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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:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-023562
Article Type:	Protocol
Date Submitted by the Author:	12-Apr-2018
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Keywords:	Pre-eclampsia, placental growth factor, stepped wedge cluster randomised trial, point of care diagnostic test

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4 2 of women with suspected pre-eclampsia to **R**educe
5 3 maternal morbidity: a Stepped Wedge Cluster **R**andomised
6 4 **C**ontrol **T**rial) Research Study Protocol
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review only

1 **Abstract**

2 **Background**

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

12 **Methods**

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

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3 **Discussion**

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

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15 **Strengths and limitations of this study**

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

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20 **Trial registration**

21 Clinical Trials NCT02881073 (26th August 2016)

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23 **Keywords**

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3 1 Pre-eclampsia, placental growth factor, PIGF, diagnostic test, point of care, stepped wedge
4 cluster randomised controlled trial
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13 **Background**

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15 6 Pre-eclampsia (PET) is characterised by hypertension and proteinuria, complicates 2-8% of
16 7 pregnancies, and is associated with significant maternal and neonatal morbidity and
17 8 mortality (1). Currently women who present with suspected pre-eclampsia are triaged on the
18 9 basis of hypertension and dipstick proteinuria. Both of these clinical endpoints are subject to
19 10 observer error and poor test accuracy, with false positive and negative diagnoses of pre-
20 11 eclampsia occurring in clinical practice (2-5). Current biochemical tests are imperfect at
21 12 stratifying women for more intensive surveillance as they only identify advanced disease
22 13 where there is already marked end-organ damage (6). While biomarkers and imaging
23 14 techniques have been evaluated for improving detection, none have adequate sensitivity
24 15 and/or specificity for the diagnosis of pre-eclampsia (7).
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37 17 Placental growth factor (PIGF) belongs to the vascular endothelial growth factor (VEGF)
38 18 family and represents a key regulator of angiogenic events in pathological conditions. PIGF
39 19 exerts its biological function through the binding and activation of the receptor Flt-1. In pre-
40 20 eclampsia, it is thought that endothelial dysfunction leads to an increased level of a
41 21 circulating decoy receptor, known as soluble Flt-1, (sFlt-1), a soluble receptor for both
42 22 VEGF-A and PIGF (8). Circulating levels of sFlt-1 are increased in pre-eclampsia and
43 23 particularly in the early onset form of the disease, resulting in reduced levels of free VEGF-A
44 24 and PIGF in the maternal circulation. Thus, the endothelial dysfunction observed in pre-
45 25 eclampsia may be due to excess neutralisation of VEGF-A and PIGF by circulating sFlt-1.
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55 26 Levine et al. showed that in normal pregnancy, PIGF levels track the development of the
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1 placenta, peaking at about 32 weeks' gestation when the placenta is developed fully and
2 then declining until delivery (9). However, in pre-eclampsia, this rise and fall is considerably
3 lower throughout pregnancy, and levels are strikingly lower when the condition presents
4 clinically.

5 The PELICAN study was the first and largest prospective evaluation of PIGF in women
6 presenting with suspected pre-eclampsia (10). This blinded observational cohort study was
7 conducted in seven consultant-led maternity units in the UK and Ireland between January
8 2011 and February 2012. It enrolled women being investigated for suspected pre-eclampsia,
9 quantified their plasma PIGF using a point of care device, the Alere Triage PIGF test®, but
10 did not reveal the result to their clinician. The study found that a PIGF value <100 pg/ml, in
11 women presenting prior to 35 completed weeks' gestation had a negative predictive value of
12 98% (95% CI, 93 to 99.5) and a positive predictive value of 44% (95% CI, 36 to 52) in
13 determining those that would require delivery for a confirmed diagnosis of pre-eclampsia
14 within the next 14 days. The study reported a PIGF <100 pg/ml to be a better predictor than
15 all other current commonly used predictive tests of pre-eclampsia, either singly or in
16 combination (blood pressure, urinalysis or biochemical markers) with an area under the ROC
17 curve for low PIGF of 0.87 compared to 0.76 for the next best predictor.

18 The PROGNOSIS study was a prospective, multicentre, blinded, observational study
19 conducted in 14 countries from 2011 to 2014 (11). Its aim was to derive and validate a ratio
20 of serum sFlt-1 to PIGF that would be predictive of the absence or presence of pre-
21 eclampsia in the short term. It included women with singleton pregnancies from 24 weeks to
22 36+6 weeks' gestation in whom a clinical suspicion of pre-eclampsia existed. The Elecsys
23 immunoassay was used to quantify levels of PIGF and sFlt-1. The development cohort of
24 over 500 participants identified a sFlt-1:PIGF ratio of 38 as having an important predictive
25 value. The subsequent validation cohort, again with over 500 participants, reported a
26 negative predictive value of 99.3% (95% CI 97.9–99.9) for ruling out pre-eclampsia within
27 one week. Interestingly, the same cut off of 38 was predictive of the absence of fetal adverse

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

9 NICE (The National Institute for Health and Clinical Excellence, UK) has recently published
10 guidance on incorporation of PIGF testing, in addition to clinical assessment, in women
11 presenting with suspected pre-eclampsia from 20-34⁶ weeks' gestation. It advises that the
12 Triage PIGF test or Elecsys immunoassay sFlt-1/PIGF ratio test may be used, in
13 combination with clinical assessment, to "rule-out" pre-eclampsia in this group of women.
14 However, it advises that these tests should not yet be used to diagnose pre-eclampsia until
15 further research is available, specifically on how an abnormal PIGF result would affect
16 management decisions regarding timing and gestation of delivery and the outcomes
17 associated with this (13).

18 The objective of this randomised trial is to evaluate the impact of knowledge of PIGF
19 measurement on clinically relevant outcomes. We hypothesise that adding PIGF
20 measurement to current clinical assessment of women with suspected pre-eclampsia prior to
21 37 weeks' gestation will reduce associated maternal morbidity through improved risk
22 stratification, earlier diagnosis and targeted management of women with the disease. Any
23 intervention in late pregnancy may have an impact on the fetus. On the one hand, earlier
24 diagnosis of pre-eclampsia may precipitate earlier delivery and lead to an increase in
25 neonatal morbidity and mortality secondary to iatrogenic prematurity. Conversely, improved
26 identification of those neonates at highest risk of imminent placental dysfunction may reduce

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

9 **Methods and Design**

10 **Study Design**

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

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

10

11 **Setting & Participants**

12 The trial is being conducted within the Health Research Board Mother and Baby Clinical Trial
13 Network Collaborative. The Coombe Women and Infants University Hospital Dublin, Cork
14 University Maternity Hospital, University Maternity Hospital Limerick, The Royal Jubilee
15 Maternity Hospital Belfast, University College Hospital Galway, The National Maternity
16 Hospital Dublin and The Rotunda Maternity Hospital Dublin are the seven largest consultant-
17 led maternity units on the island of Ireland. Combined, they have an annual birth rate of over
18 44,000, representing over half of the country's total annual births. Women attending these
19 maternity units who present with suspected pre-term pre-eclampsia are eligible for inclusion
20 in this trial. Detailed inclusion and exclusion criteria are described (Table 1 & 2).

21

22 **Randomisation**

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

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3 1 defined to be a difference in the total sums exposed to intervention and control statuses
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5 2 being no different than the expected middle 25th percentile range of differences. To
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7 3 implement this, 10,000 simulations of possible (unique) allocation sequences were
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9 4 performed. From this, the difference in number exposed to intervention and control for each
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11 5 sequence was determined. An allocation sequence was then selected at random from those
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13 6 falling within the middle 25th percentile range of differences (14-16).
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8 **Control**

9 Eligible women are approached and provided with detailed information about the trial, both
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11 10 verbally and written, by a trained researcher. Eligibility is determined by review of symptoms
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13 11 and signs at the time of presentation to the maternity hospital by the local researcher.
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15 12 Participants are not aware of their maternity hospitals current randomisation prior to their
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17 13 enrolment on the trial. Informed consent is obtained in accordance with ICH - GCP
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19 14 guidelines (18). Once an eligible woman has given written informed consent for inclusion in
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21 15 the study, her maternity hospitals current group allocation is revealed (Figure 2). Participants
22
23 16 enrolled in the control arm receive usual hospital care as per National guidelines; these are
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25 17 Health Service Executive/Institute of Obstetrics and Gynaecology Irish guidelines for those
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27 18 in the Republic or the NICE guidelines for those in Northern Ireland (Figure 3a and 3b) (19,
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29 19 20).

21 **Intervention**

22 Participants enrolled in the intervention arm have their plasma PIGF quantified in addition to
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24 23 routine hospital investigations. The PIGF result is made immediately available to the
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26 24 participants clinical team and documented clearly in the participant's medical notes. A
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28 25 suggested further management algorithm is provided to the clinician based on both the
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30 26 degree of hypertension present and the PIGF result. (Figure 4). This algorithm advocates
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32 27 increased frequency of review for those participants identified as having an abnormal PIGF
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34 28 result. The final decision regarding frequency of review remains with the treating clinician. If

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3 1 4 weeks or more pass and the participant re-presents with symptoms suggestive of pre-
4 2 eclampsia, a repeat PIGF quantification may be performed as long as the inclusion/exclusion
5 3 criteria are still satisfied.
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10 5 **PIGF Quantification**

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12 6 Maternal plasma PIGF quantification is performed on an ethylenediaminetetraacetic acid
13 7 (EDTA) venous blood sample obtained in the standard fashion. Plasma is obtained through
14 8 centrifugation and the sample is then processed immediately using a CE marked validated
15 9 point of care platform; the automated Triage® Meterpro (ALERE San Diego, CA). Each
16 10 hospital has the necessary equipment in situ and appropriately trained researchers in place,
17 11 to perform this test as per manufacturer's guidelines. The PIGF measurement is reported as
18 12 the absolute value in pg/ml within 30 minutes of sampling.
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14 **Outcome Measure**

15 ***Primary Outcome Measure***

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

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3 1 Secondary outcomes include each component of the primary outcome reported individually
4 as well as further maternal and neonatal assessments such as mode of delivery, antenatal
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6 3 detection of growth restriction and use of antihypertensive agents (Table 5 & 6)

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8 4 A separate health economic evaluation is assessing the intervention's economic impact.
9
10 5 This is achieved through the use of participant quality of life (QoL) questionnaires (EQ-5D &
11 6 SF-36), (25, 26) a specially designed study specific participant costing questionnaire and by
12 7 assessment of costs to the health service of community based/ inpatient/day case care,
13 8 through chart review at discharge (27-29).
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20 **Data collection**

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22 11 Trial data captured locally at site by researchers are transmitted securely using an electronic
23 12 clinical record form (eCRF) to a specific database developed by MedSciNet. Baseline
24 13 demographic data, QoL questionnaires and the PIGF result are entered live to the eCRF at
25 14 point of recruitment. The full eCRF is completed after discharge from the maternity hospital
26 15 post-delivery, and includes neonatal and maternal medical outcome, costing questionnaire &
27 16 repeat QoL questionnaires. All data entered to the eCRF is pseudo-anonymised with each
28 17 participant identified by a unique study number. The identifier key is kept separately locally
29 18 at site in a secure location. The data system is built to the same security and confidentiality
30 19 standards as those of hospital electronic health records. The data at each participating
31 20 centre are handled in accordance with local regulatory legislation and Ethics Committee
32 21 approval. A detailed description of schedule and timing of data collection is provided (Figure
33 22 5).
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48 **Sample Size**

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50 25 The sample size was fixed by the number of sites and the study duration. It is anticipated
51 26 that the total sample size will be in the region of 4000 participants; split across 7 clusters and
52 27 the 8 time periods in the design (equivalent to a cluster-period size of about 71). With a
53 28 sample size of 4000 and using a two-sided type I error rate of 0.025 (to allow for two co-
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1 primary outcomes), we determined the power to detect a 7% reduction in maternal morbidity
2 (relative risk reduction of 20%) from 35% to 28% in the intervention i.e. 'active' group. This is
3 assuming an ICC in the region of 0.01; but also consider Sensitivity to a range of ICC values
4 between 0.005 and 0.05. The second co-primary outcome is adverse neonatal outcomes.
5 Due to scarcity of information on the ICC, the same ICC as for the maternal outcome is
6 assumed. Current rates of adverse events are around 10%. We determine power to detect
7 an absolute change in neonatal adverse outcomes of 6%.

8
9 To allow for the longitudinal nature of the trial, where correlations may differ between
10 observations in the same cluster-period; and those measured in different cluster periods, we
11 incorporate cluster-auto correlations (CAC). There is little information to support likely values
12 for the CAC, so we are guided by values in the literature and explore sensitivity across a
13 range of values (0.64, 0.80 and 0.96) (30, 31).

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16 The power has been estimated using an online RShiny App. (32, 33) We have not included
17 transition periods in the calculation but given the transition periods are just one week in
18 length, this is not expected to significantly affect power. There has been no allowance for
19 varying cluster sizes as this is currently not something which is technically possible in a
20 stepped wedge study. Sample size calculations were performed assuming linear mixed
21 models with categorical effects for time; random cluster and random cluster by period
22 effects. (34) Under these assumptions, we constructed power curves, which reveal that
23 under most anticipated scenarios the trial will have in the region of 80% power (Figures 6 &
24 7). (31, 35)

25 26 **Data Analysis**

27 ***Clinical Outcome***

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3 1 The primary aim of the study is to evaluate whether there is a difference in the two
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5 2 composite outcomes before and after exposure to the intervention. Mixed effects regression
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7 3 models will be used to allow for the clustering within sites. Calendar time will also be
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9 4 adjusted for since the intervention is sequentially rolled-out both by including fixed
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11 5 categorical time effects and random cluster by categorical time effects (36).

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13 6 The primary estimate of the treatment effects will therefore be cluster and time adjusted.
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15 7 Time adjustment is essential, as it is a stepped wedge trial. Log Poisson regression models
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17 8 with robust variance estimation (to allow for misspecification of binomial errors) will be used
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19 9 so as to allow estimates of relative risks (37); to estimate risk differences corresponding
20
21 10 Binomial models with log links will be fitted. Secondary analysis will adjust for individual and
22
23 11 cluster level covariates. Both individual and cluster level covariates to be included in the
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25 12 adjustment will be pre- specified. Null hypotheses and analyses for secondary outcomes
26
27 13 take a similar form to that for the primary outcome, and where outcomes are not binary,
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29 14 analysis will be using the generalized linear mixed model. Transformations will be performed
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31 15 where data are markedly not normally distributed. For the analysis adjusted for covariates
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33 16 and for the secondary outcomes (unadjusted) multiple imputation methods will be used if the
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35 17 proportion of missing data is more than about 5%, and this multiple imputation will also allow
36
37 18 for the clustered and temporal nature of the trial. It is not expected that there will be any
38
39 19 missing data in the primary outcome; as it will be assumed that if the outcome is present
40
41 20 then it will be recorded and if it is not recorded we will assume it is absent. This is a standard
42
43 21 and realistic assumption. Results will be presented as adjusted risk ratios with confidence
44
45 22 intervals (CI) and risk differences to allow full appreciation of clinical effect. To allow for the
46
47 23 two primary outcomes, we will follow good practice and adjust for this multiplicity using a
48
49 24 Bonferroni correction and so report 97.5% confidence intervals.

50
51 25

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53 26 For secondary continuous outcomes mean differences will be reported and 99% confidence
54
55 27 intervals for secondary outcomes. We will report latent intra-cluster correlations for all
56
57 28 outcomes, along with 95% confidence intervals. Pre-specified subgroup analysis will be

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

8 ***Health Economic Outcome***

9 The economic evaluation will be informed by a decision analytical model, which will be
10 designed and constructed for the study to reflect the maternal and fetal pathway and health
11 states. Employing a decision analytical model allows for the extrapolation of existing data
12 and the opportunity to systematically synthesise evidence from various sources. Primary
13 data on maternal health outcomes will be available from the study with the distribution of
14 EQ-5D-5L & SF-36 questionnaires which will inform the estimation of Quality Adjusted Life
15 Years (QALYs). Fetal outcomes will be informed by secondary sources. A systematic
16 literature review will be conducted, the results of which will be used to inform a meta-
17 analysis so as to estimate fetal quality of life outcomes for the estimation of QALYs. Primary
18 data on resource utilisation will be collected using the costing questionnaire. The costs and
19 effects of the intervention and comparator will be compared to estimate an incremental cost
20 effectiveness ratio in a Cost Utility Analysis. To address parameter and structural
21 uncertainties, a probabilistic sensitivity analysis (PSA) will be performed.

23 **Discussion**

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

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2
3 1 outcome event rate (iii) and retention / attrition i.e. gaining outcomes data on all women
4
5 2 included.

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8 3 A recruitment feasibility audit conducted in Cork University Maternity Hospital (CUMH) over
9
10 4 the course of a typical week in July 2016 identified 21 women who would be eligible for
11
12 5 inclusion in the PARROT Ireland study. This would equate to almost 1100 women per
13
14 6 annum in CUMH, approximately 13% of its annual delivery rate. This is in keeping with the
15
16 7 quoted 10% incidence of hypertensive disorders of pregnancy (HDP) in the population (38).
17
18 8 It is anticipated that over the 24 month duration of the study across the 7 hospitals
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20 9 approximately 11,500 women will meet the study inclusion criteria (13% of the combined
21
22 10 annual delivery rate), and of these 4,000 will be recruited into this trial (33% of those
23
24 11 eligible). As inclusion in the trial will be optional and require informed consent from
25
26 12 participants, not all eligible women in each unit will be included. Projected inclusion rates will
27
28 13 be apparent via a dedicated MedSciNet database pre-programmed, available online and
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30 14 contemporaneously updated, allowing prompt action to intervene when not optimal. A
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32 15 conservative requirement of <50% of all eligible women to be recruited in order to reach
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34 16 targets has deliberately been chosen and successful recruitment of the same population in
35
36 17 the PELICAN study is reassuring.

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39 19 As participation in the trial does not require any extra attendances/input from the participant
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41 20 for the remainder of the pregnancy, it is likely that retention of participants will not be an
42
43 21 issue. Similarly, the data outcome to assess for maternal and neonatal morbidity can be
44
45 22 readily obtained post-delivery following discharge of the participant from their stored medical
46
47 23 records locally at each unit. However, in order to fully examine the health economic
48
49 24 outcomes there exists a reliance on the return of completed questionnaires by the participant
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51 25 post-delivery. To minimise attrition rates, the researcher at each site will endeavour to meet
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53 26 with each participant post-delivery prior to their discharge and encourage them to complete
54
55 27 the health economic questionnaires.

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3 1 The primary aim of the PARROT Ireland trial is to establish the effectiveness of revealed
4 2 plasma PIGF measurement in reducing maternal morbidity (with assessment of neonatal
5 3 safety in parallel) in women presenting with suspected pre-eclampsia prior to 37 weeks'
6 4 gestation. Should the trial show a reduction in maternal morbidity without an increase in
7 5 neonatal morbidity, or indeed a reduction in neonatal morbidity with no change in maternal
8 6 morbidity, it would provide a strong argument for its incorporation into routine obstetric
9 7 practice. The long-term aim of the trial is to demonstrate if PIGF measurement enables
10 8 appropriate antenatal stratification of women presenting with suspected pre-eclampsia.
11 9 Avoiding unnecessary hospital admission would be both clinically and economically
12 10 beneficial. In contrast, those at increased risk of imminent adverse events, identified by an
13 11 abnormal PIGF result, would have hospital resources re-directed to them. We anticipate that
14 12 this trial will provide a definitive result on the benefits of PIGF testing which will act to
15 13 influence international clinical practice.

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Abbreviations

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1 **Declarations**

2 **Ethics approval and consent to participate**

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

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

11 University College Hospital Galway EC: Ref 50/12

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

13 National Maternity Hospital EC: EC 20.2016

14 University Hospital Limerick EC: Ref: 68/16

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

16 Rotunda Hospital EC: REC-2016-020..

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18 **Consent for publication**

19 Not Applicable

20

21 **Availability of data and material**

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

25

26 **Competing interests**

27 The authors declare that they have no competing interests.

1 **Funding**

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

6 **Authors' contributions**

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

13 **Acknowledgements**

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

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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;
<i>“sustained hypertension with systolic BP \geq 140 or diastolic BP \geq 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”</i>
• \geq 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 \geq 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 \geq 48 hrs.
 - Birthweight \leq 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 (*Ventouse or Forceps*)
 - Severe hypertension (systolic BP \geq 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 \geq 160mmHG or diastolic BP \geq 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 $<100 \times 10^9/L$)*
 - *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 μ mol/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 $<10^{\text{th}}$ 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 \leq 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

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

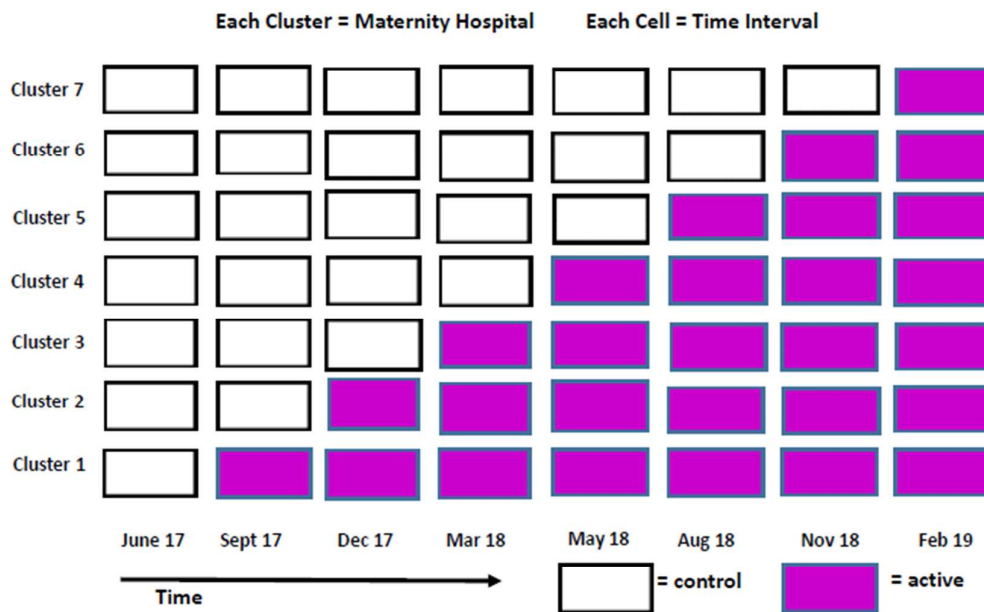


Figure 1; Stepped Wedge Cluster Randomised Design for PARROT Ireland

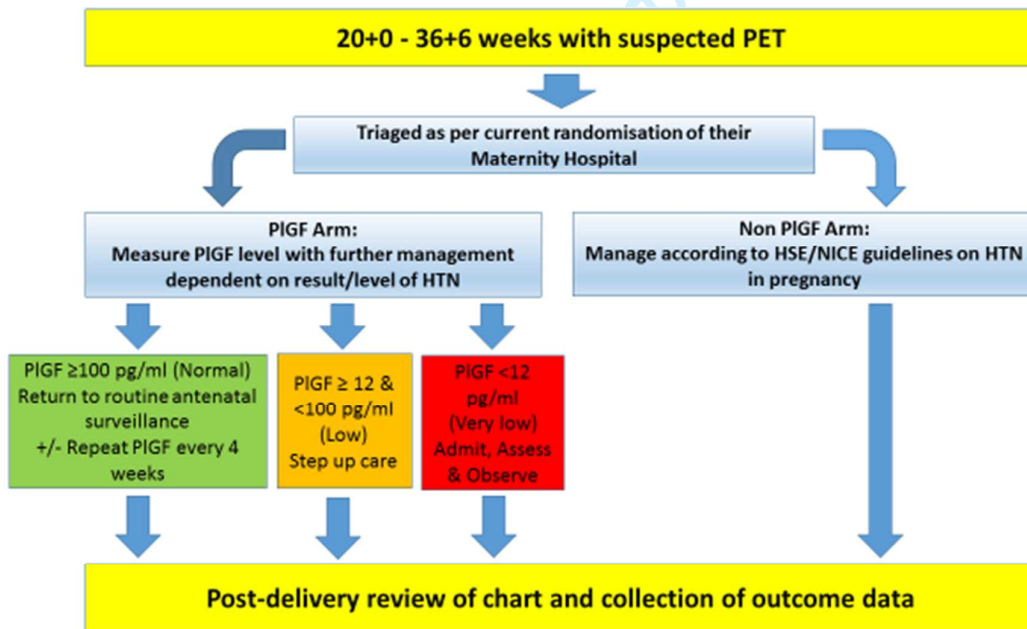


Figure 2; Trial Schematic for PARROT Ireland

PARROT IRELAND **Management Algorithm PARROT Ireland_Republic**

If patient enrolled in CONTROL arm – manage according to degree of hypertension present

Normotensive or mild hypertension: BP up to 149/99 mmHg

Test for proteinuria weekly
 PET bloods at presentation then as per routine clinical care
 Do not treat BP
 Fetal US if < 34 weeks

Moderate hypertension: BP 150/100–159/109 mmHg

Commence BP Treatment
 Measure BP and urine at least twice a week
 (If PCR > 30, do not repeat)
 PET bloods at presentation then as per routine clinical care
 Fetal US if < 34 weeks

Severe hypertension: BP ≥ 160/110mmHg

Admit to hospital until BP stabilises
 Commence BP Treatment
 Measure BP at least x 4/day while inpatient
 Test for proteinuria
 (if PCR < 30 check daily and once > 30 do not repeat)
 PET bloods at presentation, repeat at least weekly.
 Fetal US, AFI, Doppler & CTG

Management Algorithm Version 3.0 25th October 2017

PARROT IRELAND **Management Algorithm PARROT Ireland_Belfast**

If patient enrolled in CONTROL arm – manage according to degree of hypertension present

Normotensive or mild hypertension: BP up to 149/99 mmHg

Do not admit/treat BP
 Measure BP weekly
 Test for proteinuria at each visit
 Only those bloods for routine antenatal care

Moderate hypertension: BP 150/100–159/109 mmHg

Commence BP Treatment
 Measure BP and urine at least twice a week
 PET bloods at presentation do not repeat if no further proteinuria

Severe hypertension: BP ≥ 160/110mmHg

Admit to hospital until BP stabilises
 Commence BP Treatment
 Measure BP at least x 4/day while inpatient
 Test for proteinuria daily
 PET bloods at presentation, repeat weekly.

Management Algorithm Version 3.0 25th October 2017

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


		Management Algorithm PARROT Ireland			
If patient enrolled in ACTIVE arm – integrate additional information from PIGF test as suggested below					
Normotensive or mild hypertension: BP up to 149/99 mmHg		Moderate hypertension: BP 150/100–159/109 mmHg		Severe hypertension: BP ≥ 160/110mmHg	
<12 pg/ml (Highly abnormal) Check PET Bloods	Urgent further investigation Fetal US for growth & doppler If normal repeat doppler weekly CTG from 26 weeks Daily review	<12 pg/ml (Highly abnormal) Check PET Bloods	Urgent further investigation Fetal US for growth & doppler If normal repeat doppler weekly CTG from 26 weeks Daily Review	<12 pg/ml (Highly abnormal) Check PET Bloods	Admit. Fetal US for growth & doppler CTG from 26 weeks –Daily CTG If normal repeat doppler weekly If BP stable and PCR <30 consider daily out patient review
≥12 and <100 pg/ml (Abnormal) Check PET Bloods	Needs further investigation Fetal growth & doppler within 72 hours At least twice weekly review	≥12 and <100 pg/ml (Abnormal) Check PET Bloods	Home if no immediate clinical concern Fetal US growth & Dopplers within 72 hours At least twice weekly review	≥12 and <100 pg/ml (Abnormal) Check PET Bloods	Fetal growth & doppler within 72 hours Consider out patient review once BP controlled—at least twice weekly.
≥100 pg/ml (Normal) Check PET Bloods	Out patient care –weekly review May have repeat PIGF testing at >4weeks Repeat PET bloods only as per clinical care If <32 weeks or very high risk for PET may review twice weekly	≥100 pg/ml (Normal) Check PET Bloods	Home if no immediate clinical concerns Weekly review May have repeat PIGF testing at >4weeks Repeat PET Bloods only as per clinical care If <32 weeks or very high risk for PET may review twice weekly	≥100 pg/ml (Normal) Check PET Bloods	Out patient review once BP controlled and no immediate concerns –twice weekly Repeat PET bloods weekly May have repeat PIGF testing at > 4weeks
Treating clinician has final decision on clinical management			Management Algorithm Version 3.0 25 th October 2017		

Figure 4; Suggested Management Algorithm for Intervention for PARROT Ireland

1

	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		

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

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

4 ^b PIGF testing depends on Institutional randomisation allocation.

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

7 ^d Only at biobanking sites

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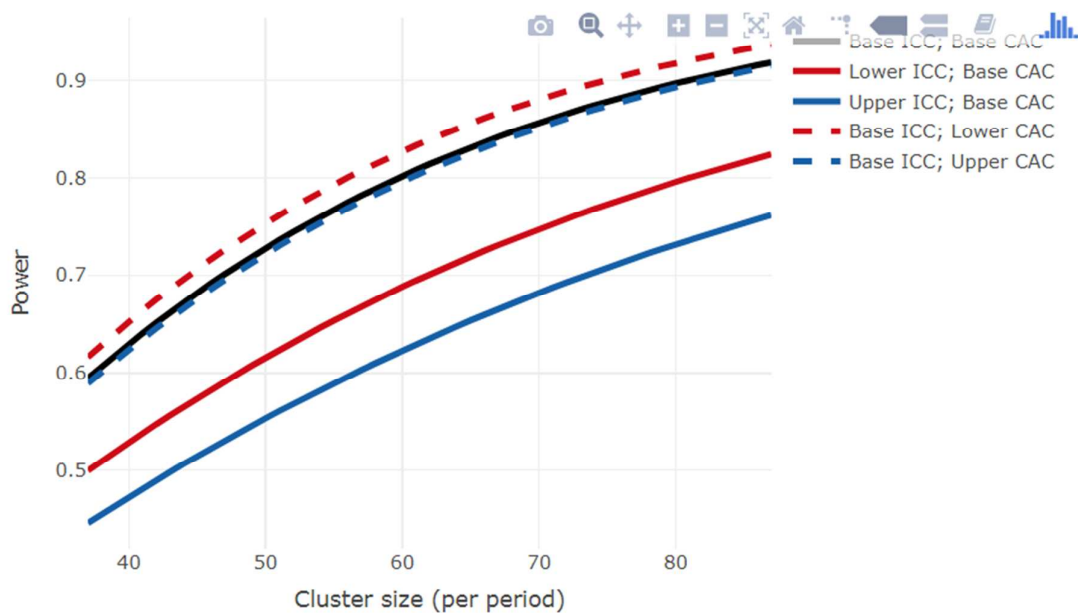
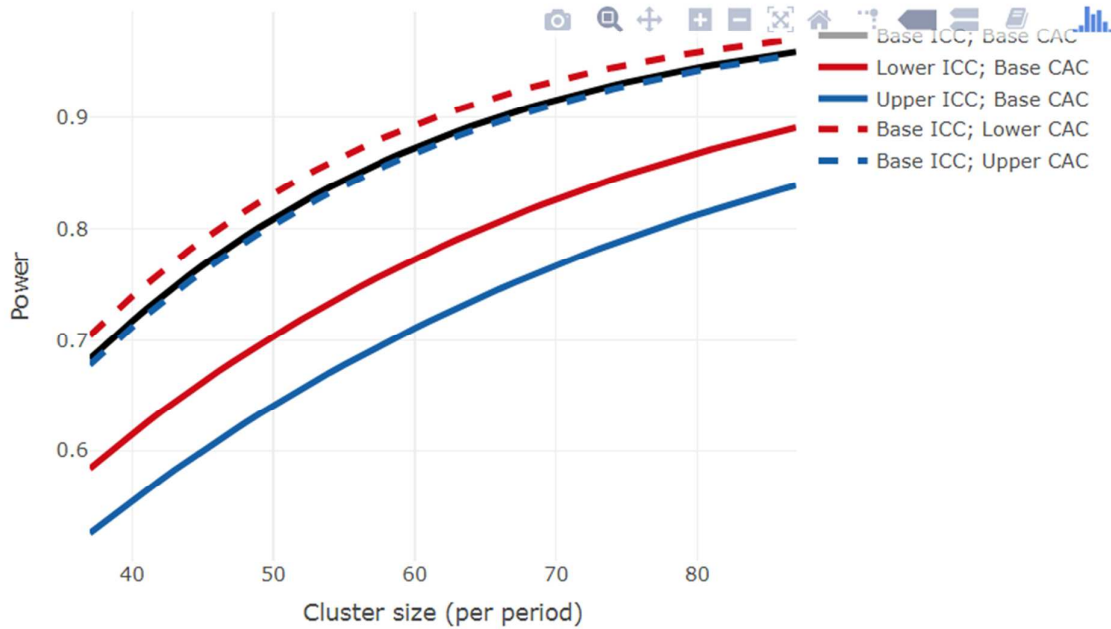


Figure 6; Power Curve for PARROT Ireland for Maternal Adverse Outcomes

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.

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

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

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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	<u>1</u>
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	<u>2</u>
	2b	All items from the World Health Organization Trial Registration Data Set	<u>9-11</u>
Protocol version	3	Date and version identifier	<u>2</u>
Funding	4	Sources and types of financial, material, and other support	<u>4-5</u>
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	<u>4</u>
	5b	Name and contact information for the trial sponsor	<u>4</u>
	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	<u>33</u>
	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)	<u>34</u>

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	<u>14-16</u>
	6b	Explanation for choice of comparators	<u>14-16</u>
Objectives	7	Specific objectives or hypotheses	<u>16</u>
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)	<u>21-22</u>

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	<u>21</u>
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)	<u>22-23</u>
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	<u>23-24</u>
	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)	<u>23-24</u>
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	<u>25</u>
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	<u>23-24</u>
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	<u>17-20</u>
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)	<u>11/23-24</u>

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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

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3	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	<u>27-29</u>
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7	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	<u>31</u>
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10		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	<u>32</u>
11				
12		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	<u>31-32</u>
13				
14				
15	Methods: Monitoring			
16				
17	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	<u>29</u>
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22		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	<u>33</u>
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25	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	<u>29</u>
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28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	<u>32</u>
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32	Ethics and dissemination			
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34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	<u>34</u>
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36				
37	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	<u>36</u>
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3	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	<u>25</u>
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6		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	<u>27</u>
7				
8	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	<u>27-29</u>
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11	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	<u>35</u>
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14	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	<u>27-29</u>
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17	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	<u>35</u>
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20	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	<u>36</u>
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25		31b	Authorship eligibility guidelines and any intended use of professional writers	<u>36</u>
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27		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	<u>36</u>
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29	Appendices			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	<u>41-46</u>
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34	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	<u>27</u>
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37 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.
 38 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons
 39 "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.
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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:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-023562.R1
Article Type:	Protocol
Date Submitted by the Author:	02-Oct-2018
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Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Obstetrics and gynaecology, Research methods, Health economics

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

SCHOLARONE™
Manuscripts

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4 1 **PARROT Ireland: (P**lacental growth factor in **A**ssessment
5 2 of women with suspected pre-eclampsia to **R**educe
6 3 maternal morbidity: a Stepped Wedge Cluster **R**andomised
7 4 **C**ontrol **T**rial) Research Study Protocol
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14 8 **Trial registration**

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17 9 Clinical Trials NCT02881073 (26th August 2016)

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20 10 **Current Protocol:**

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22 11 Version 9.0 Dated: 13 November 2017

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1 **Abstract**

2 **Introduction**

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

11 **Methods and Analysis**

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

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56 2 **Ethics and Dissemination**
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9 3 Ethical approval has been granted from each of the seven maternity hospitals involved in the
10 4 trial. The results of the trial will be presented both nationally and internationally at conference
11 5 and published in an international peer-reviewed journal.
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1718 7 **Strengths and limitations of this study**
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- 21 8 - Randomised Trial
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- 23 9 - Multiple sites with wide geographic distribution
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- 25 10 - Stepped wedge design
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- 27 11 - PIGF testing only in the Intervention arm
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30 12
3132 13 **Keywords**
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35 14 Pre-eclampsia, placental growth factor, PIGF, diagnostic test, point of care, stepped wedge
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37 15 cluster randomised controlled trial
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1 Background

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

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

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3 1 The PELICAN study was the first and largest prospective evaluation of PIGF in women
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5 2 presenting with suspected pre-eclampsia (13). This blinded observational cohort study was
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7 3 conducted in seven consultant-led maternity units in the UK and Ireland between January
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9 4 2011 and February 2012. It enrolled women being investigated for suspected pre-eclampsia,
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11 5 quantified their plasma PIGF using a point of care device, the Alere Triage PIGF test ®, but
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13 6 did not reveal the result to their clinician. The study found that a PIGF value <100 pg/ml, in
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15 7 women presenting prior to 35 completed weeks' gestation had a negative predictive value of
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17 8 98% (95% CI, 93 to 99.5) and a positive predictive value of 44% (95% CI, 36 to 52) in
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19 9 determining those that would require delivery for a confirmed diagnosis of pre-eclampsia within
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21 10 the next 14 days. The study reported a PIGF <100 pg/ml to be a better predictor than all other
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23 11 current commonly used predictive tests of pre-eclampsia, either singly or in combination (blood
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25 12 pressure, urinalysis or biochemical markers) with an area under the ROC curve for low PIGF
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27 13 of 0.87 compared to 0.76 for the next best predictor.

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32 14 The PROGNOSIS study was a prospective, multicentre, blinded, observational study
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34 15 conducted in 14 countries from 2011 to 2014 (14). Its aim was to derive and validate a ratio of
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36 16 serum sFlt-1 to PIGF that would be predictive of the absence or presence of pre-eclampsia in
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38 17 the short term. It included women with singleton pregnancies from 24 weeks to 36+6 weeks'
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40 18 gestation in whom a clinical suspicion of pre-eclampsia existed. The Elecsys immunoassay
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42 19 was used to quantify levels of PIGF and sFlt-1. The development cohort of over 500
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44 20 participants identified a sFlt-1:PIGF ratio of 38 as having an important predictive value. The
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46 21 subsequent validation cohort, again with over 500 participants, reported a negative predictive
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48 22 value of 99.3% (95% CI 97.9–99.9) for ruling out pre-eclampsia within one week. Interestingly,
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50 23 the same cut off of 38 was predictive of the absence of fetal adverse outcomes within 1 week;
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52 24 negative predictive value of 99.3% [95% CI, 97.9 to 99.9]. The study showed that an sFlt-1:
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54 25 PIGF ratio of 38 or lower can be used to predict the short-term absence of pre-eclampsia and
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56 26 adverse fetal events in women in whom the syndrome is suspected clinically (15). The positive
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58 27 predictive value; a diagnosis of preeclampsia, eclampsia, or the HELLP syndrome within 4
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1 weeks, was 36.7% (95% CI, 28.4 to 45.7) using the same sFlt-1: PIGF ratio of 38. Post hoc
2 analysis however showed this was still an improvement in prediction compared to the use of
3 clinical variables such as blood pressure and urinalysis alone.

4 NICE (The National Institute for Health and Clinical Excellence, UK) has recently published
5 guidance on incorporation of PIGF testing, in addition to clinical assessment, in women
6 presenting with suspected pre-eclampsia from 20-34⁺⁶ weeks' gestation. It advises that the
7 Triage PIGF test or Elecsys immunoassay sFlt-1/PIGF ratio test may be used, in combination
8 with clinical assessment, to "rule-out" pre-eclampsia in this group of women. However, it
9 advises that these tests should not yet be used to diagnose pre-eclampsia until further
10 research is available, specifically on how an abnormal PIGF result would affect management
11 decisions regarding timing and gestation of delivery and the outcomes associated with this
12 (16).

13 The objective of this randomised trial is to evaluate the impact of knowledge of PIGF
14 measurement on clinically relevant outcomes. We hypothesise that adding PIGF
15 measurement to current clinical assessment of women with suspected pre-eclampsia prior to
16 37 weeks' gestation will reduce associated maternal morbidity through improved risk
17 stratification, earlier diagnosis and targeted management of women with the disease. Any
18 intervention in late pregnancy may have an impact on the fetus. On the one hand, earlier
19 diagnosis of pre-eclampsia may precipitate earlier delivery and lead to an increase in neonatal
20 morbidity and mortality secondary to iatrogenic prematurity. Conversely, improved
21 identification of those neonates at highest risk of imminent placental dysfunction may reduce
22 neonatal morbidity by allowing for timely intervention. It is therefore imperative that full
23 evaluation of both potential benefit and harm is conducted before PIGF testing is implemented
24 routinely into clinical practice. If this trial demonstrates a beneficial impact on maternal
25 morbidity and/or neonatal morbidity, alongside a favourable health economic assessment,
26 then there would be a strong case for incorporating PIGF testing into routine clinical

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3 1 investigations for women presenting with suspected pre-eclampsia before 37 weeks' gestation
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5 2 in a wide variety of healthcare settings.
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4 **Methods and Design**

5 **Study Design**

6 PARROT Ireland is a multi-centre, stepped wedge cluster-controlled trial of PIGF
7 measurement in women presenting with suspected pre-eclampsia from 20 weeks and prior to
8 37 weeks' gestation. As implementation of a diagnostic test may alter physician management,
9 a cluster design was chosen rather than individual randomisation. This allows for a change in
10 management to occur at a hospital rather than at an individual woman level, which is
11 preferable in trials involving a diagnostic test and allows the clinical influence of the additional
12 test to be evaluated in a pragmatic fashion (17). Each maternity hospital acts as a cluster. All
13 clusters commenced the trial in the control arm and in turn, each cluster transitions at random
14 from the control to the intervention at pre-specified time points. Once a cluster has changed
15 over to the intervention, it continues as such for the remainder of the trial so that by the end
16 of the trial all clusters will be in the intervention arm (Figure1). A stepped wedge design was
17 chosen so as to increase the social acceptability of the trial to the 7 hospitals (the stake holders
18 /decision makers in all of the hospitals expressed a desire to participate in a trial in which they
19 were guaranteed to get the intervention); and because a trial with just 7 clusters risks baseline
20 imbalance in a parallel design.

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

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

4 **Setting & Participants**

5 The trial is being conducted within the Health Research Board Mother and Baby Clinical Trial
 6 Network Collaborative. The Coombe Women and Infants University Hospital Dublin, Cork
 7 University Maternity Hospital, University Maternity Hospital Limerick, The Royal Jubilee
 8 Maternity Hospital Belfast, University College Hospital Galway, The National Maternity
 9 Hospital Dublin and The Rotunda Maternity Hospital Dublin are the seven largest consultant-
 10 led maternity units on the island of Ireland. Combined, they have an annual birth rate of over
 11 44,000, representing over half of the country's total annual births. Women attending these
 12 maternity units who present with suspected pre-term pre-eclampsia are eligible for inclusion
 13 in this trial. Detailed inclusion and exclusion criteria are described (Table 1 & 2).

15 **Table 1: Inclusion Criteria**

17 Pregnant women between 20+0 and 36+6 weeks of gestation (inclusive) 18 with a; 19 • Singleton pregnancy 20 • Aged 18 years or over 21 • Able to give informed consent 22 • Presenting with suspected pre-eclampsia: (one or more of the 23 following) 24 • Hypertension 25 • Dipstick proteinuria 26 • Headache 27 • Visual disturbances 28 • Epigastric or right upper quadrant pain 29 • Increasing oedema 30 • Suspected fetal growth restriction 31 • If the healthcare provider deems that the woman requires further 32 evaluation for possible pre-eclampsia 33

35 **Table 2: Exclusion Criteria**

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

20 Randomisation

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

34 Control

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

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

12 **Intervention**

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

27 **PIGF Quantification**

1
2
3 1 Maternal plasma PIGF quantification is performed on an ethylenediaminetetraacetic acid
4
5 2 (EDTA) venous blood sample obtained in the standard fashion. Plasma is obtained through
6
7 3 centrifugation and the sample is then processed immediately using a CE marked validated
8
9 4 point of care platform; the automated Triage® Meterpro (ALERE San Diego, CA). Each
10
11 5 hospital has the necessary equipment in situ and appropriately trained researchers in place,
12
13 6 to perform this test as per manufacturer's guidelines. The PIGF measurement is reported as
14
15 7 the absolute value in pg/ml within 30 minutes of commencing processing of the sample. All
16
17 8 samples taken will be analysed without delay by the researcher after venepuncture has
18
19 9 occurred and in accordance with manufacturers instructions. The Triage© PIGF test platform
20
21 10 and consumables necessary to perform testing are brought to the cluster just at the point of
22
23 11 transition to intervention. It is therefore not available at site for use while the site is in the
24
25 12 control arm.
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31 **Patient and Public Involvement**

32 Patients/ public were not involved in the development of this trial.
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37 **Outcome Measure**

38 ***Primary Outcome Measure***

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41 19 To evaluate if the intervention is beneficial to both women and their babies and more
42
43 20 importantly to ensure it is not harmful to either, the study has two equally important co-primary
44
45 21 outcome measures. These are maternal morbidity and neonatal morbidity. For maternal
46
47 22 morbidity assessment, an adaption of the fullPIERS score is used (Table 3). The definition of
48
49 23 hepatic dysfunction is based on ALT rather than INR, requirement for ICU admission is
50
51 24 included as well as the presences of severe hypertension. Severe systolic hypertension is an
52
53 25 independent risk factor for stroke in pregnancy and in high resource settings uncontrolled
54
55 26 hypertension is the main cause of death in women with pre-eclampsia. (24-26) The interval
56
57 27 from diagnosis of pre-eclampsia to delivery is not a suitable outcome measure to use, as we
58
59 28 are aware that knowledge of PIGF result may alter clinician management and expedite

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

11
 12 **Table 3: Components of the Maternal Morbidity Composite Score**

-
- 14 • Confirmed placental abruption
 - 15 • Intensive Care Admission
 - 16 • CNS compromise;
 17 *Generalized tonic clonic seizure due to eclampsia, GCS*
 18 *<13, cerebral haemorrhage/ infarct, cortical blindness,*
 19 *retinal detachment, Transient ischaemic attack, reversible*
 20 *ischaemic neurological deficit*
 - 21 • Cardiorespiratory compromise;
 22 *myocardial ischaemia/ infarction, SpO2 <90%, >50% FiO2 for >1hr,*
 23 *intubation (other than for Caesarean section), pulmonary oedema, need*
 24 *for positive inotrope support*
 - 25 • Haematological compromise;
 26 *transfusion of any blood product, platelet count <100 x 109/l;*
 - 27 • Liver compromise;
 28 *hepatic dysfunction (ALT or AST >70 IU/L, haematoma, rupture;*
 - 29 • Kidney compromise;
 30 *acute renal insufficiency (creatinine >150 micromol/l); hemodialysis*
 - 31 • Severe hypertension
 32 *(systolic BP ≥ 160 mmHg on at least one occasion)*

33
 34
 35
 36 **Table 4: Components of the Neonatal Morbidity Composite Score**

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

- 1 • Admission to neonatal unit
- 2 • Respiratory distress syndrome
- 3 • Interventricular haemorrhage
- 4 • Retinopathy of prematurity
- 5 • Confirmed infection (*confirmed on blood or CSF cultures*)
- 6 • Necrotising enterocolitis

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

9 **Secondary outcome measure**

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

18 **Table 5: Secondary Outcomes -Maternal**

-
- 19 • Final diagnosis of hypertensive disorder of pregnancy (*Chronic*
 20 *HTN, Gestational HTN or pre-eclampsia*)
 - 21 • Gestation at diagnosis of pre-eclampsia
 - 22 • use of 1 or more antihypertensive drugs
 - 23 • Instrumental Delivery (*Ventouse or Forceps*)
 - 24 • Severe hypertension (systolic BP \geq 160 mmHg on at least one occasion)
 - 25 • Maternal morbidity by fullPIERS model
 - 26 • *Confirmed placental abruption*
 - 27 • *Intensive care admission*
 - 28 • *Central Nervous System Compromise*
 - 29 • *Cardiorespiratory Compromise*
 - 30 • *Haematological Compromise*
 - 31 • *Liver Compromise*
 - 32 • *Kidney Compromise*
 - 33 • Progression to severe pre-eclampsia as defined by ACOG practice bulletin
 - 34 • *Systolic BP \geq 160mmHG or diastolic BP \geq 110mmHG on 2*
 35 *occasions at least 4 hours apart while the patient is on bed rest*
 36 *(unless antihypertensive therapy is initiated before this time)*
 - 37 • *Thrombocytopenia (Platelet count $<$ 100 x 10⁹/L)*
 - 38 • *Impaired liver function as indicated by abnormally elevated blood*
 39 *concentrations of liver enzymes (to twice normal concentration),*
 40 *severe persistent right upper quadrant or epigastric pain*
 41 *unresponsive to medication and not accounted for by an*
 42 *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 PIGF result are entered live to the eCRF at point of recruitment. The full eCRF is completed after discharge from the maternity hospital

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

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

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

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2
3 1 ^b PIGF testing depends on Institutional randomisation allocation. ^c PIGF testing will be
4 2 repeated if readmission for suspected preeclampsia. May be repeated more than once. No
5 3 more often than 4 weekly. ^d Only at biobanking sites
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11 5 **Sample Size**

12
13 6 The sample size was fixed by the number of sites and the study duration. It is anticipated that
14 7 the total sample size will be in the region of 4000 participants; split across 7 clusters and the
15 8 8 time periods in the design (equivalent to a cluster-period size of about 71). With a sample
16 9 size of 4000 and using a two-sided type I error rate of 0.025 (to allow for two co-primary
17 10 outcomes), we determined the power to detect a 7% reduction in maternal morbidity (relative
18 11 risk reduction of 20%) from 35% to 28% in the intervention i.e. 'active' group (based on a
19 12 reported rate of adverse maternal outcome in the region of 35% in the PELICAN trial).(13)
20 13 (33)This is assuming an ICC in the region of 0.01; but also consider Sensitivity to a range of
21 14 ICC values between 0.005 and 0.05. The second co-primary outcome is adverse neonatal
22 15 outcomes. Due to scarcity of information on the ICC, the same ICC as for the maternal
23 16 outcome is assumed. Current rates of adverse events are around 10%. We determine power
24 17 to detect an absolute change in neonatal adverse outcomes of 6%.
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19 To allow for the longitudinal nature of the trial, where correlations may differ between
20 observations in the same cluster-period; and those measured in different cluster periods, we
21 incorporate cluster-auto correlations (CAC). There is little information to support likely values
22 for the CAC, so we are guided by values in the literature and explore sensitivity across a range
23 of values (0.64, 0.80 and 0.96). (34, 35)
24

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

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

6 **Data Analysis**

7 ***Clinical Outcome***

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

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

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

13
14 For secondary continuous outcomes mean differences will be reported and 99% confidence
15 intervals for secondary outcomes. We will report latent intra-cluster correlations for all
16 outcomes, along with 95% confidence intervals. Pre-specified subgroup analysis will be
17 undertaken on the primary outcome based on women presenting <35 weeks' gestation versus
18 >35 weeks' gestation; size of unit and final confirmed diagnosis. The stepped wedge trial
19 design will also allow investigation of treatment effect heterogeneity across clusters and time.
20 These exploratory analyses will be reported using 99% confidence intervals. Analysis will be
21 conducted by intention to treat and sites will be considered exposed to the intervention post
22 randomised cross-over date.

23 24 **Health Economic Outcome**

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

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3 1 maternal health outcomes will be available from the study with the distribution of EQ-5D-5L &
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5 2 SF-36 questionnaires which will inform the estimation of Quality Adjusted Life Years
6
7 3 (QALYs). Neonatal outcomes will be informed by secondary sources. A systematic literature
8
9 4 review will be conducted to identify QOL/utilities (or proxies for same) associated with neonate
10
11 5 outcomes which will be incorporated into the decision analytical model to estimate QALYs.
12
13 6 Primary data on resource utilisation will be collected using the costing questionnaire. The
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15 7 costs and effects of the intervention and comparator will be compared to estimate an
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17 8 incremental cost effectiveness ratio in a Cost Utility Analysis. To address parameter and
18
19 9 structural uncertainties, a probabilistic sensitivity analysis (PSA) will be performed.
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11 **Trial Management**

12 Day to day running of the trial will be coordinated by the Trial Management Group (TMG). The
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14 TMG consist of the lead site investigator plus the project manager and the clinical fellow. The
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16 TMG will act on behalf of the Sponsor and will be responsible to the Trial Steering Committee
17
18 (TSC) to ensure that all Sponsors' responsibilities are carried out. The TSC is comprised of
19
20 all Principal Investigators as well as the TMG, sponsor, HRB and representatives from
21
22 Statistics, economics, neonatology, laboratory and a lay person. The role of the TSC is to
23
24 provide overall supervision of the trial. In particular, the TSC will concentrate on the progress
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26 of the trial, adherence to the protocol, participant safety and consideration of new information.
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21 **Data Monitoring**

22 To provide protection for study participants an independent data monitoring committee (DMC)
23
24 has been appointed for this trial. The DMC comprises of 4 members who are not involved with
25
26 any other aspect of the trial. They include an Obstetrician, a neonatologist, a statistician and
27
28 a midwife. The DMC met and ratified their charter and have advised that all serious adverse
29
30 events such as stillbirth/neonatal death or profound maternal morbidity in the Intervention arm
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32 of the study be reported to them immediately. The DMC will receive regular updates on the
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34 progress of the trial every quarter from the trail management group (TMG). The purpose of
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1 these updates is for the DMC to; 1) ensure the quality of data collection 2) ensure that the
2 intervention is being rolled out according to the randomisation plan 3) monitor balance
3 between arms to monitor for potential selection biases and 4) ensure PIGF testing is not
4 overwhelmingly better or worse than no PIGF testing with respect to maternal morbidity with
5 neonatal morbidity. Once 1500 outcomes are available an interim analysis will be conducted
6 and reviewed by the DMC. The interim analysis will report on the co-primary outcomes, follow
7 the same methods as those of the primary analysis, and examine if there is proof beyond
8 reasonable doubt that one particular intervention is definitely indicated or definitely contra-
9 indicated in terms of a net difference of a major endpoint. There will be no formal stopping
10 criteria put in place, but the DMC will be guided by the knowledge that proof beyond
11 reasonable doubt cannot be specified precisely, but a difference of at least three standard
12 deviations in an interim analysis of the primary outcome would be consistent with strong level
13 of evidence. No allowance for this interim analysis has been made in power calculations.
14 There will be no stopping of the trial for futility as the study will be underpowered to detect
15 small effects.

16 Discussion

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

21 A recruitment feasibility audit conducted in Cork University Maternity Hospital (CUMH) over
22 the course of a typical week in July 2016 identified 21 women who would be eligible for
23 inclusion in the PARROT Ireland study. This would equate to almost 1100 women per annum
24 in CUMH, approximately 13% of its annual delivery rate. This is in keeping with the quoted
25 10% incidence of hypertensive disorders of pregnancy (HDP) in the population (42). It is
26 anticipated that over the 22 month duration of the study across the 7 hospitals approximately

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2
3 1 10,486 women will meet the study inclusion criteria (13% of the combined annual delivery
4 rate), and of these 4,000 will be recruited into this trial (approximately 38% of those eligible).
5
6 2
7 3 As inclusion in the trial will be optional and require informed consent from participants, not all
8
9 4 eligible women in each unit will be included. Projected inclusion rates will be apparent via a
10
11 5 dedicated MedSciNet database pre-programmed, available online and contemporaneously
12
13 6 updated, allowing prompt action to intervene when not optimal. A conservative requirement of
14
15 7 <50% of all eligible women to be recruited in order to reach targets has deliberately been
16
17 8 chosen and successful recruitment of the same population in the PELICAN study is
18
19 9 reassuring. As with any study we may get a higher or lower incidence of the primary outcome
20
21 10 of interest than anticipated. We should get an early indication of this at the interim analysis.
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26 12 As participation in the trial does not require any extra attendances/input from the participant
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28 13 for the remainder of the pregnancy, it is likely that retention of participants will not be an issue.
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30 14 Similarly, the data outcome to assess for maternal and neonatal morbidity can be readily
31
32 15 obtained post-delivery following discharge of the participant from their stored medical records
33
34 16 locally at each unit. However, in order to fully examine the health economic outcomes there
35
36 17 exists a reliance on the return of completed questionnaires by the participant post-delivery. To
37
38 18 minimise attrition rates, the researcher at each site will endeavour to meet with each
39
40 19 participant post-delivery prior to their discharge and encourage them to complete the health
41
42 20 economic questionnaires. In the PELICAN study only 1% of the cohort were lost to follow up.
43
44 21 The risk of incomplete data collection of outcomes in studies such as this is more relevant if
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46 22 women deliver in a different unit to that which they are recruited in to the trial. However, all
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48 23 seven clusters in our trial are large tertiary referral units and patient transfer during pregnancy
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50 24 is rare. We are therefore confident that the likely rate of loss to follow up will be similar and in
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52 25 the order of 1%.

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57 26 There are a number of advantages with the use of stepped wedge design. It allows a phased
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59 27 implementation of the intervention, which is preferable when commencement in all clusters
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3 1 simultaneously would be challenging. As all clusters ultimately receive the intervention, it
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5 2 increases willingness of the clusters to partake in the trial. We acknowledge that seven
6
7 3 clusters is a small number of clusters and this is an important limitation of the study. Mostly
8
9 4 this is a limitation because it will mean that the findings have questionable generalisability.
10
11 5 But, if these clusters are representative then the findings may still be generalizable in part.
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13 6 The other limitation that seven clusters brings about is questionable internal reliability.
14
15 7 However, because all of the clusters receive both the intervention and control condition, the
16
17 8 clusters serve as their own controls. Not only does this lessen the impact of chance imbalance
18
19 9 but it also increases the power of the study (particularly so when the ICC is large, as is the
20
21 10 case here). The study does only have in the region of 80% power and should parameters such
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23 11 as the ICC be very different to that which we have assumed, then it is correct that the study
24
25 12 might be underpowered. To ensure that this is properly accounted for at the analysis stage,
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27 13 we will report appropriate CIs around all point estimates, so the impact of any impression is
28
29 14 properly reported.

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34 15 Another potential limitation worth noting is the slightly different management algorithm for one
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36 16 cluster, Belfast, in the control arm. The Belfast control arm algorithm is taken directly from the
37
38 17 NICE Hypertension in Pregnancy guidelines. All other clusters are using an algorithm taken
39
40 18 from the HSE Guidelines for Hypertension in Pregnancy. The two are essentially the same
41
42 19 except the HSE algorithm also includes a recommendation for a fetal ultrasound in cases
43
44 20 where the participant is <34 weeks gestation. It is not anticipated that the difference in these
45
46 21 algorithms should have any bearing on the overall trial results. We will conduct a sensitivity
47
48 22 analysis with the Belfast site removed and see if the result remains consistent.

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52 23 Ideally PIGF testing should be performed for all participants enrolled in the study, with blinding
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54 24 of the result for those in the control arm. This would allow for test performance statistics to be
55
56 25 performed. Unfortunately, testing of control participants will not be conducted in our trial, which
57
58 26 is a notable limitation of the study.

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3 1 The primary aim of the PARROT Ireland trial is to establish the effectiveness of revealed
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5 2 plasma PIGF measurement in reducing maternal morbidity (with assessment of neonatal
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7 3 safety in parallel) in women presenting with suspected pre-eclampsia prior to 37 weeks'
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9 4 gestation. Should the trial show a reduction in maternal morbidity without an increase in
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11 5 neonatal morbidity, or indeed a reduction in neonatal morbidity with no change in maternal
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13 6 morbidity, it would provide a strong argument for its incorporation into routine obstetric
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15 7 practice. The long-term aim of the trial is to demonstrate if PIGF measurement enables
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17 8 appropriate antenatal stratification of women presenting with suspected pre-eclampsia.
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19 9 Avoiding unnecessary hospital admission would be both clinically and economically beneficial.
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21 10 In contrast, those at increased risk of imminent adverse events, identified by an abnormal
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23 11 PIGF result, would have hospital resources re-directed to them. We anticipate that this trial
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25 12 will provide a definitive result on the benefits of PIGF testing which will act to influence
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27 13 international clinical practice.
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33 15 A separate RCT, also entitled "PARROT", has completed recruitment in the United Kingdom
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35 16 since the end of 2017. Although recruiting a similar population of women and using the same
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37 17 PIGF platform, the primary outcome measure for the two RCT's is different, with the UK
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39 18 PARROT trial focusing on time from enrolment to diagnosis. Both studies are using the same
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41 19 electronic clinical record forms developed by MedSciNet and thus will have a large cross-over
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43 20 of data. The advantage of having these two similar RCT's conducted almost simultaneously
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45 21 is that robust information on the impact of incorporation of PIGF into clinical care will be
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47 22 generated. In addition the potential exists for a collaborative project such as an individual
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49 23 participant data meta-analyses in the future.
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Abbreviations

1	2	ALT: Alanine Aminotransferase
2	3	AST: Aspartate Aminotransferase
3	4	CAC: cluster-auto correlations
4	5	CI: Confidence Interval
5	6	CNS: Central Nervous System
6	7	CSF: Cerebrospinal Fluid
7	8	DBP: Diastolic Blood Pressure
8	9	EC: Ethics Committee
9	10	eCRF: Electronic Clinical Report Form
10	11	Flt-1: fms-like tyrosine kinase 1
11	12	GCS: Glasgow Coma Scale
12	13	HDP: Hypertensive Disorder of Pregnancy
13	14	HSE: Health Service Executive
14	15	ICC: Intraclass Correlation Coefficient
15	16	INFANT: The Irish Centre for Fetal and Neonatal Translational Research
16	17	NICE: National Institute for Clinical Excellence
17	18	NICU: Neonatal Intensive Care Unit
18	19	NNU: Neonatal Unit
19	20	PARROT: Placental growth factor in Assessment of women with suspected pre-
20	21	eclampsia to Reduce maternal morbidity: a Stepped Wedge Cluster
21	22	Randomised Control Trial
22	23	PIL: Patient Information Leaflet
23	24	PIGF: Placental Growth Factor
24	25	PSA: Probabilistic Sensitivity Analysis
25	26	QALY: Quality Adjusted life year
26	27	QoL: Quality of Life
27	28	RCT: Randomised Controlled Trial
28	29	SBP: Systolic Blood Pressure
29	30	sFlt-1: soluble fms-like tyrosine kinase 1
30	31	VEGF: Vascular endothelial growth factor

1 **Declarations**

2 **Ethics approval and consent to participate**

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

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

10 University College Hospital Galway EC: Ref 50/12

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

12 National Maternity Hospital EC: EC 20.2016

13 University Hospital Limerick EC: Ref: 68/16

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

15 Rotunda Hospital EC: REC-2016-020..

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17 **Dissemination**

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

1 **Figure Legends**

2 *Figure 1; Stepped Wedge Cluster Randomised Design for PARROT Ireland*

3 *Figure 2; Trial Schematic for PARROT Ireland*

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

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

8 *Figure 4; Suggested Management Algorithm for Intervention for PARROT Ireland*

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

10 *Figure 6; Power Curve for PARROT Ireland for Neonatal Adverse Outcomes*

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12 **Availability of data and material**

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

16

17 **Competing interests**

18 The authors declare that they have no competing interests.

19

20 **Funding & Trial Sponsor**

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

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1 **Authors' contributions**

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

8 **Acknowledgements**

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

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For peer review only

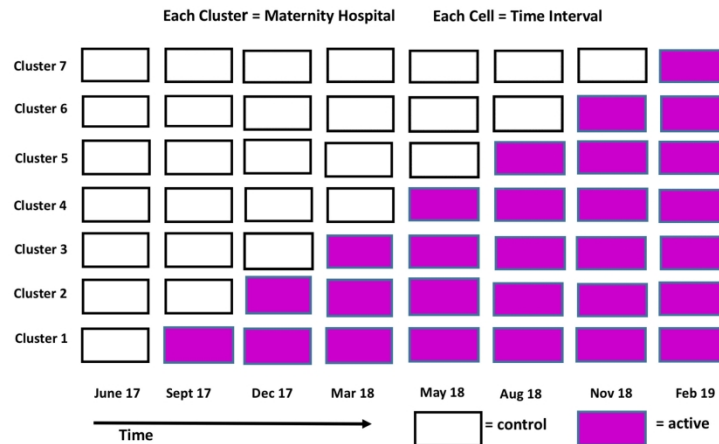


Figure 1; Stepped Wedge Cluster Randomised Design for PARROT Ireland

Figure 1; Stepped Wedge Cluster Randomised Design for PARROT Ireland

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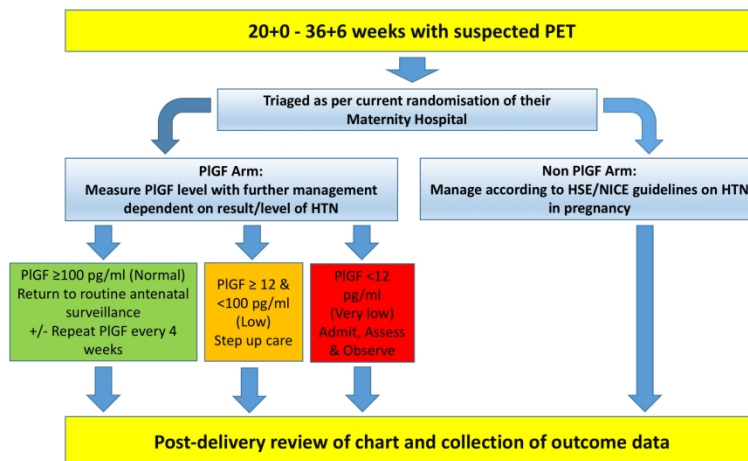


Figure 2; Trial Schematic for PARROT Ireland

Figure 2; Trial Schematic for PARROT Ireland

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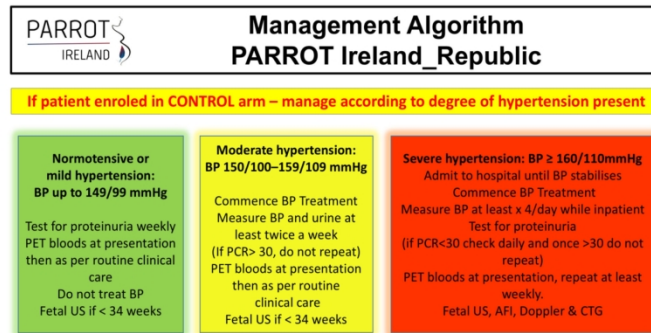


Figure 3a; Management Algorithm for Control arm based on HSE guidelines for PARROT Ireland

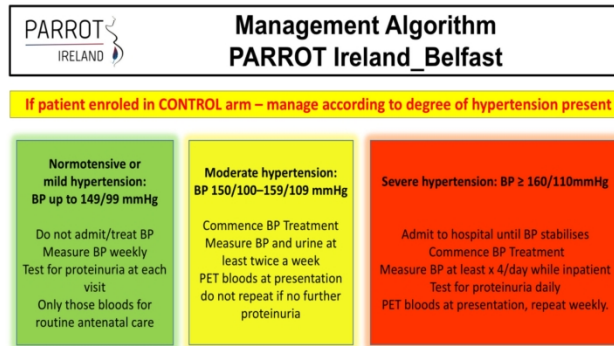


Figure 3b; Management Algorithm for Control arm based on NICE guidelines for PARROT Ireland

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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

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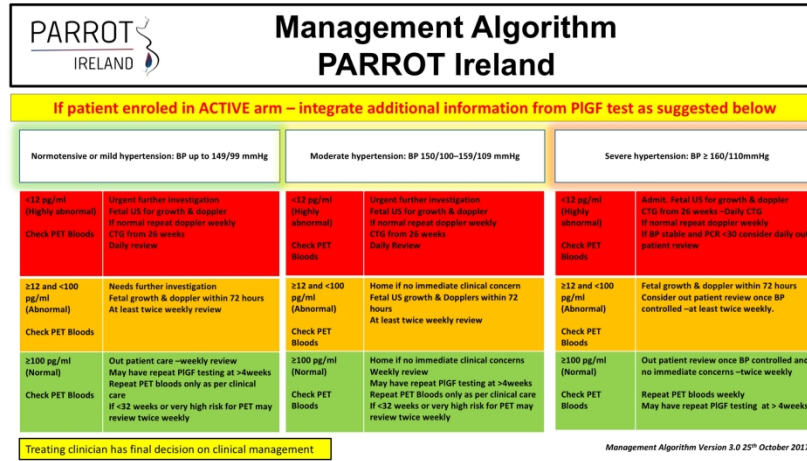


Figure 4; Suggested Management Algorithm for Intervention for PARROT Ireland

Figure 4; Suggested Management Algorithm for Intervention for PARROT Ireland

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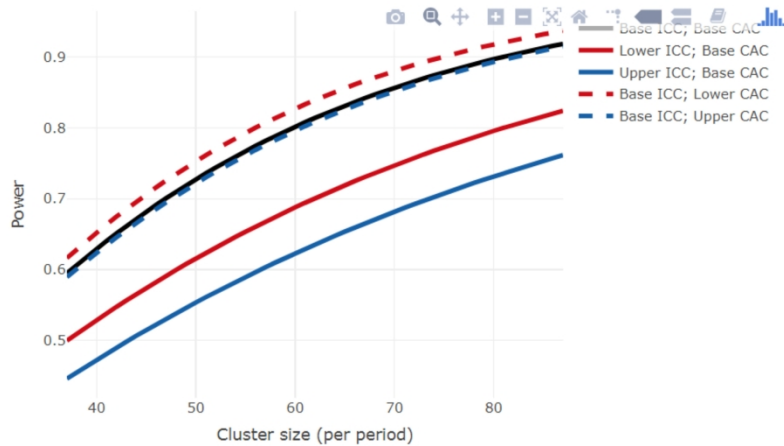


Figure 5; Power Curve for PARROT Ireland for Maternal Adverse Outcomes

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.

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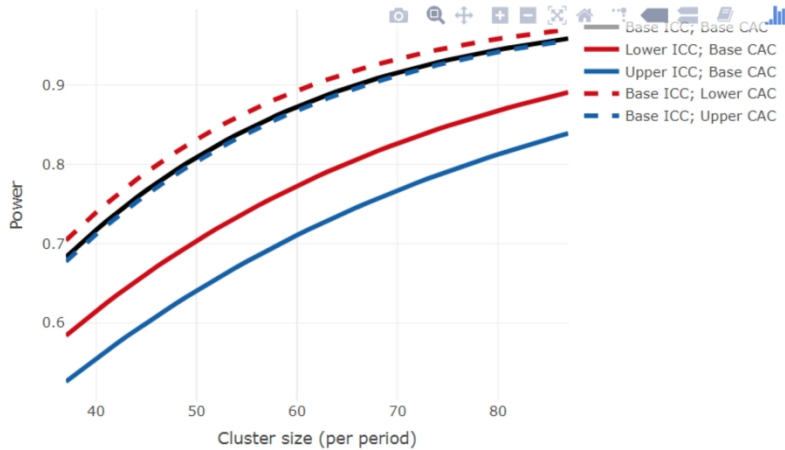


Figure 6: Power Curve for PARROT Ireland for Neonatal Adverse Outcomes

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.

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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	<u>1</u>
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	<u>1</u>
	2b	All items from the World Health Organization Trial Registration Data Set	<u>Supplementary Material</u>
Protocol version	3	Date and version identifier	<u>1</u>
Funding	4	Sources and types of financial, material, and other support	<u>25</u>
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	<u>1-2, 25</u>
	5b	Name and contact information for the trial sponsor	<u>25</u>
	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	<u>25</u>

1			
2			
3	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)	<u>19</u>
4			
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11	Introduction		
12			
13	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	<u>5-7</u>
14			
15			
16		6b Explanation for choice of comparators	<u>10-11</u>
17	Objectives	7 Specific objectives or hypotheses	<u>7</u>
18			
19	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)	<u>8</u>
20			
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22			
23	Methods: Participants, interventions, and outcomes		
24			
25	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	<u>9</u>
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28	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)	<u>9-10</u>
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31	Interventions	11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	<u>10-11</u>
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34		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)	<u>10-11</u>
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37		11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	<u>10-11</u>
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40		11d Relevant concomitant care and interventions that are permitted or prohibited during the trial	<u>10-11</u>
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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	<u>12-14</u>
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)	<u>16</u>
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	<u>16</u>
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	<u>19</u>

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	<u>10</u>
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	<u>10</u>
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	<u>10</u>
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	<u>10</u>
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	<u>10</u>

Methods: Data collection, management, and analysis

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2				
3	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related	<u>15</u>
4	methods		processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of	
5			study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.	
6			Reference to where data collection forms can be found, if not in the protocol	
7				
8		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be	<u>20</u>
9			collected for participants who discontinue or deviate from intervention protocols	
10				
11	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality	<u>15</u>
12			(eg, double data entry; range checks for data values). Reference to where details of data management	
13			procedures can be found, if not in the protocol	
14				
15	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the	<u>17-18</u>
16			statistical analysis plan can be found, if not in the protocol	
17				
18		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	<u>17-18</u>
19				
20		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any	
21			statistical methods to handle missing data (eg, multiple imputation)	<u>17-18</u>
22				
23				
24	Methods: Monitoring			
25				
26	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of	<u>20-21</u>
27			whether it is independent from the sponsor and competing interests; and reference to where further details	
28			about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not	
29			needed	
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31		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim	<u>20-21</u>
32			results and make the final decision to terminate the trial	
33				
34	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse	<u>20-21</u>
35			events and other unintended effects of trial interventions or trial conduct	
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37	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent	<u>20-21</u>
38			from investigators and the sponsor	
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Ethics and dissemination

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

Appendices

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3	Informed consent	32	Model consent form and other related documentation given to participants and authorised surrogates	
4	materials			<u>Supplementary</u>
5				<u>Material</u>
6				
7	Biological	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular	<u>N/A</u>
8	specimens		analysis in the current trial and for future use in ancillary studies, if applicable	
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10 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.
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