Hospital, Royal College of Surgeons in Ireland, Dublin Cotter, Amanda; Department of Obstetrics and Gynaecology, Graduate Entry Medical School, University of Limerick Devane, Declan; HRB Trials Methodology Research Network; National Univeristy of Ireland, Galway Hunter, Alyson; Royal Maternity Hospital, Grosvenor Road, BT12 6BB McAuliffe, Fionnuala; UCD Perinatal Research Centre, School of Medicine, University College Dublin, National Maternity Hospital, Dublin, Ireland Morrison, John; National University of Ireland Galway, Obstetrics and Gynaecology Murphy, Deirdre; Trinity College Dublin & Coombe Women & Infants University Hospital Dublin 8, Republic of Ireland Khashan, Ali; University College Cork, Department of Epidemiology and Public Health; The Irish Centre for Fetal and Neonatal Translational Research (INFANT), University College Cork, Ireland McElroy, Brendan; Economics Department, University College Cork, Cork, Ireland Murphy , A; University College Cork, Economics Department Dempsey, E; University College Cork, Department of Paediatrics and Child Health; The Irish Centre for Fetal and Neonatal Translational Research (INFANT), University College Cork, Ireland O'Donoghue, Keelin; Dept. of Obstetrics and Gynaecology, University College Cork; The Irish Centre for Fetal and Neonatal Translational Research (INFANT), University College Cork, Ireland Kenny, Louise; University of Liverpool School of Life Sciences, Department of Women's and Children's Health; The Irish Centre for Fetal and Neonatal Translational Research (INFANT), University College Cork, Ireland
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Obstetrics and gynaecology, Research methods, Health economics

Keywords:	Pre-eclampsia, placental growth factor, stepped wedge cluster randomised trial, point of care diagnostic test

PARROT Ireland: (Placental growth factor in Assessment of women with suspected pre-eclampsia to Reduce maternal morbidity: a Stepped Wedge Cluster Randomised Control Trial) Research Study Protocol

Trial registration

Clinical Trials NCT02881073 (26th August 2016)

Current Protocol:

Version 9.0 Dated: 13 November 2017

*Corresponding author
Deirdre Hayes-Ryan[1,2*]
Email: deirdre.hayesryan@ucc.ie

Karla Hemming[3]
Email: k.hemming@bham.ac.uk

Fionnaula Breathnach[4]
Email: fbreathnach@rcsi.ie

Amanda Cotter[5]
Email: amanda.cotter@ul.ie`

Declan Devane[1,6,7]
Email: declan.devane@nuigalway.ie

Alyson Hunter[8]
Email: alyson.hunter@belfasttrust.hscni.net

Fionnuala M McAuliffe[9]
Email: fionnuala.mcauliffe@ucd.ie

Morrison John J.[7,10]
Email: john.morrison@nuigalway.ie

Deirdre J Murphy[11]
Email: MURPHYD4@tcd.ie

Ali Kashan[1,12]
Email: a.khashan@ucc.ie

Brendan McElroy[13]
Email: b.mcelroy@ucc.ie

Aileen Murphy[13]
Email: aileen.murphy@ucc.ie

Eugene Dempsey[1,2]
Email: G.Dempsey@ucc.ie

Keelin O'Donoghue[1,2]
Email: k.odonoghue@ucc.ie

Louise C Kenny[1,14]
Email: L.Kenny@ucc.ie

[1]The Irish Centre for Fetal and Neonatal Translational Research (INFANT), University College Cork, Ireland
[2]Cork University Maternity Hospital, Cork, Ireland
[3]University of Birmingham, United Kingdom
[4]Rotunda Hospital, Parnell Square W, Dublin 1, Ireland
[5]University Maternity Hospital Limerick
[6]HRB Trials Methodology Research Network
[7]National University of Ireland, Galway, Ireland
[8]Royal Jubilee Maternity Hospital, Belfast, Northern Ireland
[9]UCD Perinatal Research Centre, School of Medicine, University College Dublin, National Maternity Hospital, Dublin, Ireland
[10]Department of Obstetrics & Gynaecology, National University of Ireland Galway
[11]Trinity College Dublin & Coombe Women & Infants University Hospital Dublin 8, Republic of Ireland
[12] School of Public Health, University College Cork, Cork, Ireland
[13]Economics Department, University College Cork, Cork, Ireland
[14] Department of Women's and Children's Health, Liverpool Women's Hospital, University of Liverpool, UK

Abstract

Introduction

Women presenting with suspected pre-eclampsia are currently triaged on the basis of hypertension and dipstick proteinuria. This may result in significant false positive and negative diagnoses resulting in increased morbidity or unnecessary intervention. Recent data suggests that placental growth factor testing may be a useful adjunct in the management of women presenting with preterm pre-eclampsia. The primary objective of this trial is to determine if the addition of placental growth factor testing to the current clinical assessment of women with suspected preterm pre-eclampsia, is beneficial for both mothers and babies.

Methods and Analysis

This is a multicentre, stepped wedge cluster, randomised trial aiming to recruit 4000 women presenting with symptoms suggestive of preterm pre-eclampsia between 20 and 36+6 weeks' gestation. The intervention of an unblinded point of care test, performed at enrolment, will quantify maternal levels of circulating plasma placental growth factor. The intervention will be rolled out sequentially, based on randomisation, in the seven largest maternity units on the island of Ireland. Primary outcome is a composite outcome of maternal morbidity (derived from the modified fullPIERS model). To ensure we are not reducing maternal morbidity at the expense of earlier delivery and worse neonatal outcomes, we have established a co-primary outcome which will examine the effect of the intervention on neonatal morbidity, assessed using a composite neonatal score. Secondary analyses will examine further clinical outcomes (such as mode of delivery, antenatal detection of growth restriction and use of antihypertensive agents) as well as a health economic analysis, of incorporation of placental growth factor testing into routine care.

Ethics and Dissemination

Ethical approval has been granted from each of the seven maternity hospitals involved in the trial. The results of the trial will be presented both nationally and internationally at conference and published in an international peer-reviewed journal.

Strengths and limitations of this study

- Randomised Trial
- Multiple sites with wide geographic distribution
- Stepped wedge design
- PlGF testing only in the Intervention arm

Keywords

Pre-eclampsia, placental growth factor, PlGF, diagnostic test, point of care, stepped wedge cluster randomised controlled trial

Background

Pre-eclampsia is characterised by hypertension and proteinuria, complicates 2-8% of pregnancies, and is associated with significant maternal and neonatal morbidity and mortality (1). Currently women who present with suspected pre-eclampsia are triaged on the basis of hypertension and dipstick proteinuria. Both of these clinical endpoints are subject to observer error and poor test accuracy, with false positive and negative diagnoses of pre-eclampsia occurring in clinical practice (2-5). Current biochemical tests are imperfect at stratifying women for more intensive surveillance as they only identify advanced disease where there is already marked end-organ damage (6). While biomarkers and imaging techniques have been evaluated for improving detection, none have adequate sensitivity and/or specificity for the diagnosis of pre-eclampsia (7).

Placental growth factor (PlGF) belongs to the vascular endothelial growth factor (VEGF) family and represents a key regulator of angiogenic events in pathological conditions (8). PlGF exerts its biological function through the binding and activation of the receptor Flt-1 (9, 10). In pre-eclampsia, it is thought that endothelial dysfunction leads to an increased level of a circulating decoy receptor, known as soluble Flt-1, (sFlt-1), a soluble receptor for both vascular endothelial growth factor type A (VEGF-A) and PlGF (11). Circulating levels of sFlt-1 are increased in pre-eclampsia and particularly in the early onset form of the disease, resulting in reduced levels of free VEGF-A and PlGF in the maternal circulation. Thus, the endothelial dysfunction observed in pre-eclampsia may be due to excess neutralisation of VEGF-A and PlGF by circulating sFlt-1. Levine et al. showed that in normal pregnancy, PlGF levels track the development of the placenta, peaking at about 32 weeks' gestation when the placenta is developed fully and then declining until delivery (12). However, in pre-eclampsia, this rise and fall is considerably lower throughout pregnancy, and levels are strikingly lower when the condition presents clinically.

The PELICAN study was the first and largest prospective evaluation of PlGF in women presenting with suspected pre-eclampsia (13). This blinded observational cohort study was conducted in seven consultant-led maternity units in the UK and Ireland between January 2011 and February 2012. It enrolled women being investigated for suspected pre-eclampsia, quantified their plasma PlGF using a point of care device, the Alere Triage PlGF test ®, but did not reveal the result to their clinician. The study found that a PlGF value <100 pg/ml, in women presenting prior to 35 completed weeks' gestation had a negative predictive value of 98% (95% CI, 93 to 99.5) and a positive predictive value of 44% (95% CI, 36 to 52) in determining those that would require delivery for a confirmed diagnosis of pre-eclampsia within the next 14 days. The study reported a PlGF <100 pg/ml to be a better predictor than all other current commonly used predictive tests of pre-eclampsia, either singly or in combination (blood pressure, urinalysis or biochemical markers) with an area under the ROC curve for low PlGF of 0.87 compared to 0.76 for the next best predictor.

The PROGNOSIS study was a prospective, multicentre, blinded, observational study conducted in 14 countries from 2011 to 2014 (14). Its aim was to derive and validate a ratio of serum sFlt-1 to PlGF that would be predictive of the absence or presence of pre-eclampsia in the short term. It included women with singleton pregnancies from 24 weeks to 36+6 weeks' gestation in whom a clinical suspicion of pre-eclampsia existed. The Elecsys immunoassay was used to quantify levels of PlGF and sFlt-1. The development cohort of over 500 participants identified a sFlt-1:PlGF ratio of 38 as having an important predictive value. The subsequent validation cohort, again with over 500 participants, reported a negative predictive value of 99.3% (95% CI 97.9–99.9) for ruling out pre-eclampsia within one week. Interestingly, the same cut off of 38 was predictive of the absence of fetal adverse outcomes within 1 week; negative predictive value of 99.3% [95% CI, 97.9 to 99.9]. The study showed that an sFlt-1: PlGF ratio of 38 or lower can be used to predict the short-term absence of pre-eclampsia and adverse fetal events in women in whom the syndrome is suspected clinically (15). The positive predictive value; a diagnosis of preeclampsia, eclampsia, or the HELLP syndrome within 4

weeks, was 36.7% (95% CI, 28.4 to 45.7) using the same sFlt-1: PlGF ratio of 38. Post hoc analysis however showed this was still an improvement in prediction compared to the use of clinical variables such as blood pressure and urinalysis alone.

NICE (The National Institute for Health and Clinical Excellence, UK) has recently published guidance on incorporation of PlGF testing, in addition to clinical assessment, in women presenting with suspected pre-eclampsia from 20-34^{+6} weeks' gestation. It advises that the Triage PlGF test or Elecsys immunoassay sFlt-1/PlGF ratio test may be used, in combination with clinical assessment, to "rule-out" pre-eclampsia in this group of women. However, it advises that these tests should not yet be used to diagnose pre-eclampsia until further research is available, specifically on how an abnormal PlGF result would affect management decisions regarding timing and gestation of delivery and the outcomes associated with this (16).

The objective of this randomised trial is to evaluate the impact of knowledge of PlGF measurement on clinically relevant outcomes. We hypothesise that adding PlGF measurement to current clinical assessment of women with suspected pre-eclampsia prior to 37 weeks' gestation will reduce associated maternal morbidity through improved risk stratification, earlier diagnosis and targeted management of women with the disease. Any intervention in late pregnancy may have an impact on the fetus. On the one hand, earlier diagnosis of pre-eclampsia may precipitate earlier delivery and lead to an increase in neonatal morbidity and mortality secondary to iatrogenic prematurity. Conversely, improved identification of those neonates at highest risk of imminent placental dysfunction may reduce neonatal morbidity by allowing for timely intervention. It is therefore imperative that full evaluation of both potential benefit and harm is conducted before PlGF testing is implemented routinely into clinical practice. If this trial demonstrates a beneficial impact on maternal morbidity and/or neonatal morbidity, alongside a favourable health economic assessment, then there would be a strong case for incorporating PlGF testing into routine clinical

investigations for women presenting with suspected pre-eclampsia before 37 weeks' gestation in a wide variety of healthcare settings.

Methods and Design

Study Design

PARROT Ireland is a multi-centre, stepped wedge cluster-controlled trial of PlGF measurement in women presenting with suspected pre-eclampsia from 20 weeks and prior to 37 weeks' gestation. As implementation of a diagnostic test may alter physician management, a cluster design was chosen rather than individual randomisation. This allows for a change in management to occur at a hospital rather than at an individual woman level, which is preferable in trials involving a diagnostic test and allows the clinical influence of the additional test to be evaluated in a pragmatic fashion (17). Each maternity hospital acts as a cluster. All clusters commenced the trial in the control arm and in turn, each cluster transitions at random from the control to the intervention at pre-specified time points. Once a cluster has changed over to the intervention, it continues as such for the remainder of the trial so that by the end of the trial all clusters will be in the intervention arm (Figure1). A stepped wedge design was chosen so as to increase the social acceptability of the trial to the 7 hospitals (the stake holders /decision makers in all of the hospitals expressed a desire to participate in a trial in which they were guaranteed to get the intervention); and because a trial with just 7 clusters risks baseline imbalance in a parallel design.

The trial will continue for a period of twenty-two months, and with seven clusters the interval between transitions is approximately three months in duration. A restricted method of randomisation was used to provide a balance in total (expected) number of observations across intervention and control periods (details below) (18-20). There is a short transition period of one week whenever a new cluster transitions from control to the intervention. Data collected during this transition period will not be included in any analysis of outcomes.

Recruitment will stop on a pre-specified fixed date in late April 2019 and the study will end when the last recruited participant and neonate are discharged and all outcome data collected.

Setting & Participants

The trial is being conducted within the Health Research Board Mother and Baby Clinical Trial Network Collaborative. The Coombe Women and Infants University Hospital Dublin, Cork University Maternity Hospital, University Maternity Hospital Limerick, The Royal Jubilee Maternity Hospital Belfast, University College Hospital Galway, The National Maternity Hospital Dublin and The Rotunda Maternity Hospital Dublin are the seven largest consultant-led maternity units on the island of Ireland. Combined, they have an annual birth rate of over 44,000, representing over half of the country's total annual births. Women attending these maternity units who present with suspected pre-term pre-eclampsia are eligible for inclusion in this trial. Detailed inclusion and exclusion criteria are described (Table 1 & 2).

Table 1: Inclusion Criteria

Pregnant women between 20+0 and 36+6 weeks of gestation (inclusive) with a;
• Singleton pregnancy
• Aged 18 years or over
• Able to give informed consent
• Presenting with suspected pre-eclampsia: (one or more of the following)
  • Hypertension
  • Dipstick proteinuria
  • Headache
  • Visual disturbances
  • Epigastric or right upper quadrant pain
  • Increasing oedema
  • Suspected fetal growth restriction
  • If the healthcare provider deems that the woman requires further evaluation for possible pre-eclampsia

Table 2: Exclusion Criteria

- Confirmed pre-eclampsia at point of enrolment;
  "sustained hypertension with systolic BP ≥ 140 or diastolic BP ≥ 90 on at least two occasions at least 4hrs apart) with significant quantified proteinuria (>300mg protein on 24hr collection or urine protein creatinine ratio >30mg/mmol) or abnormal pre-eclampsia bloods"
- ≥37 weeks gestation
- Multiple pregnancy
- Abnormal pre-eclampsia bloods (new onset reduced number of platelets or deranged liver function/renal function tests, identified during routine care prior to enrolment and not attributable to anything other than pre-eclampsia).
- Decision regarding imminent delivery already made
- Lethal fetal abnormality present
- Previous participation in PELICAN trial in a prior pregnancy
- Participation in a conflicting trial at the same time as PARROT Ireland
- Plan to use off protocol PIGF testing

Randomisation

The trial statisticians for the study developed a randomisation sequence for site transition from control to intervention; however, the order of site transitioning is concealed from sites and principal investigators until 12 weeks prior to the sites transition date. An allocation sequence was randomly selected (i.e. a cross-over order for the 7 clusters) from a set of random sequences constrained so that the sum of the total cluster sizes in the intervention status was similar to the total sum of the cluster sizes in the control status. Similar was defined to be a difference in the total sums exposed to intervention and control statuses being no different than the expected middle 25th percentile range of differences. To implement this, 10,000 simulations of possible (unique) allocation sequences were performed. From this, the difference in number exposed to intervention and control for each sequence was determined. An allocation sequence was then selected at random from those falling within the middle 25th percentile range of differences (17-19).

Control

Eligible women are approached and provided with detailed information about the trial, both verbally and written, by a trained researcher. Eligibility is determined by review of symptoms

and signs at the time of presentation to the maternity hospital by the local researcher. Participants are not aware of their maternity hospitals current randomisation prior to their enrolment on the trial. Informed consent is obtained in accordance with ICH - GCP guidelines (21). Once an eligible woman has given written informed consent for inclusion in the study, her maternity hospitals current group allocation is revealed (Figure 2). Participants enrolled in the control arm receive usual hospital care as per National guidelines; these are Health Service Executive/Institute of Obstetrics and Gynaecology Irish guidelines for those in the Republic or the NICE guidelines for those in Northern Ireland (Figure 3a and 3b) (22, 23). Eligible women who are approached but who decline to participate in the trial will continue to receive usual hospital care.

Intervention

Participants enrolled in the intervention arm have their plasma PlGF quantified in addition to routine hospital investigations. The PlGF result is made immediately available to the participants clinical team and documented clearly in the participant's medical notes. A suggested further management algorithm is provided to the clinician based on both the degree of hypertension present and the PlGF result. (Figure 4). This algorithm advocates increased frequency of review for those participants identified as having an abnormal PlGF result. The final decision regarding frequency of review remains with the treating clinician. If 4 weeks or more pass and the participant re-presents with symptoms suggestive of pre-eclampsia, a repeat PlGF quantification may be performed as long as the inclusion/exclusion criteria are still satisfied. In certain sites the option of plasma Biobanking will be available. Participants will be consented separately for this. For those who give consent, a portion of the specimen taken will be used to measure the level of PlGF in the plasma and the remainder of the sample will be stored in University College Cork Biobanking facility.

PlGF Quantification

Maternal plasma PlGF quantification is performed on an ethylenediaminetetraacetic acid (EDTA) venous blood sample obtained in the standard fashion. Plasma is obtained through centrifugation and the sample is then processed immediately using a CE marked validated point of care platform; the automated Triage® Meterpro (ALERE San Diego, CA). Each hospital has the necessary equipment in situ and appropriately trained researchers in place, to perform this test as per manufacturer's guidelines. The PlGF measurement is reported as the absolute value in pg/ml within 30 minutes of commencing processing of the sample. All samples taken will be analysed without delay by the researcher after venepuncture has occurred and in accordance with manufacturers instructions. The Triage© PlGF test platform and consumables necessary to perform testing are brought to the cluster just at the point of transition to intervention. It is therefore not available at site for use while the site is in the control arm.

Patient and Public Involvement

Patients/ public were not involved in the development of this trial.

Outcome Measure

Primary Outcome Measure

To evaluate if the intervention is beneficial to both women and their babies and more importantly to ensure it is not harmful to either, the study has two equally important co-primary outcome measures. These are maternal morbidity and neonatal morbidity. For maternal morbidity assessment, an adaption of the fullPIERS score is used (Table 3). The definition of hepatic dysfunction is based on ALT rather than INR, requirement for ICU admission is included as well as the presences of severe hypertension. Severe systolic hypertension is an independent risk factor for stroke in pregnancy and in high resource settings uncontrolled hypertension is the main cause of death in women with pre-eclampsia. (24-26) The interval from diagnosis of pre-eclampsia to delivery is not a suitable outcome measure to use, as we are aware that knowledge of PlGF result may alter clinician management and expedite

delivery (27). For neonatal morbidity assessment, babies are dichotomised into having or not having identified neonatal morbidity by means of a composite neonatal score (Table 4). In order to avoid subjectivity in the diagnosis of morbidity, the majority of components of the neonatal composite score are objective measures; pH < 7.2, positive cultures, admission to NICU. We acknowledge that some subjectivity can arise with staging of disease hence why all stages of each disease will be captured and will comprise the composite outcome; NEC Stage 1-3, IVH Grade 1-4 and ROP Stage 1-5. Neonatal outcomes and morbidity will be captured from local case note review, as documented by the treating neonatologist. In cases where any uncertainty is present, the researcher will discuss the case with the local PI and or the trial clinical fellow and a consensus will be reached

Table 3: Components of the Maternal Morbidity Composite Score

- Confirmed placental abruption
- Intensive Care Admission
- CNS compromise;
  Generalized tonic clonic seizure due to eclampsia, GCS <13, cerebral haemorrhage/ infarct, cortical blindness, retinal detachment, Transient ischaemic attack, reversible ischaemic neurological deficit
- Cardiorespiratory compromise;
  myocardial ischaemia/ infarction, SpO2 <90%, >50% FiO2 for >1hr, intubation (other than for Caesarean section), pulmonary oedema, need for positive inotrope support
- Haematological compromise;
  transfusion of any blood product, platelet count <100 x 109/l;
- Liver compromise;
  hepatic dysfunction (ALT or AST >70 IU/L, haematoma, rupture;
- Kidney compromise;
  acute renal insufficiency (creatinine >150 micromol/l); hemodialysis
- Severe hypertension
  (systolic BP ≥ 160 mmHg on at least one occasion)

Table 4: Components of the Neonatal Morbidity Composite Score

- Perinatal death or death before hospital discharge
- NICU admission for ≥48 hrs.
- Birthweight ≤ 5th customised centile*
- Apgar score <7 at 5 minutes
- Umbilical artery acidosis at birth (cord pH <7.2)

- Admission to neonatal unit
- Respiratory distress syndrome
- Interventricular haemorrhage
- Retinopathy of prematurity
- Confirmed infection (*confirmed on blood or CSF cultures*)
- Necrotising enterocolitis

**Customised birth weight at delivery is calculated using the GROW centile*

Secondary outcome measure

Secondary outcomes include each component of the primary outcome reported individually as well as further maternal and neonatal assessments such as mode of delivery and use of antihypertensive agents (Table 5 & 6). Fetal growth restriction, identified on antenatal ultrasound, has been included as a secondary outcome measure of neonatal morbidity. As PlGF correlates well with placental dysfunction it may be able to differentiate between those babies with pathological growth restriction rather than constitutional growth restriction and hence improve neonatal outcomes.

Table 5: Secondary Outcomes -Maternal

- Final diagnosis of hypertensive disorder of pregnancy (*Chronic HTN, Gestational HTN or pre-eclampsia*)
- Gestation at diagnosis of pre-eclampsia
- use of 1 or more antihypertensive drugs
- Instrumental Delivery (V*entouse or Forceps*)
- Severe hypertension (systolic BP ≥ 160 mmHg on at least one occasion)
- Maternal morbidity by fullPIERS model
    - *Confirmed placental abruption*
    - *Intensive care admission*
    - *Central Nervous System Compromise*
    - *Cardiorespiratory Compromise*
    - *Haematological Compromise*
    - *Liver Compromise*
    - *Kidney Compromise*
- Progression to severe pre-eclampsia as defined by ACOG practice bulletin
    - *Systolic BP ≥ 160mmHG or diastolic BP ≥ 110mmHG on 2 occasions at least 4 hours apart while the patient is on bed rest (unless antihypertensive therapy is initiated before this time)*
    - *Thrombocytopenia (Platelet count <100 x 109/L)*
    - *Impaired liver function as indicated by abnormally elevated blood concentrations of liver enzymes (to twice normal concentration), severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by an alternative diagnoses, or both*

- *Progressive renal insufficiency (serum creatinine concentration greater than 1.1mg/dL (150 µmol/L) or a doubling of the serum creatinine concentration in the absence of other renal disease)*
- *Pulmonary oedema*
- *New onset cerebral or visual disturbances*

- Elective delivery: induction of labour or Caesarean section
- Caesarean section: emergency and elective

Table 6: Secondary Outcomes -Neonatal

- Fetal growth restriction identified on antenatal ultrasound*
  (Estimated Fetal Weight and/or abdominal circumference <10th customised centile, abnormality in umbilical artery doppler velocity or reduced level of amniotic fluid)
- Gestation at delivery
- Perinatal death or death before hospital discharge
- Admission to NICU
- NICU admission for ≥48 hours
- Birthweight ≤ 5th customised centile
- Apgar score <7 at 5 minutes
- Umbilical artery acidosis at birth (*arterial cord pH <7.2*)
- Respiratory distress syndrome
- Interventricular haemorrhage
- Retinopathy of prematurity
- Confirmed infection (*confirmed on blood or CSF cultures*)
- Necrotising enterocolitis

**Antenatal detection of Fetal Growth restriction is based on formal ultrasound assessment of fetal biometry using the Hadlock formula.*

A separate health economic evaluation is assessing the intervention's economic impact. This is achieved through the use of participant quality of life (QoL) questionnaires (EQ-5D & SF-36), (28, 29) a specially designed study specific participant costing questionnaire and by assessment of costs to the health service of community based/ inpatient/day case care, through chart review at discharge (30-32).

Data collection

Trial data captured locally at site by researchers are transmitted securely using an electronic clinical record form (eCRF) to a specific database developed by MedSciNet. Baseline demographic data, QoL questionnaires and the PlGF result are entered live to the eCRF at point of recruitment. The full eCRF is completed after discharge from the maternity hospital

post-delivery, and includes neonatal and maternal medical outcome, costing questionnaire & repeat QoL questionnaires. All data entered to the eCRF is pseudo-anonymised with each participant identified by a unique study number. The identifier key is kept separately locally at site in a secure location. The data system is built to the same security and confidentiality standards as those of hospital electronic health records. The data at each participating centre are handled in accordance with local regulatory legislation and Ethics Committee approval. A detailed description of schedule and timing of data collection is provided (Table 7).

	On presentation with suspected PET Between 20+0 and 36+6 weeks	From enrollment to discharge post delivery		Discharge post delivery	
	In-person visit	Chart	In-person visit	Chart	In-person completed
Randomisation-Institutional level	X				
Inclusion/Exclusion	X				
Informed Consent	X				
Demographics		X[a]			
History, Comorbidities		X[a]			
Con Medications		X[a]		X	
Physical Measurements		X[a]			
Clinical readings		X[a]			
PIGF[b] measurement	X		X[c]		
Biobank sample[d]	X				
Fetal assessments				X	
Prenatal admissions				X	
Maternal PET bloods				X	
Newborn data				X	
Neonatal outcome				X	
Maternal outcome				X	
Complications				X	
Postnatal admissions				X	
Clinical Management				X	
Final Outcomes				X	
EQ-5D, SF-36	X				X
Costing questionnaire					X
In person visits	X		X[c]		

Table 7; SPIRIT Flow Diagram for Schedule of events in PARROT Ireland

[a] May be captured in chart review or in consultation with participant at any time following enrolment.

[b] PIGF testing depends on Institutional randomisation allocation. [c] PIGF testing will be repeated if readmission for suspected preeclampsia. May be repeated more than once. No more often than 4 weekly. [d] Only at biobanking sites

Sample Size

The sample size was fixed by the number of sites and the study duration. It is anticipated that the total sample size will be in the region of 4000 participants; split across 7 clusters and the 8 time periods in the design (equivalent to a cluster-period size of about 71). With a sample size of 4000 and using a two-sided type I error rate of 0.025 (to allow for two co-primary outcomes), we determined the power to detect a 7% reduction in maternal morbidity (relative risk reduction of 20%) from 35% to 28% in the intervention i.e. 'active' group (based on a reported rate of adverse maternal outcome in the region of 35% in the PELICAN trial).(13) (33)This is assuming an ICC in the region of 0.01; but also consider Sensitivity to a range of ICC values between 0.005 and 0.05. The second co-primary outcome is adverse neonatal outcomes. Due to scarcity of information on the ICC, the same ICC as for the maternal outcome is assumed. Current rates of adverse events are around 10%. We determine power to detect an absolute change in neonatal adverse outcomes of 6%.

To allow for the longitudinal nature of the trial, where correlations may differ between observations in the same cluster-period; and those measured in different cluster periods, we incorporate cluster-auto correlations (CAC). There is little information to support likely values for the CAC, so we are guided by values in the literature and explore sensitivity across a range of values (0.64, 0.80 and 0.96). (34, 35)

The power has been estimated using an online RShiny App. (36, 37) We have not included transition periods in the calculation but given the transition periods are just one week in length, this is not expected to significantly affect power. There has been no allowance for varying cluster sizes as this is currently not something which is technically possible in a stepped wedge

study. Sample size calculations were performed assuming linear mixed models with categorical effects for time; random cluster and random cluster by period effects. (38) Under these assumptions, we constructed power curves, which reveal that under most anticipated scenarios the trial will have in the region of 80% power (Figures 5 & 6). (35, 39)

Data Analysis

Clinical Outcome

The primary aim of the study is to evaluate whether there is a difference in the two composite outcomes before and after exposure to the intervention. There will be no double counting of outcomes, individuals not events will be presented for the composite . Mixed effects regression models will be used to allow for the clustering within sites. Calendar time will also be adjusted for since the intervention is sequentially rolled-out both by including fixed categorical time effects and random cluster by categorical time effects (40).

The primary estimate of the treatment effects will therefore be cluster and time adjusted. Time adjustment is essential, as it is a stepped wedge trial. Log Poisson regression models with robust variance estimation (to allow for misspecification of binomial errors) will be used so as to allow estimates of relative risks (41); to estimate risk differences corresponding Binomial models with log links will be fitted. Secondary analysis will adjust for individual and cluster level covariates. In the first instance, comparative estimates of differences between groups will be adjusted for variables used in the randomisation procedure (eg; site, time and hospital size). Further, more fully adjusted analyses, will also be performed. These more fully adjusted analyses will adjust for gestational age at recruitment, maternal age, smoking status, maternal BMI, public versus private obstetric care and maternal co-morbities such as Chronic Renal Disease, SLE/APS & Diabetes. It will also adjust for hospital size (< or >5000 deliveries/annum). Categorised continuous variables (e.g. age) will be treated as continuous variables in this adjustment. If covariate adjustment is not practical, unadjusted estimates will be produced and it will be made clear in the output why this occurred (e.g. not possible due to low event rate lack of model convergence). Null hypotheses and analyses for secondary

outcomes take a similar form to that for the primary outcome, and where outcomes are not binary, analysis will be using the generalized linear mixed model. Transformations will be performed where data are markedly not normally distributed. For the analysis adjusted for covariates and for the secondary outcomes (unadjusted) multiple imputation methods will be used if the proportion of missing data is more than about 5%, and this multiple imputation will also allow for the clustered and temporal nature of the trial. It is not expected that there will be any missing data in the primary outcome; as it will be assumed that if the outcome is present then it will be recorded and if it is not recorded we will assume it is absent. This is a standard and realistic assumption. Results will be presented as adjusted risk ratios with confidence intervals (CI) and risk differences to allow full appreciation of clinical effect. To allow for the two primary outcomes, we will follow good practice and adjust for this multiplicity using a Bonferroni correction and so report 97.5% confidence intervals.

For secondary continuous outcomes mean differences will be reported and 99% confidence intervals for secondary outcomes. We will report latent intra-cluster correlations for all outcomes, along with 95% confidence intervals. Pre-specified subgroup analysis will be undertaken on the primary outcome based on women presenting <35 weeks' gestation versus >35 weeks' gestation; size of unit and final confirmed diagnosis. The stepped wedge trial design will also allow investigation of treatment effect heterogeneity across clusters and time. These exploratory analyses will be reported using 99% confidence intervals. Analysis will be conducted by intention to treat and sites will be considered exposed to the intervention post randomised cross-over date.

Health Economic Outcome

The economic evaluation will be informed by a decision analytical model, which will be designed and constructed for the study to reflect the maternal and fetal pathway and health states. Employing a decision analytical model allows for the extrapolation of existing data and the opportunity to systematically synthesise evidence from various sources. Primary data on

maternal health outcomes will be available from the study with the distribution of EQ-5D-5L & SF-3F6 questionnaires which will inform the estimation of Quality Adjusted Life Years (QALYs). Neonatal outcomes will be informed by secondary sources. A systematic literature review will be conducted to identify QOL/utilities (or proxies for same) associated with neonate outcomes which will be incorporated into the decision analytical model to estimate QALYs. Primary data on resource utilisation will be collected using the costing questionnaire. The costs and effects of the intervention and comparator will be compared to estimate an incremental cost effectiveness ratio in a Cost Utility Analysis. To address parameter and structural uncertainties, a probabilistic sensitivity analysis (PSA) will be performed.

Trial Management

Day to day running of the trial will be coordinated by the Trial Management Group (TMG). The TMG consist of the lead site investigator plus the project manager and the clinical fellow. The TMG will act on behalf of the Sponsor and will be responsible to the Trial Steering Committee (TSC) to ensure that all Sponsors' responsibilities are carried out. The TSC is comprised of all Principal Investigators as well as the TMG, sponsor, HRB and representatives from Statistics, economics, neonatology, laboratory and a lay person. The role of the TSC is to provide overall supervision of the trial. In particular, the TSC will concentrate on the progress of the trial, adherence to the protocol, participant safety and consideration of new information.

Data Monitoring

To provide protection for study participants an independent data monitoring committee (DMC) has been appointed for this trial. The DMC comprises of 4 members who are not involved with any other aspect of the trial. They include an Obstetrician, a neonatologist, a statistician and a midwife. The DMC met and ratified their charter and have advised that all serious adverse events such as stillbirth/neonatal death or profound maternal morbidity in the Intervention arm of the study be reported to them immediately. The DMC will receive regular updates on the progress of the trial every quarter from the trail management group (TMG). The purpose of

these updates is for the DMC to; 1) ensure the quality of data collection 2) ensure that the intervention is being rolled out according to the randomisation plan 3) monitor balance between arms to monitor for potential selection biases and 4) ensure PIGF testing is not overwhelmingly better or worse than no PIGF testing with respect to maternal morbidity with neonatal morbidity. Once 1500 outcomes are available an interim analysis will be conducted and reviewed by the DMC. The interim analysis will report on the co-primary outcomes, follow the same methods as those of the primary analysis, and examine if there is proof beyond reasonable doubt that one particular intervention is definitely indicated or definitely contra-indicated in terms of a net difference of a major endpoint. There will be no formal stopping criteria put in place, but the DMC will be guided by the knowledge that proof beyond reasonable doubt cannot be specified precisely, but a difference of at least three standard deviations in an interim analysis of the primary outcome would be consistent with strong level of evidence. No allowance for this interim analysis has been made in power calculations.

There will be no stopping of the trial for futility as the study will be underpowered to detect small effects.

Discussion

Based on previous experience during the PELICAN study, an analysis of success criteria and barriers to our proposed study was conducted. Potential barriers include the overestimation of (i) identification of eligible women by the research team, (ii) primary outcome event rate (iii) and retention / attrition i.e. gaining outcomes data on all women included.

A recruitment feasibility audit conducted in Cork University Maternity Hospital (CUMH) over the course of a typical week in July 2016 identified 21 women who would be eligible for inclusion in the PARROT Ireland study. This would equate to almost 1100 women per annum in CUMH, approximately 13% of its annual delivery rate. This is in keeping with the quoted 10% incidence of hypertensive disorders of pregnancy (HDP) in the population (42). It is anticipated that over the 22 month duration of the study across the 7 hospitals approximately

10,486 women will meet the study inclusion criteria (13% of the combined annual delivery rate), and of these 4,000 will be recruited into this trial (approximately 38% of those eligible). As inclusion in the trial will be optional and require informed consent from participants, not all eligible women in each unit will be included. Projected inclusion rates will be apparent via a dedicated MedSciNet database pre-programmed, available online and contemporaneously updated, allowing prompt action to intervene when not optimal. A conservative requirement of <50% of all eligible women to be recruited in order to reach targets has deliberately been chosen and successful recruitment of the same population in the PELICAN study is reassuring. As with any study we may get a higher or lower incidence of the primary outcome of interest than anticipated. We should get an early indication of this at the interim analysis.

As participation in the trial does not require any extra attendances/input from the participant for the remainder of the pregnancy, it is likely that retention of participants will not be an issue. Similarly, the data outcome to assess for maternal and neonatal morbidity can be readily obtained post-delivery following discharge of the participant from their stored medical records locally at each unit. However, in order to fully examine the health economic outcomes there exists a reliance on the return of completed questionnaires by the participant post-delivery. To minimise attrition rates, the researcher at each site will endeavour to meet with each participant post-delivery prior to their discharge and encourage them to complete the health economic questionnaires. In the PELICAN study only 1% of the cohort were lost to follow up. The risk of incomplete data collection of outcomes in studies such as this is more relevant if women deliver in a different unit to that which they are recruited in to the trial. However, all seven clusters in our trial are large tertiary referral units and patient transfer during pregnancy is rare. We are therefore confident that the likely rate of loss to follow up will be similar and in the order of 1%.

There are a number of advantages with the use of stepped wedge design. It allows a phased implementation of the intervention, which is preferable when commencement in all clusters

simultaneously would be challenging. As all clusters ultimately receive the intervention, it increases willingness of the clusters to partake in the trial. We acknowledge that seven clusters is a small number of clusters and this is an important limitation of the study. Mostly this is a limitation because it will mean that the findings have questionable generalisability. But, if these clusters are representative then the findings may still be generalizable in part. The other limitation that seven clusters brings about is questionable internal reliability. However, because all of the clusters receive both the intervention and control condition, the clusters serve as their own controls. Not only does this lessen the impact of chance imbalance but it also increases the power of the study (particularly so when the ICC is large, as is the case here). The study does only have in the region of 80% power and should parameters such as the ICC be very different to that which we have assumed, then it is correct that the study might be underpowered. To ensure that this is properly accounted for at the analysis stage, we will report appropriate CIs around all point estimates, so the impact of any impression is properly reported.

Another potential limitation worth noting is the slightly different management algorithm for one cluster, Belfast, in the control arm. The Belfast control arm algorithm is taken directly from the NICE Hypertension in Pregnancy guidelines. All other clusters are using an algorithm taken from the HSE Guidelines for Hypertension in Pregnancy. The two are essentially the same except the HSE algorithm also includes a recommendation for a fetal ultrasound in cases where the participant is <34 weeks gestation. It is not anticipated that the difference in these algorithms should have any bearing on the overall trial results. We will conduct a sensitivity analysis with the Belfast site removed and see if the result remains consistent.

Ideally PlGF testing should be performed for all participants enrolled in the study, with blinding of the result for those in the control arm. This would allow for test performance statistics to be performed. Unfortunately, testing of control participants will not be conducted in our trial, which is a notable limitation of the study.

The primary aim of the PARROT Ireland trial is to establish the effectiveness of revealed plasma PlGF measurement in reducing maternal morbidity (with assessment of neonatal safety in parallel) in women presenting with suspected pre-eclampsia prior to 37 weeks' gestation. Should the trial show a reduction in maternal morbidity without an increase in neonatal morbidity, or indeed a reduction in neonatal morbidity with no change in maternal morbidity, it would provide a strong argument for its incorporation into routine obstetric practice. The long-term aim of the trial is to demonstrate if PlGF measurement enables appropriate antenatal stratification of women presenting with suspected pre-eclampsia. Avoiding unnecessary hospital admission would be both clinically and economically beneficial. In contrast, those at increased risk of imminent adverse events, identified by an abnormal PlGF result, would have hospital resources re-directed to them. We anticipate that this trial will provide a definitive result on the benefits of PlGF testing which will act to influence international clinical practice.

A separate RCT, also entitled “PARROT”, has completed recruitment in the United Kingdom since the end of 2017. Although recruiting a similar population of women and using the same PlGF platform, the primary outcome measure for the two RCT’s is different, with the UK PARROT trial focusing on time from enrolment to diagnosis. Both studies are using the same electronic clinical record forms developed by MedSciNet and thus will have a large cross-over of data. The advantage of having these two similar RCT’s conducted almost simultaneously is that robust information on the impact of incorporation of PlGF into clinical care will be generated. In addition the potential exists for a collaborative project such as an individual participant data meta-analyses in the future.

Abbreviations

ALT: Alanine Aminotransferase
AST: Aspartate Aminotransferase
CAC: cluster-auto correlations
CI: Confidence Interval
CNS: Central Nervous System
CSF: Cerebrospinal Fluid
DBP: Diastolic Blood Pressure
EC: Ethics Committee
eCRF: Electronic Clinical Report Form
Flt-1: fms-like tyrosine kinase 1
GCS: Glasgow Coma Scale
HDP: Hypertensive Disorder of Pregnancy
HSE: Health Service Executive
ICC: Intraclass Correlation Coefficient
INFANT: The Irish Centre for Fetal and Neonatal Translational Research
NICE: National Institute for Clinical Excellence
NICU: Neonatal Intensive Care Unit
NNU: Neonatal Unit
PARROT: Placental growth factor in Assessment of women with suspected pre-eclampsia to Reduce maternal morbidity: a Stepped Wedge Cluster Randomised Control Trial
PIL: Patient Information Leaflet
PlGF: Placental Growth Factor
PSA: Probabilistic Sensitivity Analysis
QALY: Quality Adjusted life year
QoL: Quality of Life
RCT: Randomised Controlled Trial
SBP: Systolic Blood Pressure
sFlt-1: soluble fms-like tyrosine kinase 1
VEGF: Vascular endothelial growth factor

Declarations

Ethics approval and consent to participate

The trial is being conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with Good Clinical Practice and applicable regulatory requirements. The local ethics committee at each participating site has reviewed the trial protocol, including the patient information and informed consent form, and full ethical approval granted. Each eligible woman identified is required to give written informed consent prior to her inclusion in the trial. A GCP trained researcher at the local site obtains this consent.

Clinical Research Ethics Committee Cork: ECM 3 (h) 08/11/16

University College Hospital Galway EC: Ref 50/12

Coombe Womens & Infants University Hospital EC: Study No 20-2016

National Maternity Hospital EC: EC 20.2016

University Hospital Limerick EC: Ref: 68/16

Health Research Authority (Belfast): 16/WM/0484

Rotunda Hospital EC: REC-2016-020..

Dissemination

The success of the trial will be dependent entirely upon the collaboration of clinicians in the participating hospitals and those who hold key responsibility for the trial. Hence, the credit for the study will be assigned to the key collaborator(s) from a participating site as it is crucial that those taking credit for the work have actually carried it out. The results of the trial will be reported first to trial collaborators. The results from the PARROT Ireland trial will be published in an established peer reviewed journal. At least one publication of the main results will be made. Links to the publication will be provided in all applicable trial registers. Dissemination of results to participants will take place via the media, trial website and relevant participant organisations. Collaborating investigators will play a vital role in disseminating the results to colleagues and participants.

Figure Legends

Figure 1; Stepped Wedge Cluster Randomised Design for PARROT Ireland

Figure 2; Trial Schematic for PARROT Ireland

Figure 3a; Management Algorithm for Control arm based on HSE guidelines for PARROT Ireland

Figure 3b; Management Algorithm for Control arm based on NICE guidelines for PARROT Ireland

Figure 4; Suggested Management Algorithm for Intervention for PARROT Ireland

Figure 5; Power Curve for PARROT Ireland for Maternal Adverse Outcomes

Figure 6: Power Curve for PARROT Ireland for Neonatal Adverse Outcomes

Availability of data and material

The dataset generated from this study is saved onto a secure electronic database and after close of the study will be archived in line with GCP regulations. The anonymised completed dataset will be available from the chief investigator of the trial upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding & Trial Sponsor

The PARROT Ireland trial is funded by the Health Research Board Mother and Baby Clinical Trial Network Ireland (HRB CTN-2014-010). The trial is sponsored by University College Cork, Ireland. Neither the funders nor trial sponsor had a role in the design of the study and will not have any role in analyses, interpretation of the data, or decision to submit results.

Authors' contributions

All authors (DHR, KH, FB, AC, DD, AH, FM, JM, DM, AK, BM, AM, ED, KO'D & LK) contributed to the overall study design and specific methodologies. LK conceived and designed the study with DD. LK and DHR produced the detailed protocol, with input from all authors. DHR drafted the manuscript with assistance from KH, KOD and LK. All authors have critically read, contributed with inputs and revisions and approved the final manuscript.

Acknowledgements

The authors would like to thank PARROT Ireland participants and the associated maternity units and staff for their support and involvement in this study.

References

1. Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. Lancet. 2005;365(9461):785-99.
2. Meyer NL, Mercer BM, Friedman SA, Sibai BM. Urinary dipstick protein: a poor predictor of absent or severe proteinuria. American journal of obstetrics and gynecology. 1994;170(1 Pt 1):137-41.
3. Waugh JJ, Bell SC, Kilby MD, Blackwell CN, Seed P, Shennan AH, et al. Optimal bedside urinalysis for the detection of proteinuria in hypertensive pregnancy: a study of diagnostic accuracy. BJOG : an international journal of obstetrics and gynaecology. 2005;112(4):412-7.
4. Kuo VS, Koumantakis G, Gallery ED. Proteinuria and its assessment in normal and hypertensive pregnancy. American journal of obstetrics and gynecology. 1992;167(3):723-8.
5. Villar J, Repke J, Markush L, Calvert W, Rhoads G. The measuring of blood pressure during pregnancy. American journal of obstetrics and gynecology. 1989;161(4):1019-24.
6. ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. Obstetrics and gynecology. 2002;99(1):159-67.
7. Meads CA, Cnossen JS, Meher S, Juarez-Garcia A, ter Riet G, Duley L, et al. Methods of prediction and prevention of pre-eclampsia: systematic reviews of accuracy and effectiveness literature with economic modelling. Health Technology Assessment. 2008;12(6):1-+.
8. Maglione D, Guerriero V, Viglietto G, Delli-Bovi P, Persico MG. Isolation of a human placenta cDNA coding for a protein related to the vascular permeability factor. Proceedings of the National Academy of Sciences. 1991;88(20):9267-71.
9. De Vries C, Escobedo JA, Ueno H, Houck K, Ferrara N, Williams LT. The fms-like tyrosine kinase, a receptor for vascular endothelial growth factor. Science. 1992;255(5047):989-91.
10. Kanno S, Oda N, Abe M, Terai Y, Ito M, Shitara K, et al. Roles of two VEGF receptors, Flt-1 and KDR, in the signal transduction of VEGF effects in human vascular endothelial cells. Oncogene. 2000;19(17):2138-46.
11. Hayman R, Brockelsby J, Kenny L, Baker P. Preeclampsia: The endothelium, circulating factor(s) and vascular endothelial growth factor. Journal of the Society for Gynecologic Investigation. 1999;6(1):3-10.
12. Levine RJ, Maynard SE, Qian C, Lim KH, England LJ, Yu KF, et al. Circulating Angiogenic Factors and the Risk of Preeclampsia. New England Journal of Medicine. 2004;350(7):672-83.
13. Chappell LC, Duckworth S, Seed PT, Griffin M, Myers J, Mackillop L, et al. Diagnostic Accuracy of Placental Growth Factor in Women With Suspected Preeclampsia A Prospective Multicenter Study. Circulation. 2013;128(19):2121-31.
14. Zeisler H, Llurba E, Chantraine F, Vatish M, Staff AC, Sennström M, et al. Predictive Value of the sFlt-1:PlGF Ratio in Women with Suspected Preeclampsia. New England Journal of Medicine. 2016;374(1):13-22.
15. Zeisler H, Llurba E, Chantraine F, Vatish M, Staff AC, Sennstrom M, et al. Predictive Value of the sFlt-1:PlGF Ratio in Women with Suspected Preeclampsia. New England Journal of Medicine. 2016;374(1):13-22.
16. PlGF-based testing to help diagnose suspected pre-eclampsia (Triage PlGF test, Elecsys immunoassay sFlt-1/PlGF ratio, DELFIA Xpress PlGF 1-2-3 test, and BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ra [cited May 2016]. Diagnostics guidance [DG23] Published date: May 2016:[Available from: https://www.nice.org.uk/guidance/dg23/chapter/1-Recommendations.
17. Hemming K, Haines TP, Chilton PJ, Girling AJ, Lilford RJ. The stepped wedge cluster randomised trial: rationale, design, analysis, and reporting. BMJ : British Medical Journal. 2015;350.
18. Bland JM. Cluster randomised trials in the medical literature: two bibliometric surveys. BMC medical research methodology. 2004;4:21-.
19. Brown CA, Lilford RJ. The stepped wedge trial design: a systematic review. BMC medical research methodology. 2006;6:54-.

20. Stolberg HO, Norman G, Trop I. Randomized controlled trials. American Journal of Roentgenology. 2004;183(6):1539-44.
21. GCP. ICH HARMONISED TRIPARTITE GUIDELINE, GUIDELINE FOR GOOD CLINICAL PRACTICE E6(R1) 1996. Available from: https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf.
22. HSE. THE MANANGEMENT OF HYPERTENSION IN PREGNANCY. 2016. p. 1-32.
23. NICE. Hypertension in Pregnancy 2010. Available from: https://www.nice.org.uk/guidance/cg107.
24. Cantwell R, Clutton-Brock T, Cooper G, Dawson A, Drife J, Garrod D, et al. Saving Mothers' Lives: Reviewing maternal deaths to make motherhood safer: 2006-2008. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. BJOG : an international journal of obstetrics and gynaecology. 2011;118 Suppl 1:1-203.
25. Schutte JM, Schuitemaker NWE, Van Roosmalen J, Steegers EAP, Dutch Maternal Mortality C. Substandard care in maternal mortality due to hypertensive disease in pregnancy in the Netherlands. BJOG: An International Journal of Obstetrics & Gynaecology. 2008;115(6):732-6.
26. Martin Jr JN, Thigpen BD, Moore RC, Rose CH, Cushman J, May W. Stroke and severe preeclampsia and eclampsia: A paradigm shift focusing on systolic blood pressure. Obstetrics and gynecology. 2005;105(2):246-54.
27. Sharp A, Chappell L, Dekker G, Pelletier S, Garnier Y, Zeren O, et al. OP 2 Placental growth factor informed management of suspected pre-eclampsia and/or fetal growth restriction – The MAPPLE cohort study. Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health. 2017;9(Supplement C):9-10.
28. EQ-5D. Available from: www.euroqol.org
29. SF 6D. Available from: https://www.sheffield.ac.uk/scharr/sections/heds/mvh/sf-6d
30. EuroQol--a new facility for the measurement of health-related quality of life. Health policy (Amsterdam, Netherlands). 1990;16(3):199-208.
31. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Medical care. 1992;30(6):473-83.
32. Brazier J, Usherwood T, Harper R, Thomas K. Deriving a preference-based single index from the UK SF-36 Health Survey. Journal of clinical epidemiology. 1998;51(11):1115-28.
33. Chappell LC, Duckworth S, Seed PT, Griffin M, Myers J, Mackillop L, et al. Diagnostic Accuracy of Placental Growth Factor in Women With Suspected Preeclampsia A Prospective Multicenter Study. Circulation. 2013;128(19):2121-31.
34. Martin J, Girling A, Nirantharakumar K, Ryan R, Marshall T, Hemming K. Intra-cluster and inter-period correlation coefficients for cross-sectional cluster randomised controlled trials for type-2 diabetes in UK primary care. Trials. 2016;17:402.
35. Hooper R, Bourke L. Cluster randomised trials with repeated cross sections: alternatives to parallel group designs. BMJ : British Medical Journal. 2015;350.
36. Hemming K. Available from: https://clusterrcts.shinyapps.io/rshinyapp/.
37. Campbell MK, Fayers PM, Grimshaw JM. Determinants of the intracluster correlation coefficient in cluster randomized trials: the case of implementation research. Clinical trials (London, England). 2005;2(2):99-107.
38. Hemming K, Taljaard M. Sample size calculations for stepped wedge and cluster randomised trials: a unified approach. Journal of clinical epidemiology. 2016;69:137-46.
39. Hemming K, Eldridge S, Forbes G, Weijer C, Taljaard M. How to design efficient cluster randomised trials. Bmj. 2017;358:j3064.
40. Hemming K, Taljaard M, Forbes A. Analysis of cluster randomised stepped wedge trials with repeated cross-sectional samples. Trials. 2017;18:101.

41. Zou GY. A modified Poisson regression approach to prospective studies with binary data. American Journal of Epidemiology. 2004;159(7):702-6.

42. Duley L. The Global Impact of Pre-eclampsia and Eclampsia. Seminars in Perinatology. 2009;33(3):130-7.

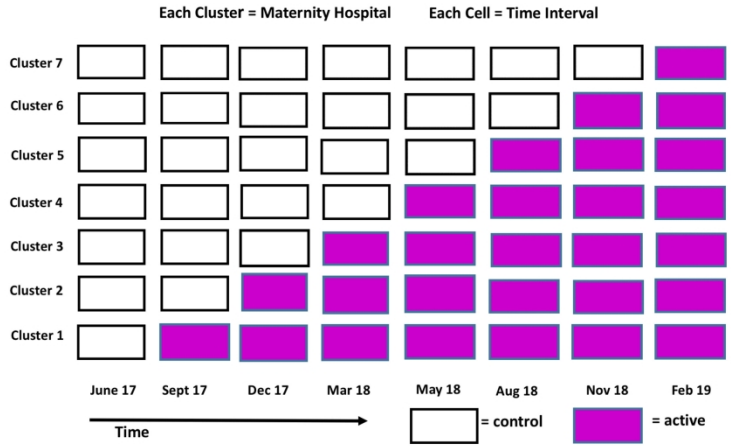

Figure 1; Stepped Wedge Cluster Randomised Design for PARROT Ireland

Figure 1; Stepped Wedge Cluster Randomised Design for PARROT Ireland

297x209mm (300 x 300 DPI)

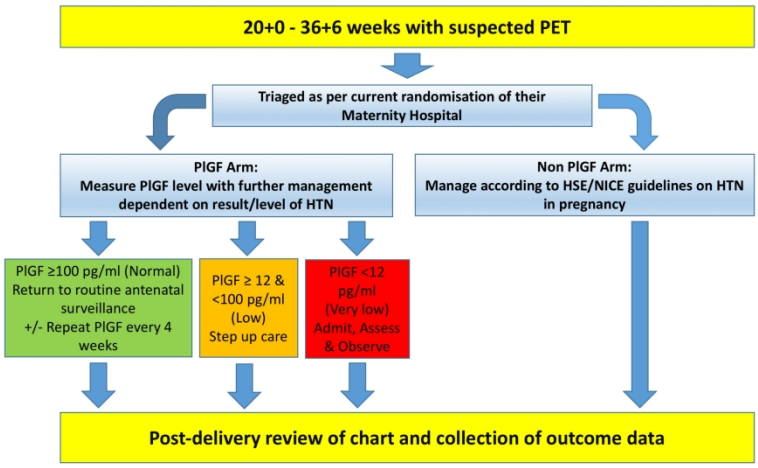

Figure 2; Trial Schematic for PARROT Ireland

Figure 2; Trial Schematic for PARROT Ireland

297x209mm (300 x 300 DPI)

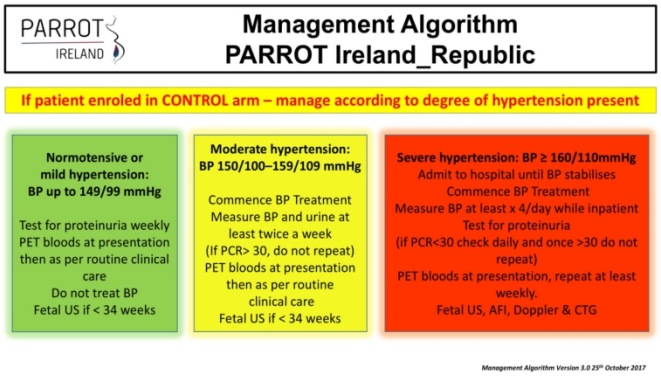

Figure 3a; Management Algorithm for Control arm based on HSE guidelines for PARROT Ireland

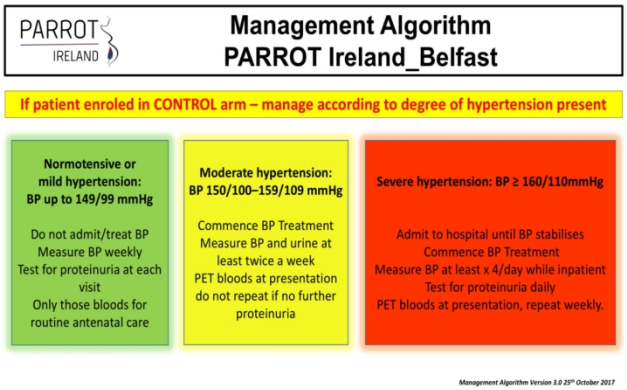

Figure 3b; Management Algorithm for Control arm based on NICE guidelines for PARROT Ireland

Figure 3a; Management Algorithm for Control arm based on HSE guidelines for PARROT Ireland
Figure 3b; Management Algorithm for Control arm based on NICE guidelines for PARROT Ireland

209x297mm (300 x 300 DPI)

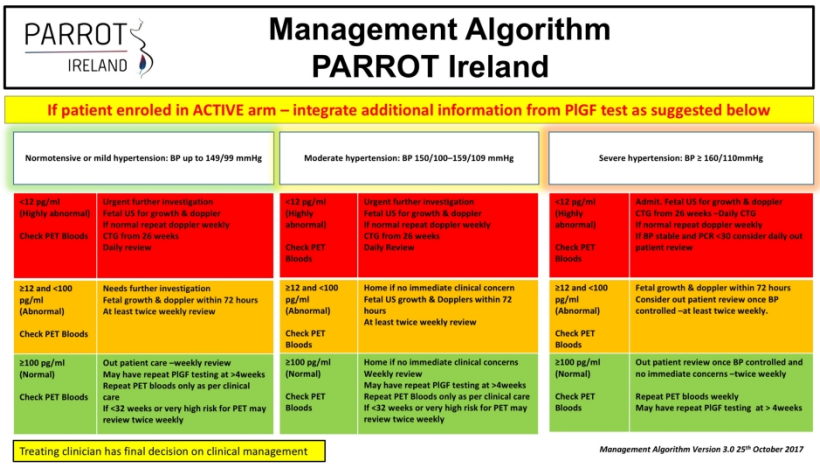

Figure 4; Suggested Management Algorithm for Intervention for PARROT Ireland

Figure 4; Suggested Management Algorithm for Intervention for PARROT Ireland

297x209mm (300 x 300 DPI)

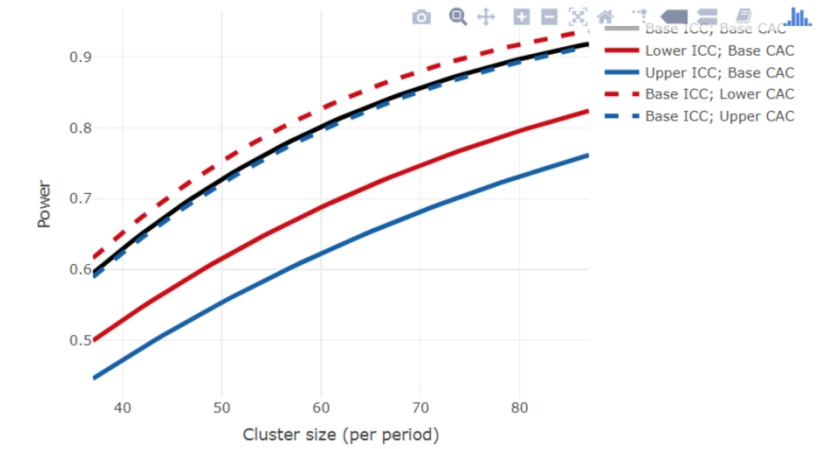

Figure 5; Power Curve for PARROT Ireland for Maternal Adverse Outcomes

Figure 5; Power Curve for PARROT Ireland for Maternal Adverse Outcomes

Caption: Calculation assumes a stepped wedge design with 7 clusters randomised to 7 sequences (8 cluster-periods); a cross-sectional design; Base-case ICC is 0.001; lower ICC is 0.005; upper ICC is 0.01; base-case CAC is 0.8; lower CAC is 0.64; upper CAC is 0.96. Proportion under the control condition is 0.35 and under the intervention condition is 0.28; significance level is 0.025 (see text for justification) and test is two sided. Assumes large sample normal approximations.

297x209mm (300 x 300 DPI)

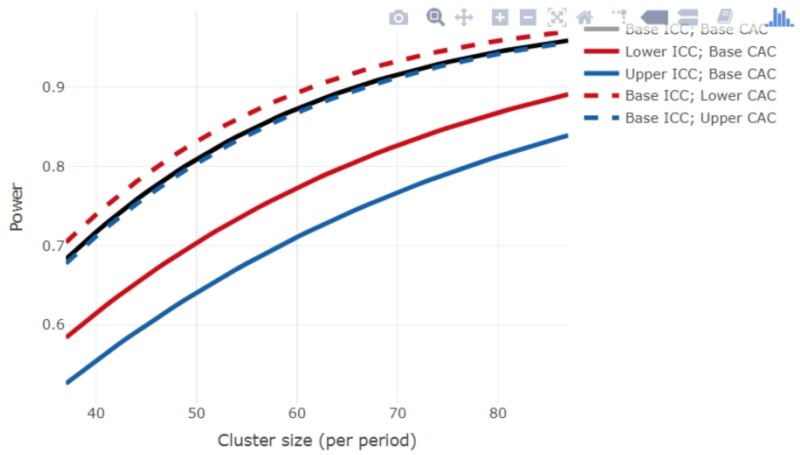

Figure 6: Power Curve for PARROT Ireland for Neonatal Adverse Outcomes

Figure 6: Power Curve for PARROT Ireland for Neonatal Adverse Outcomes

Caption: Calculation assumes a stepped wedge design with 7 clusters randomised to 7 sequences (8 cluster-periods); a cross-sectional design; Base-case ICC is 0.001; lower ICC is 0.005; upper ICC is 0.01; base-case CAC is 0.8; lower CAC is 0.64; upper CAC is 0.96. Proportion under the control condition is 0.1 and under the intervention condition is 0.155; significance level is 0.025 (see text for justification) and test is two sided. Assumes large sample normal approximations.

297x209mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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	1
	2b	All items from the World Health Organization Trial Registration Data Set	Supplementary Material
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	25
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-2, 25
	5b	Name and contact information for the trial sponsor	25
	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	25

	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)	19
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	5-7
	6b	Explanation for choice of comparators	10-11
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)	8
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	9
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)	9-10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-11
	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)	10-11
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10-11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10-11

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	12-14
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)	16
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	16
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	19
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	10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10
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	15
	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	20
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	15
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	17-18
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17-18
	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)	17-18
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	20-21
	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	20-21
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	20-21
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	20-21

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	24
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)	19
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10-11
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	11
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	15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	25
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	26
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	25
	31b	Authorship eligibility guidelines and any intended use of professional writers	25
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	25

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary Material
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*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.