Repeat placental growth factor-based testing in women with suspected preterm pre-eclampsia (PARROT-2): a multicentre, parallel-group, superiority, randomised controlled trial

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Summary

Background Placental growth factor (PlGF)-based testing has high diagnostic accuracy for predicting pre-eclampsia needing delivery, significantly reducing time to diagnosis and severe maternal adverse outcomes. The clinical benefit of repeat PlGF-based testing is unclear. We aimed to determine whether repeat PlGF-based testing (using a clinical management algorithm and nationally recommended thresholds) reduces adverse perinatal outcomes in pregnant individuals with suspected preterm pre-eclampsia.

Methods In this multicentre, parallel-group, superiority, randomised controlled trial, done in 22 maternity units across England, Scotland, and Wales, we recruited women aged 18 years or older with suspected pre-eclampsia between 22 weeks and 0 days of gestation and 35 weeks and 6 days of gestation. Women were randomly assigned (1:1) to revealed repeat PlGF-based testing or concealed repeat testing with usual care. The intervention was not masked to women or partners, or clinicians or data collectors, due to the nature of the trial. The trial statistician was masked to intervention allocation. The primary outcome was a perinatal composite of stillbirth, early neonatal death, or neonatal unit admission. The primary analysis was by the intention-to-treat principle, with a per-protocol analysis restricted to women managed according to their allocation group. The trial was prospectively registered with the ISRCTN registry, ISRCTN 85912420.

Findings Between Dec 17, 2019, and Sept 30, 2022, 1253 pregnant women were recruited and randomly assigned treatment; one patient was excluded due to randomisation error. 625 women were allocated to revealed repeat PlGF-based testing and 627 women were allocated to usual care with concealed repeat PlGF-based testing (mean age 32·3 [SD 5·7] years; 879 [70%] white). One woman in the concealed repeat PlGF-based testing group was lost to follow-up. There was no significant difference in the primary perinatal composite outcome between the revealed repeat PlGF-based testing group (195 [31·2%]) of 625 women) compared with the concealed repeat PlGF-based testing group (174 [27·8%] of 626 women; relative risk 1·21 [95% CI 0·95–1·33]; p=0·18). The results from the per-protocol analysis were similar. There were four serious adverse events in the revealed repeat PlGF-based testing group and six in the concealed repeat PlGF-based testing group; all serious adverse events were deemed unrelated to the intervention by the site principal investigators and chief investigator.

Interpretation Repeat PlGF-based testing in pregnant women with suspected pre-eclampsia was not associated with improved perinatal outcomes. In a high-income setting with a low prevalence of adverse outcomes, universal, routine repeat PlGF-based testing of all individuals with suspected pre-eclampsia is not recommended.

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Introduction

Hypertensive disorders of pregnancy affect 10% of the pregnant population, predominantly comprising chronic hypertension, gestational hypertension, and pre-eclampsia. Pre-eclampsia affects 2·8% of women and birthing people (referred to subsequently as women).[1] 25% of pre-eclampsia cases in singleton pregnancies occur before 37 weeks' gestation, and women with preterm pre-eclampsia are more likely to have maternal or perinatal complications.[2] Suspected pre-eclampsia affects approximately 10% of pregnancies, although this is difficult to accurately ascertain as suspected pre-eclampsia does not have an International Classification of Diseases-10 code.[3] Pregnant women presenting with symptoms and signs of suspected pre-eclampsia account for a substantial proportion of the workload within maternity care.[4,5] Better methods of early identification and risk stratification are needed to reduce maternal and

Research in context

Evidence before this study

We searched PubMed for original articles published in English before July 1, 2019, with the search terms "pre-eclampsia" AND "repeat testing" AND "angiogenic factor" OR "placental growth factor" OR "trial". We found no published trial evidence that evaluated the clinical impact of repeat placental growth factor (PlGF)-based testing in suspected preterm pre-eclampsia. We found several small, observational studies investigating test performance of repeat PlGF-based testing and association with clinically relevant outcomes. These studies suggested high sensitivity and negative predictive value of first repeat PlGF-based test in determining need for delivery for pre-eclampsia and highlighted possible distinct trajectories in angiogenic biomarker concentrations in women who later developed pre-eclampsia or severe adverse outcomes. However, the potential clinical utility and cost-effectiveness of repeat PlGF-based testing had not been assessed within a randomised controlled trial.

Added value of this study

Our individual-level randomised controlled trial provides evidence of the clinical impact of repeat PlGF-based testing on adverse perinatal and maternal outcomes, and time to diagnosis, in women with suspected preterm pre-eclampsia. In 22 hospitals across England, Scotland, and Wales, repeat PlGF-based testing was evaluated in participants who received an initial PlGF-based test for suspected pre-eclampsia in accordance with UK national guidance. We found no notable difference in severe adverse perinatal or maternal outcomes. There was a reduction in time to diagnosis of pre-eclampsia, but also a reduction in gestational age at delivery, an increase in preterm birth before 34 weeks' gestation, and an increase in caesarean birth with repeat PlGF-based testing. To our knowledge, this is the first multicentre randomised controlled trial of repeat PlGF-based testing in individuals with suspected preterm pre-eclampsia.

Implications of all the available evidence

The clinical benefit of a PlGF-based test on one occasion when pre-eclampsia is suspected remains clear, as recommended in national and international guidance. Regarding repeat PlGF-based testing, our study supports high test performance for repeat PlGF-based tests predicting need for delivery for pre-eclampsia within 14 days, as suggested in previous smaller studies. Although repeat testing facilitates faster diagnosis, this did not correlate with a reduction in severe adverse perinatal or maternal outcomes, in this high-income setting with low prevalence of events. Our findings provide novel evidence that do not support a policy of routine repeat PlGF-based testing in all individuals with suspected preterm pre-eclampsia, as recommended in some international guidelines. Further work might highlight a subgroup of individuals who might benefit from repeat testing; evaluation stratified by PlGF-based test type or initial result category might affect maternal or perinatal outcomes.

perinatal morbidity and mortality and to optimise resource allocation.

Abnormally low concentrations of placental growth factor (PlGF) and high concentrations of soluble fms-like tyrosine kinase-1 (sFlt-1) were first identified 25 years ago in a small retrospective case-control study of patients with pre-eclampsia.[6] Subsequently, longitudinal and cross-sectional cohort studies of angiogenic biomarkers showed that PlGF concentrations are significantly lower and sFlt-1 concentrations significantly higher, both in pregnancies with pre-eclampsia and those with later developed pre-eclampsia.[7,8] Abnormal angiogenic imbalance has been identified up to 10 weeks before the onset of the clinical syndrome of pre-eclampsia.[9]

A multicentre diagnostic test accuracy study[4] showed that PlGF >5th centile (≥100 pg/mL) has high test performance, ruling out pre-eclampsia needing delivery within 14 days with a negative predictive value (NPV) of 0·98 (95% CI 0·93–0·995). The 2019 PARROT-1 trial[5] investigated PlGF-based testing in 1023 participants in a multicentre stepped-wedge cluster-randomised controlled trial.[5] Findings from the study showed that revealed PlGF-based testing, compared with usual care with concealed PlGF-based testing, reduced time to diagnosis of pre-eclampsia (1·9 days *vs* 4·1 days, time ratio 0·36 [95% CI 0·15–0·87]) and maternal severe adverse outcomes (4% *vs* 5%; adjusted odds ratio 0·32 [95% CI 0·11-0·96]).[10] Following this, PlGF-based testing is recommended by the National Institute for Health and Care Excellence (NICE) and the International Society for the Study of Hypertension in Pregnancy on one occasion when preterm pre-eclampsia is first suspected.[11,12]

National guidance in the UK has clearly identified the need to evaluate repeat PlGF-based testing and the impact on maternal and perinatal complications, including stillbirth, neonatal death, neonatal unit admission, and prematurity.[13] Before repeat PlGF-based testing becomes routine, it needs to be established if it is clinically effective and cost-effective, and what added benefit (or not) repeat PlGF-based testing offers after the initial PlGF-based test. Trials of diagnostic tests and how they are implemented are surprisingly infrequent, but robust evaluation provides a strong evidence base for informing policy, practice, and guidelines. Widespread uncertainty and unwanted variation exists in practice around the purported benefits of repeat PlGF-based testing due to scarce evidence. We hypothesised that repeat testing would influence surveillance strategies that would impact perinatal outcomes, decreasing neonatal unit admissions (and associated reduced perinatal morbidity and mortality) as well as potentially avoiding unnecessary iatrogenic preterm delivery through appropriate rule-out of

pre-eclampsia. Therefore, we aimed to determine whether revealed repeat PlGF-based testing (with a clinical management algorithm using published NICE guidance with threshold values provided), reduced stillbirth, neonatal death, and neonatal unit admission, or other maternal or perinatal adverse outcomes, in women with suspected preterm pre-eclampsia.

Methods

Study design and participants

We conducted this individual-level, multicentre, parallel-group, superiority, randomised controlled trial in 22 consultant-led maternity units in England, Scotland, and Wales, each responsible for 3000–9000 deliveries per year (appendix pp 2–3).[14] Women were eligible to participate in the trial if they were aged 18 years or older, with a singleton pregnancy, a live fetus, and were at between 22 weeks and 0 days' gestation and 35 weeks and 6 days' gestation at the time of the initial PlGF-based test for suspected pre-eclampsia. Suspected pre-eclampsia was defined as at least one of the following: new onset or worsening hypertension, proteinuria according to dipstick testing, severe headache or neurological symptoms, right upper quadrant or epigastric pain, suspected fetal growth restriction in association with pre-eclampsia, or abnormal maternal blood tests in keeping with disease (thrombocytopenia, haemolysis, or renal or hepatic dysfunction). Individuals could self-refer with suspected pre-eclampsia, or pre-eclampsia could be identified at antenatal appointments by a health-care professional. Women could participate in the study regardless of the initial PlGF-based test result, but women with a confirmed diagnosis of preterm pre-eclampsia documented in the medical records before the initial PlGF-based test were not eligible for participation in the trial. All participants provided written consent. The trial protocol has been previously published.[14] There were no substantial changes to the published study design, methods, or outcomes after the start of the trial. A perinatal morbidity composite outcome was added after starting recruitment but before the protocol was published. The trial was approved by the Cambridge East Research Ethics Committee (number 19/EE/0322).

Randomisation and masking

Participants were randomly assigned (1:1) on an individual basis to revealed repeat PlGF-based testing or usual care with concealed repeat PlGF-based testing using a minimisation algorithm to ensure approximate balance between maternity unit, gestational age at randomisation (22 weeks and 0 days to 27 weeks and 6 days, 28 weeks to 31 weeks and 6 days, and >32 weeks and 0 days), and primary indication for testing (hypertension or other). Randomisation was provided by a secure, web-based randomisation program (MedSciNet, Stockholm, Sweden) and extensively checked for balance and predictability by the trial statistician (PTS) before initiating the trial. The intervention was not masked to women or partners, or clinicians or data collectors, due to the nature of the trial. The trial statistician was masked to intervention allocation. All women presenting with suspected preterm pre-eclampsia received an initial revealed PlGF-based test, in line with UK national guidance.[11,13]

Procedures

PlGF-based immunoassays are diagnostic tests recommended for the initial assessment of suspected pre-eclampsia; all regulatory approvals were in place. At the time of inception of the trial, two immunoassays were recommended for clinical use in the UK: the PlGF-based test (QuidelOrtho, Galway, Ireland) and the Elecsys immunoassay sFlt-1/PlGF ratio (Roche, Burgess Hill, UK).[15,16] Maternity units implementing either test for the initial assessment of preterm pre-eclampsia were eligible to participate in the trial. The QuidelOrtho PlGF-based test is a single-use, fluorescence immunoassay device, used with the CE-marked Triage MeterPro point-of-care analyser (QuidelOrtho, Galway, Ireland). The Roche sFlt-1/PlGF ratio combines the results from two CE-marked sandwich electrochemiluminescence immunoassays (Elecsys PlGF and Elecsys sFlt-1 assays). Coefficients of variation have been established and are acceptable for use in clinical practice. Repeat tests were analysed at each unit in real time using the same process as the initial test. According to UK NICE guidance,[13] the QuidelOrtho PlGF-based test has a rule-out threshold of more than 100 pg/mL for pre-eclampsia requiring delivery within 14 days, with an NPV of 98% and a rule-in threshold of less than 12 pg/mL. The Roche sFlt-1/PlGF ratio has a rule-out threshold of less than 38 for pre-eclampsia requiring delivery within 7 days, with an NVP of 99% and a rule-in threshold of more than 85.

See Online for appendix

In the revealed repeat PlGF-based testing group, women and the clinicians caring for them were aware of the repeat PlGF-based test results; in addition to other clinical features, the repeat PlGF-based test results informed surveillance strategies and clinical management plans, integrated with the Hypertension in Pregnancy Guideline from the UK NICE.[11] All participating sites had implemented initial PlGF-based testing in accordance with UK NICE guidance before commencing the trial. Repeat testing was incorporated into clinical management similarly to the initial test result (ie, guiding management and surveillance strategies). Additionally, a clinical management algorithm (aligned with UK NICE guidance) was supplied by the PARROT-2 co-investigator group to sites with guidance on how to interpret repeat results, supplemented by regular training sessions (appendix pp 30–31). When pre-eclampsia was not ruled out (PlGF <100 pg/mL or sFlt-1/PlGF ratio >38), the management algorithm suggested considering increased surveillance, with regular monitoring and fetal ultrasound. When PlGF was less than 12 pg/mL or if the sFlt-1/PlGF ratio was

more than 85, the management algorithm suggested assessing as pre-eclampsia, with increased surveillance. When the PlGF-based test result changed category with a subsequent repeat test, then the surveillance strategy would be revised accordingly. The management algorithm clearly stated that abnormal PlGF-based test result alone was not an indication for delivery.

In the concealed repeat testing group, women were asked to provide one extra tube of blood, as far as possible at the same time as routine clinical blood tests, up to four times during the rest of their pregnancy until delivery or a maximum of four repeat tests, and regardless of whether a diagnosis of pre-eclampsia had been made. It was emphasised to participating sites that there are insufficient data regarding PlGF-based testing beyond 37 weeks' gestation and in confirmed pre-eclampsia, and that care in these situations should follow UK national guidelines. The repeat sampling strategy was as follows: if the initial result was abnormal (PlGF <100 pg/mL or sFlt-1/PlGF ratio >38), sampling was planned weekly (±2 days), and if the initial result was normal (PlGF ≥100 pg/mL or sFlt-1/PlGF ratio ≤38), sampling was planned every 2 weeks (±7 days) if asymptomatic, or sooner if re-presenting with new symptoms or signs of suspected pre-eclampsia 7 days or more from last sample.

Repeat concealed samples were centrifuged and plasma aliquots (for the QuidelOrtho PlGF-based test) or serum aliquots (for the Roche sFlt-1/PlGF ratio test) were extracted and stored at –80°C. The samples were batch processed at the coordinating centre or collaborating sites, once the participants had given birth. The results remained concealed to the research team until the database was locked to clinical outcomes.

Trained site research teams approached women individually to confirm eligibility, and to provide verbal and written information about the trial. A clinician (obstetrician or midwife) or a member of the research team (principal investigator, research midwife, or research nurse) obtained written informed consent. Baseline data were entered on the secure trial database and the participant was randomised and informed of the group allocation. All other aspects of management were expected to be in line with national guidance in the UK.[11] Repeat testing visits were performed in the context of provision of clinical care, where possible, when investigations (including blood pressure, urinalysis, and blood tests) were performed according to the clinical situation. New signs and symptoms of pre-eclampsia were recorded during these repeat testing visits. If repeat testing visits were performed outside of the context of clinical care, no additional monitoring was recommended in the study protocol, so that the repeat concealed testing group received usual care.

Clinical outcomes were recorded on the trial database, through thorough clinical notes review by trained researchers. Participants and their infants were followed up until primary hospital discharge, or the end of the trial (whichever came first).

Outcomes

The primary outcome was a composite of stillbirth, early neonatal death (within 7 days of delivery), or neonatal unit admission (physical separation of an infant from their mother or parent) before infant hospital discharge. The PARROT-1 trial[5] demonstrated reduction in maternal adverse outcomes with a single PlGF-based test, and the PARROT-2 trial was therefore planned to examine whether repeat testing might impact perinatal outcomes. The components of the composite were chosen as perinatal outcomes that pregnant women and clinicians rate as important (in the absence of wider agreed consensus on a composite neonatal outcome). Neonatal unit admission, involving separation of the baby from the mother, included admission for neonatal morbidity from all causes, and is rated of great importance by lay participants. In our high-income setting, perinatal deaths are rare, and powering the trial on perinatal death would not be feasible. But as this outcome is of catastrophic severity, lay advisers recommended inclusion in the composite primary outcome. There is considerable difficulty in choosing the perinatal outcome for this trial and similar trials. There is no national or international consensus on a composite perinatal outcome that is readily adjudicated and represents the multifaceted impact of hypertensive disorders of pregnancy. Therefore, the primary perinatal composite outcome was chosen above, with an additional perinatal severe morbidity composite as specified.

Full details of the secondary outcomes are in the published protocol.[14] As recommended by neonatologists and lay advisers, after starting recruitment but before publishing the protocol, we added a perinatal morbidity composite, including stillbirth, neonatal death, bronchopulmonary dysplasia, retinopathy of prematurity, severe necrotising enterocolitis, brain injury, and late-onset sepsis (all components were previously included). Other tested perinatal secondary outcomes included the individual components of the primary perinatal composite, gestational age at delivery, birthweight less than the tenth percentile (using Intergrowth-21st standards), and survival to discharge without severe morbidity[17] (defined as survival to discharge without bronchopulmonary dysplasia, retinopathy of prematurity, severe necrotising enterocolitis, brain injury, or late-onset sepsis). Perinatal outcomes were captured by routine clinical descriptors, listed in the clinical discharge summary. Additional descriptive perinatal outcomes included late neonatal death (within 28 days of delivery), birthweight less than the third percentile (using Intergrowth-21st standards), the components of the perinatal morbidity composite, and umbilical artery pH at birth (where measured).

Tested maternal secondary outcomes included a severe adverse maternal outcome composite[18] (using the same severe adverse maternal outcome composite as the primary outcome of the PARROT-1 trial[5]), proportion of women diagnosed with pre-eclampsia (as defined by the International Society for the Study of Hypertension in

Pregnancy[12]), severe hypertension (systolic blood pressure ≥160 mm Hg) with or without medication, and mode of birth (vaginal, assisted vaginal, or caesarean birth). Concealed repeat PlGF-based test performance for delivery within 14 days of PlGF-based test was analysed to avoid treatment paradox. Components of the severe adverse maternal outcome composite were reported as coded in routine clinical documentation and verified by two members of the central research team (AH and JS). These components were maternal death; CNS (eclampsia, Glasgow coma score <13, stroke or reversible ischaemic neurological deficit, transient ischaemic attack, cortical blindness or retinal detachment, or posterior reversible encephalopathy); cardiorespiratory (positive inotropic support, infusion of a third parenteral antihypertensive drug, myocardial ischaemia or infarction, peripheral oxygen saturation <90%, ≥50% fraction of inspired oxygen for >1 h, intubation [other than for caesarean birth], or pulmonary oedema); haematological (transfusion of any blood product or platelet count $<50\times10^9$ per L with no transfusion); hepatic (hepatic dysfunction, hepatic haematoma, or rupture); renal (acute renal insufficiency [creatinine >150 µmol/L with no pre-existing renal disease], acute renal failure [creatinine >200 µmol/L with pre-existing renal disease], or dialysis); or placental abruption. Additional descriptive maternal outcomes were abnormal fetal ultrasound features, labour onset (spontaneous, induced, or pre-labour caesarean birth), indications for delivery, and postpartum haemorrhage (>1000 mL).

Maternal health-care resource use included hospital attendances, ultrasound scans, inpatient days, and intensive care unit days. Perinatal health care resource use included intensive care unit days, high dependency unit days, and special care unit days.

Statistical analysis

CONSORT guidelines were followed in the analysis and presentation of results. In determining the sample size, we based estimates of the primary outcome composite on the PELICAN study[4] and the PARROT-1 trial[5] combined. Assuming a baseline event rate of 25·7% for the primary perinatal composite, a sample of 1208 participants (604 in each group) would have 90% power to show a relative risk reduction of 30% in the primary outcome score, from 25·7% to 18·0%, at a two-sided 5% significance level. The target sample size for PARROT-2 was inflated to 1244 participants, to allow 3% loss to follow-up. The analysis primarily assessed a PlGF-based testing strategy, using one of the two tests approved by the NICE (Roche and QuidelOrtho), with exploratory analysis stratified by the test that was planned.

The primary analysis was by the intention-to-treat principle, with randomised participants analysed in their original groups, regardless of minor protocol non-adherence. Analyses were done using a two-sided type 1 error rate of 0.05. The binary composite of stillbirth, early neonatal death, or neonatal unit admission was analysed using binomial regression with a log link, adjusted for the minimisation variables, except when indicated due to failure to converge. Results are presented as a relative risk (RR; or unadjusted RR or odds ratio [OR], in case of non-convergence), with 95% CIs. Tested secondary outcomes were analysed using log binomial regression models with a log link and results presented as adjusted RRs with 95% CIs. Continuous outcomes were analysed using linear regression with log transformations as necessary. A full statistical analysis plan can be found with the published protocol.[14]

For the concealed testing group only, (to avoid treatment paradox), the test performance of the initial and the first repeat sample was assessed for prediction of pre-eclampsia with delivery within 14 days (the commonly used outcome in diagnostic test accuracy studies). Sensitivity, specificity, positive predictive value and NVP, and positive and negative likelihood ratios, using thresholds of 12 and 100 pg/mL for the QuidelOrtho PIGL test and 38 and 85 for the Roche sFlt-1/PlGF ratio, are reported with 95% CIs.

Prespecified subgroup analyses were carried out, using the statistical test of interaction,[19] to evaluate whether the effect of the intervention differs between groups identifiable at baseline, including gestation at first test (≤35 weeks' gestation or >35 weeks' gestation), first PlGF result (<100 pg/mL and ≥100 pg/mL) or first sFlt-1/PlGF ratio result (≤38 or >38), and primary indication for testing (hypertension or other).

A per-protocol analysis was conducted, restricted to women managed according to their allocation group. At the request of the data monitoring committee, per-protocol analyses were carried out both including and excluding women who gave birth before their first repeat test was due.

Descriptive statistics are reported for health-care resource use, including mean service use per participant and SD. Mean difference in resource use of revealed testing compared with concealed testing was calculated using linear regression, adjusting for gestation at randomisation and site. 95% CIs were constructed using bias corrected and accelerated bootstrap intervals. Prespecified descriptive analysis was performed to document proportion of women (with at least one repeat PlGF-based test) changing test result category between first and last test. A post-hoc exploratory analysis was undertaken to document indication for preterm delivery before 34 weeks' gestation.

Data analyses were done with Stata version 17. An independent data monitoring committee monitored the study throughout.

This study was registered prospectively with the ISRCTN registry, ISRCTN85912420.

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Dec 17, 2019, and Sept 30, 2022, 1421 women were identified as eligible, of whom 1253 (88%) were recruited, across 22 maternity units in England, Scotland, and Wales (appendix pp 2–3). One woman was randomised in error with a twin pregnancy. Of the remaining 1252 participants, 625 were assigned to revealed repeat PlGF-based testing and 627 were assigned to usual care with concealed repeat PlGF-based testing (figure 1). For the intention-to-treat analysis, data from 625 participants in the revealed repeat PlGF-based testing group and 626 participants in the concealed repeat PlGF-based testing group were included; one woman in the concealed repeat PlGF-based testing group was lost to follow-up (figure 1) Two participants assigned to concealed repeat PlGF-based testing discontinued the trial intervention, but no participants withdrew consent for follow-up data collection. No further analysis was needed to account for missing data (<1% of participants).

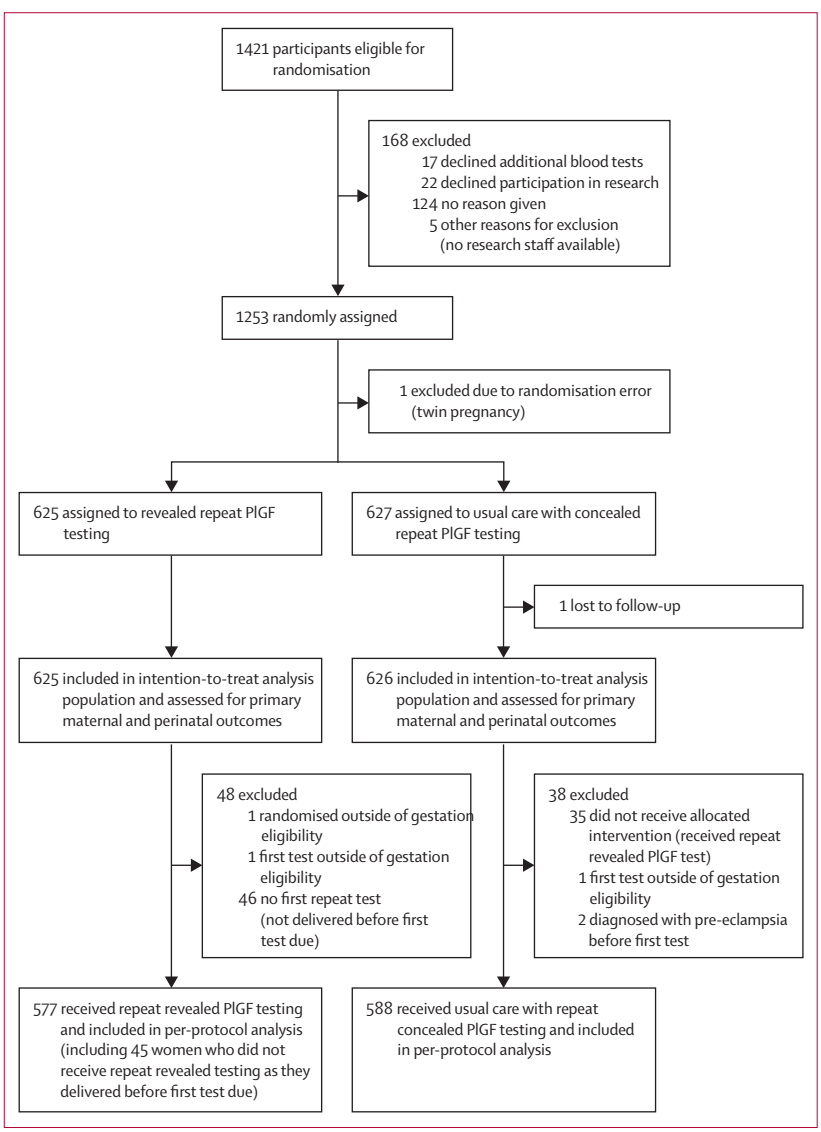

Figure 1: **Trial profile**
PlGF=placental growth factor.

	Revealed repeat PlGF-based testing group (n=625)	Concealed repeat PlGF-based testing group (n=627)
Age, years	32·1 (5·8)	32·5 (5·6)
Ethnicity or race		
White	440 (70·9%)	439 (70·5%)
Black	79 (12·7%)	74 (11·9%)
Asian (Indian, Pakistani, Bangladeshi, Sri Lankan)	73 (11·8%)	74 (11·9%)
Mixed	17 (2·7%)	20 (3·2%)
Other (including Chinese)	12 (1·9%)	16 (2·6%)
Not known	4 (0·01%)	4 (0·01%)
BMI, kg/m²	30·2 (7·5)	30·1 (7·4)
Smoking		
Never	492 (78·7%)	489 (78·1%)
Quit before pregnancy	88 (14·1%)	91 (14·5%)
Smoking at booking	22 (3·5%)	22 (3·5%)
Smoking in pregnancy	23 (3·7%)	24 (3·8%)
Deprivation quintile*		
1 (most deprived)	172 (31·1%)	146 (27·6%)
2	131 (23·7%)	144 (27·2%)
3	99 (17·9%)	104 (19·7%)
4	100 (18·1%)	86 (16·3%)
5 (least deprived)	51 (9·2%)	49 (9·3%)
Previous pregnancies with durations of ≥24 weeks		
0	304 (48·6%)	303 (48·3%)
1	187 (29·9%)	176 (28·1%)
≥2	134 (21·4%)	148 (23·6%)
Previous pre-eclampsia (of multiparous women)†	119 (37·1%)	123 (38·0%)
Medical conditions		
Pre-existing hypertension	113 (18·1%)	123 (19·6%)
Pre-existing renal disease	23 (3·7%)	31 (4·9%)
Lupus or antiphospholipid syndrome	8 (1·3%)	10 (1·6%)
Type 1 or type 2 diabetes	52 (8·3%)	49 (7·8%)
Systolic blood pressure at booking (mm Hg)	121 (15·8)	121 (13·9)
Diastolic blood pressure at booking (mm Hg)	75 (11·5)	76 (11·1)
Proteinuria at booking (≥2+ on dipstick)	7 (1·6%)	13 (2·9%)
Prophylactic aspirin prescribed	345 (55·2%)	361 (57·6%)
75 mg aspirin	103 (29·9%)	107 (29·6%)
150 mg aspirin	242 (70·1%)	254 (70·4%)

Data are mean (SD), n (%), or median (IQR). PlGF=placental growth factor. *Data are reported for 553 patients in the revealed repeat PlGF-based testing group and 520 patients in the concealed repeat PlGF-based testing group, as deprivation quintile was not known for the remaining patients. †Data are reported for 321 multiparous patients in the revealed repeat PlGF-based testing group and 324 multiparous patients in the concealed repeat PlGF-based testing group, as the remaining patients were nulliparous.

Table 1: **Baseline demographics and clinical characteristics**

	Revealed repeat PlGF testing group (n=625)	Concealed repeat PlGF testing group (n=627)
Presenting signs and symptoms (non-exclusive*)		
New-onset hypertension	293 (46·9%)	271 (43·2%)
Worsening of existing hypertension	132 (21·1%)	152 (24·2%)
Dipstick proteinuria	248 (39·7%)	268 (42·7%)
Neurological symptoms	52 (8·3%)	47 (7·5%)
Severe headache	130 (20·8%)	107 (17·1%)
Epigastric or right upper quadrant pain	36 (5·8%)	32 (5·1%)
Liver dysfunction	24 (3·8%)	20 (3·2%)
Acute renal insufficiency	32 (5·1%)	35 (5·6%)
Thrombocytopenia	8 (1·3%)	7 (1·1%)
Haemolysis or decreasing haemoglobin	5 (0·8%)	9 (1·4%)
Suspected fetal growth restriction	77 (12·3%)	79 (12·6%)
Highest blood pressure in 48 h before initial test, mm Hg		
Systolic	141 (18·0)	140 (16·6)
Diastolic	89 (13·1)	89 (12·5)
Highest dipstick proteinuria in 48 h before initial test		
None	283 (49·0%)	269 (46·4%)
Trace	54 (9·4%)	68 (11·7%)
+1	139 (24·1%)	152 (26·2%)
≥+2	101 (17·5%)	91 (15·7%)
Fetal growth abnormalities on ultrasound in 2 weeks before initial test (non-exclusive)†		
None	258 (72·7%)	260 (73·0%)
Abdominal circumference <10th percentile	40 (11·3%)	36 (10·1%)
Estimated fetal weight <10th percentile	68 (19·2%)	72 (20·2%)
Umbilical artery pulsatility index >95th percentile	25 (7·0%)	20 (5·6%)
Absent or reduced end diastolic flow	11 (3·1%)	5 (1·4%)
Middle cerebral artery pulsatility index (centiles not available)	1·81 (0·42)	1·82 (0·42)
Amniotic fluid index <5th percentile	4 (1·1%)	6 (1·7%)
Gestational diabetes	117 (18·7%)	98 (15·6%)
Gestation at randomisation		
22–27 weeks and 6 days	80 (12·8%)	81 (12·9%)
28–31 weeks and 6 days	160 (25·6%)	161 (25·7%)
>32 weeks	385 (61·6%)	385 (61·4%)
(Table 2 continues on next page)		
(Continued from previous page)		
Gestation at randomisation	32·7 (29·9–34·6)	33·0 (30·4–34·7)
Initial PlGF, pg/mL‡		
<100	194 (49·5%)	185 (46·6%)
<12	74 (18·9%)	52 (13·1%)
12–99	120 (30·6%)	133 (33·5%)
≥100	198 (50·5%)	212 (54·4%)
Initial sFlt-1/PlGF ratio§		
>38	81 (34·8%)	76 (33·0%)
≥85	39 (16·7%)	36 (15·7%)
38·1–85	42 (18·0%)	40 (17·4%)
≤38	152 (65·2%)	154 (67·0%)
Initial destination		
Home with follow-up	476 (76·2%)	502 (80·1%)
Admitted to hospital	146 (23·4%)	122 (19·5%)
Other	3 (0·5%)	3 (0·5%)
Antenatal ward	134 (21·4%)	111 (17·7%)
Labour ward	8 (1·3%)	7 (1·1%)
Obstetric high dependency unit	2 (0·3%)	4 (0·6%)
Intrauterine transfer	2 (0·3%)	0
New symptoms or signs at any repeat testing visit¶	477/1182 (40·4%)	466/1193 (39·1%)

Data are mean (SD), n (%), n/N (%), or median (IQR). PlGF=placental growth factor. sFlt-1=soluble fms-like tyrosine kinase-1. *Individuals could have more than one symptom or sign. †Data are reported for 355 patients in the revealed repeat PlGF-based testing group and 356 patients in the concealed repeat PlGF-based testing group, as the remaining patients did not have an ultrasound in the 2 weeks before the initial test. ‡Data are reported for 392 patients in the revealed repeat PlGF-based testing group and 397 patients in the concealed repeat PlGF-based testing group (the remaining patients received sFlt-1/PlGF testing). §Data are reported for 233 patients in the revealed repeat PlGF-based testing group and 230 patients in the concealed repeat PlGF-based testing group (the remaining patients received PlGF-based testing). ¶Individual patients had multiple repeat testing visits.

Table 2: **Pregnancy characteristics at first PlGF-based test**

The trial ended as the recruitment target had been reached.

Baseline characteristics were similar between the two groups, except for a chance finding of a higher proportion of women in the revealed PlGF-based testing group with a very abnormal PlGF concentration at the initial test (74 [18·9%] of 392 women in the revealed PlGF-based testing group had a PlGF <12 pg/mL, compared with 52 [13·1%] of 397 women in the concealed PlGF-based testing group; tables 1, 2).

The proportion of infants with the primary perinatal composite outcome was not significantly different in the revealed repeat PlGF-based testing group compared with the concealed repeat PlGF-based testing group (195 [31·2%] of 625 women *vs* 174 [27·8%] of 626 women; RR 1·21 (95% CI 0·95–1·33); p=0·18; table 3; figure 2). There were no significant differences between groups in the components of the perinatal composite outcome. Subgroup analysis was conducted according to the prespecified statistical analysis. There was no significant interaction between the incidence of the primary perinatal composite outcome or the severe maternal adverse outcome composite and any subgroup variables examined. In the revealed repeat PlGF-based testing group, compared with the concealed repeat PlGF-based

testing group, there was a significant reduction in the gestational age at delivery (36·7 weeks' gestation *vs* 37·1 weeks' gestation; mean difference –0·40 weeks [–0·68 to –0·12]; p=0·005) and a significant increase in the number of participants delivering before 34 weeks' gestation (90 [14·4%] of 625 women *vs* 55 [8·8%] of women; RR 1·63 [95% CI 1·19 to 2·24]; p=0·002; table 3).

	Revealed repeat PlGF-based testing group (n=625)	Concealed repeat PlGF-based testing group (n=626)	Effect size
Primary outcome*			
Composite	195 (31·2%)	174 (27·8%)	1·21 (0·95 to 1·33); p=0·18
Components of composite (non-exclusive)†			
Stillbirth*	2/625 (0·3%)	3/626 (0·5%)	0·67 (0·11 to 3·99); p=0·66
Early neonatal death*‡	1/623 (0·2%)	1/623 (0·2%)	1·00 (0·06 to 15·98); p=0·99
Neonatal unit admission*	193/625 (30·9%)	171/626 (27·3%)	1·13 (0·95 to 1·34); p=0·17
Status at birth			
Livebirth	623 (99·7%)	623 (99·5%)	..
Late neonatal death (8–27 complete days of life)‡	1/623 (0·2%)	1/623 (0·2%)	..
Gestational age at delivery, weeks§	36·7 (2·7)	37·1 (2·6)	–0·40 (–0·68 to –0·12); p=0·005
Preterm delivery <37 weeks¶	241/625 (38·6%)	212/626 (33·9%)	1·14 (0·98 to 1·32); p=0·08
Preterm delivery <34 weeks‖	90/625 (14·4%)	55/626 (8·8%)	1·63 (1·19 to 2·24); p=0·002
Birthweight percentile	43·40 (31·82)	44·24 (31·67)	..
Birthweight <10th percentile*	125/622 (20·1%)	115/626 (18·4%)	1·09 (0·87 to 1·37); p=0·44
Descriptive perinatal outcomes**			
Necrotising enterocolitis	1/623 (0·2%)	3/623 (0·5%)	..
Sepsis	5/623 (0·8%)	6/623 (1·0%)	..
Brain injury	4/623 (0·6%)	2/623 (0·3%)	..
Seizures	1/623 (0·2%)	1/623 (0·2%)	..
Retinopathy of prematurity	5/614 (0·8%)	3/614 (0·5%)	..
Chronic lung disease	7/624 (1·1%)	8/624 (1·3%)	..
Umbilical artery pH	7·24 (0·08)	7·23 (0·09)	..
Birthweight <3rd percentile	42/622 (6·8%)	35/626 (5·6%)	..
Survival to discharge without severe morbidity*	606/625 (97·0%)	605/626 (96·6%)	1·00 (0·98 to 1·02); p=0·75
Infant outcome			
Discharged home	598/625 (95·7%)	594/626 (94·9%)	..
Transferred to another hospital	22/625 (3·5%)	20/626 (3·2%)	..
Died before discharge	2/625 (0·3%)	3/626 (0·5%)	..

Data are n (%), mean (SD), n/N (%),median (IQR), or RR (95% CI). PlGF=placental growth factor. RR=risk ratio. *The comparison is the RR. Due to failure of convergence, unadjusted RRs are used. Adjusted odds ratios were very similar (1·20 [95% CI 0·95 to ~1·54]; p=0·143). †One baby in each group was admitted to the neonatal unit before an early neonatal death; therefore, the number of events of the components of the composite exceed the total number of events in the composite primary outcome. There is no double counting in the primary composite outcome. ‡Livebirth denominator has been used, excluding stillbirths. §The comparison is the mean difference, adjusted for minimisation variables. ¶The comparison is the risk ratio, adjusted for minimisation variables. ‖The comparison is the risk ratio, adjusted for indication for test only. **Neonates could have more than one adverse event.

Table 3: **Primary outcome and secondary perinatal outcomes (intention-to-treat population)**

Similar results were shown in the per-protocol analyses (appendix pp 4–9). In the revealed repeat PlGF-based testing group, the first per-protocol analysis excluded two women who did not meet inclusion criteria and were randomised or received initial test at gestations outside of the eligibility criteria as well as 46 women who did not receive a repeat test (but delivered after their first test was due; appendix pp 6–7), and the second per-protocol analysis additionally excluded 45 women who delivered before their first repeat test was due (appendix pp 8–9). Despite the difference between groups in the initial PlGF concentration being attenuated in the per-protocol analysis (excluding participants who delivered before first test due; appendix pp 4–5), the significant reduction in gestational age at delivery and increase in participants delivering before 34 weeks' gestation persisted (appendix pp 6–7).

In the revealed repeat PlGF-based testing group compared with the concealed repeat PlGF-based testing group, there was no significant difference in the proportion of women with the severe adverse maternal outcome composite (18 [2·9%[of 625 women in the revealed repeat PlGF-based testing group *vs* 16 [2·6%] of 626 women in the concealed repeat PlGF-based testing group; adjusted RR 1·13 [95% CI 0·58 to 2·20]; p=0·717; table 4; figure 2). There was an increase in the rate of caesarean birth compared with vaginal birth (427 [68·3%] of 625 women in the revealed repeat PlGF-based testing group *vs* 59·9% in the concealed repeat PlGF-based testing group; adjusted RR 1·14 [95% CI 1·05 to 1·23]; p=0·002). There was a significant reduction in the time from initial PlGF-based test to diagnosis of pre-eclampsia (19·1 [SD 20·4] days in the revealed repeat PlGF-based testing group *vs* 22·5 [22·9] days in the concealed repeat PlGF-based testing group; mean difference –3·79 days [95% CI –7·10 to –0·47]; p=0·025). There was also a significant reduction in the time from randomisation to diagnosis of pre-eclampsia (13·6 [SD 19·3] days in the revealed repeat PlGF-based testing group *vs* 16·7 [20·7] days in the concealed repeat PlGF-based testing group; mean difference –3·37 days [95% CI –6·54 to –0·19; p=0·038]; similar results were seen in the per-protocol analyses (appendix pp 11–12). Additional descriptive maternal outcomes for the per-protocol analysis are shown in the appendix (pp 13–18) without comparisons as prespecified in the statistical analysis plan.[14] Fetal ultrasound abnormalities were more common in the revealed repeat PlGF-based testing group. Administration of magnesium sulfate and antenatal corticosteroids were slightly higher in the revealed repeat PlGF-based testing group.

Details of repeat PlGF-based tests are shown in the appendix (p 19) and figure 3. The numbers of participants with 0, 1, 2, 3, or 4 repeat tests, and the total number of repeat tests were similar between the two groups. Of 2583 repeat testing visits, 2221 (86%) were performed at routine clinical appointments. Of 363 participants with a normal initial PlGF result (>100 pg/mL), 131 (36·1%)

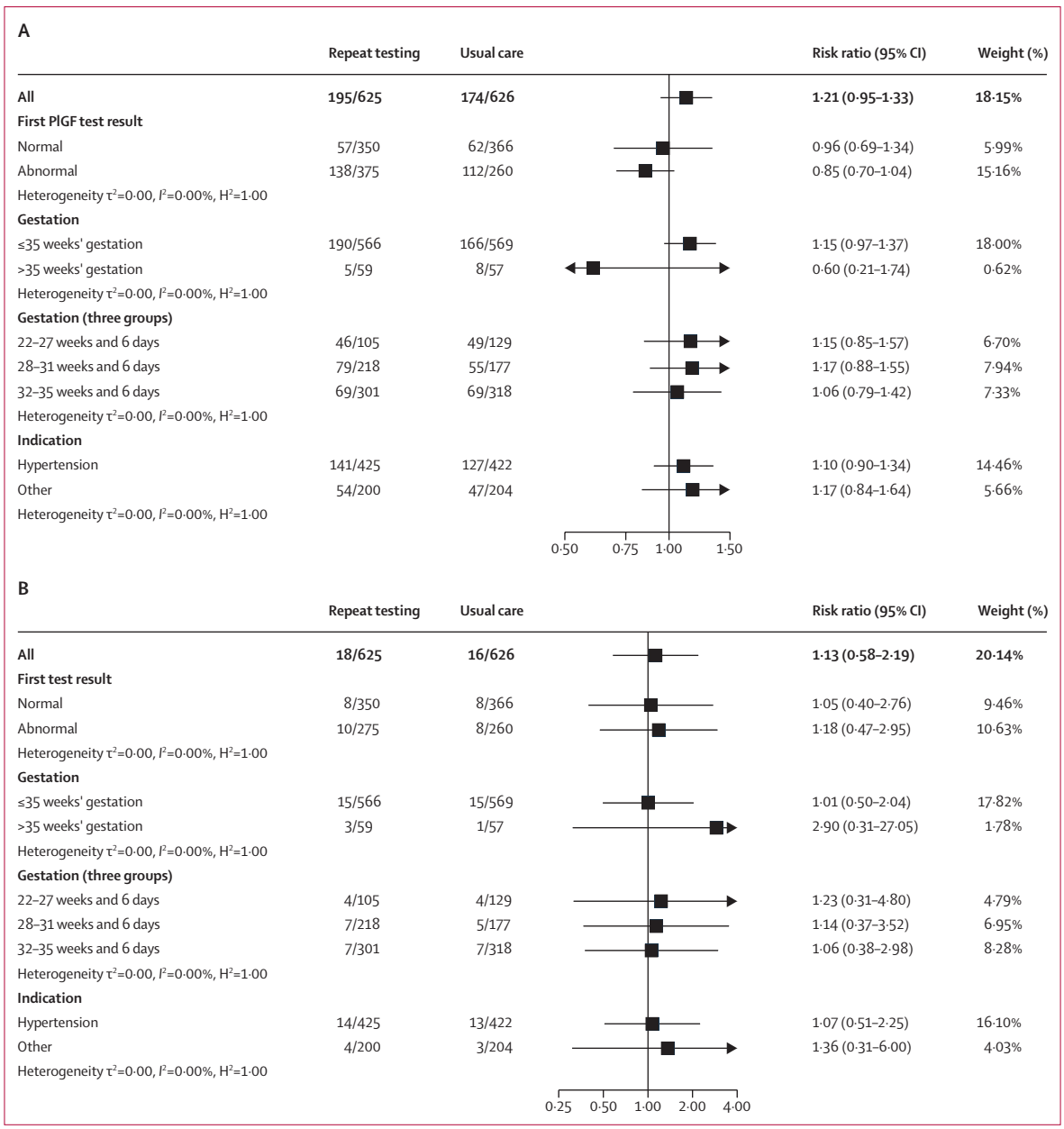

Figure 2: **Forest plot for comparing repeat testing with usual care, with prespecified subgroup analysis (intention-to-treat population)**
Forest plots show analysis of primary perinatal outcome (A) and maternal severe adverse outcome composite (B). PlGF=placental growth factor.

changed category and had a low PlGF concentration (12–99 pg/mL) by their final test, and 12 (3·3%) had a very low PlGF concentration (<12 pg/mL) by their final test (figure 3A). Low or very low initial PlGF results rarely normalised by the final test (11 [5·1%] of 217 low results and 0 [0%] of 76 very low results; figure 3A). Of 285 participants with a normal initial sFlt-1/PlGF ratio result (≤38), 52 (18·3%) changed category and had a high sFlt-1/PlGF ratio (38–85) by their last test, and 25 (8·8%) had a very high sFlt-1/PlGF ratio (>85; figure 3B). Of 142 participants with a high (n=78) or very high (n=64) sFlt-1/PlGF ratio result, five (6·4%) and three (4·7%) improved to a normal ratio result by the last test, respectively (figure 3B). There were no substantial differences between the revealed and concealed groups (appendix pp 32–37).

In the revealed repeat PlGF-based testing group compared to the concealed repeat PlGF-based testing group, there was no significant difference in neonatal intensive care or high dependency days, but there was a significantly higher number of special care days (12·3 [SD 11·5] days *vs* 9·2 [SD 11·1] days; mean difference 1·31 days (95% CI

	Revealed repeat PlGF-based testing group (n=625)	Concealed repeat PlGF-based testing group (n=626)	Adjusted risk ratio (95% CI)*
Number of individuals with adverse outcomes (defined by fullPIERS consensus)*†	18 (2·9%)	16 (2·6%)	1·13 (0·58 to 2·20); p=0·72
Number of individuals with pre-eclampsia (including those diagnosed by trial team)*	255 (40·8%)	250 (39·9%)	1·02 (0·90 to 1·17); p=0·74
Systolic blood pressure ≥160 mm Hg*	254 (40·6%)	236 (37·7%)	1·07 (0·94 to 1·22); p=0·28
Caesarean section (*vs* vaginal delivery)*	427 (68·3%)	375 (59·9%)	1·14 (1·05–1·23); p=0·002
Days to diagnosis of pre-eclampsia (first PlGF-based test to diagnosis)‡	19·1 (20·4)	22·5 (22·9)	−3·79 (−7·10 to −0·47); p=0·025
Days to diagnosis of pre-eclampsia (randomisation to diagnosis)‡	13·6 (19·3)	16·7 (20·7)	−3·37 (−6·54 to 0·19); p=0·038
Primary diagnosis (exclusive)			
Any pre-eclampsia	255 (40·8%)	248 (39·6%)	..
Pre-eclampsia (without chronic hypertension or renal disease)	218 (34·9%)	205 (32·7%)	..
Superimposed pre-eclampsia (background chronic hypertension)	27 (4·3%)	32 (5·1%)	..
Superimposed pre-eclampsia (background chronic kidney disease)	4 (0·6%)	4 (0·6%)	..
Superimposed pre-eclampsia (background chronic hypertension and chronic kidney disease)	6 (1·0%)	7 (1·1%)	..
Gestational hypertension	126 (20·2%)	115 (18·4%)	..
Gestational proteinuria	17 (2·7%)	21 (3·4%)	..
Suspected fetal growth restriction requiring delivery	30 (4·8%)	26 (4·2%)	..
Chronic hypertension only	58 (9·3%)	63 (10·1%)	..
Chronic hypertension with a small-for-gestational-age infant	23 (3·7%)	25 (4·0%)	..
Transient hypertension	16 (2·6%)	15 (2·4%)	..
None of the above	113 (18·1%)	124 (19·8%)	..

Data are n/N (%), n (%), or mean (SD). PlGF=placental growth factor. *Risk ratio adjusted for minimisation variables. †Individuals could have several adverse events. ‡The comparison is the mean difference, adjusted for minimisation variables.

Table 4: **Secondary maternal outcomes (intention-to-treat population)**

0·47–2·15); appendix p 20). There were no other differences in health resource use between groups.

The number of serious adverse events in both groups was similar: four in the revealed repeat PlGF-based testing group (two stillbirths and two neonatal deaths) and six in the concealed repeat PlGF-based testing group (one case of eclampsia, three stillbirths, and two neonatal deaths; appendix p 21). All serious adverse events were deemed unrelated to the intervention by the site principal investigators and chief investigator.

Test performance of the initial and first repeat PlGF-based test for prediction of pre-eclampsia needing delivery within 14 days are shown in the appendix (pp 22–27). Test performance of the first repeat test was similar to the initial PlGF-based test, and repeat testing retained high NPV: 97·6% (95% CI 94·1–99·4) for first repeat PlGF-based test and 96·4% (95% CI 91·7–98·8) for first repeat sFlt-1/PlGF ratio. Test performance of the first test is demonstrated for rule-in and rule-out of pre-eclampsia with delivery in 7, 14, 21, and 28 days in the appendix (pp 25–27). Time to delivery from initial PlGF-based test and first repeat PlGF-based test is shown in the appendix (pp 28–29), stratified by initial test result.

As a post-hoc sensitivity analysis requested by the data monitoring committee, considering the chance imbalance in initial PlGF concentrations, we used multiple regression to adjust for initial PlGF-based test results for the primary outcome. Adjustments for gestation of initial PlGF-based test (22 weeks and 0 days to 27 weeks and 6 days, 28 weeks to 31 weeks and 6 days, and >32 weeks and 0 days), indication for test, type of PlGF-based test, and initial result of test had no effect on our conclusions (OR for the primary outcome was 1·11 [0·85–1·45]; p=0·456].

An exploratory post-hoc analysis of indication for delivery for preterm birth before 34 weeks' gestation is shown in the appendix (p 10). Preterm delivery was driven by broadly similar proportions of fetal indications, but the numbers in some groups are too small in this exploratory analysis for further interpretation; an abnormal PlGF-based test result was not documented as an indication for delivery.

Discussion

In this pragmatic randomised controlled trial of revealed repeat PlGF-based testing, according to UK nationally recommended diagnostic thresholds, there was no evidence of a significant difference on the composite outcome of stillbirth, early neonatal death, or neonatal unit admission, compared with usual care with concealed repeat PlGF-based testing, in women with suspected preterm pre-eclampsia. Although there remains a clear evidence base for initial PlGF-based testing, routine repeat testing of all women was associated with a significant reduction in time to diagnosis, without improving downstream clinical outcomes. Our study suggests that in this population in a high-income setting with a low prevalence of adverse outcomes, routine repeat PlGF-based testing of all individuals with suspected preterm pre-eclampsia is not recommended. Repeat revealed PlGF-based testing was significantly associated with reduced gestational age at delivery, increased preterm birth before 34 weeks' gestation, and increased caesarean birth, without impacting neonatal morbidity-free survival to discharge or reducing severe maternal adverse outcomes.

Abnormal PlGF-based test results rarely normalised; given that there was no evidence of benefit on clinical outcomes, these data do not support repeat testing in women with abnormal initial results. The mechanism of increased preterm birth and caesarean section with repeat testing is unclear but might be related to clinician behaviour in response to repeated abnormal results, despite the

clinical management algorithm clearly emphasising that abnormal PlGF alone is not an indication for delivery. Normal results became abnormal by the final test in more than a quarter of participants, but the NPV of an initial normal result at predicting pre-eclampsia with delivery remained high for 3–4 weeks. Repeat testing after 3–4 weeks in women with an initial normal result might therefore have a place to detect results changing category, particularly in women who present again with suspected pre-eclampsia, but definitive evidence for beneficial impact on clinical outcomes in this subgroup remains uncertain.

The results of this randomised controlled trial support the findings of the first PARROT-1 trial[5] in relation to initial testing, which demonstrated that initial PlGF-based testing was significantly associated with reduced time to diagnosis of pre-eclampsia and reduced severe adverse maternal outcomes from 5·4% to 3·8%, with no change in perinatal adverse outcomes or gestational age at delivery.[5] All participants in the current trial received an initial revealed PlGF-based test, in keeping with national guidance; an incidence of 2·7% severe maternal adverse outcomes in both groups in this trial is therefore reassuring. This finding is particularly important as the trial was conducted through the COVID-19 pandemic when virtual monitoring was prevalent and face-to-face appointments reduced. Other potential contributory factors include a different population sample, temporal reduction in morbidity driven by other interventions, or improved familiarity with PlGF-based testing. 93% of women in both groups who delivered before 35 weeks' gestation received antenatal corticosteroids, which is higher than previously reported.[20] Administration of magnesium sulfate and antenatal corticosteroids were slightly higher in the revealed repeat PlGF-based testing group, likely relating to the higher incidence of preterm birth before 34 weeks' gestation in this group. It is of interest that the time to diagnosis of pre-eclampsia in this trial is longer than the time to diagnosis in the PARROT-1 trial. As initial PlGF-based testing has been incorporated into routine maternity care, there might be less selection bias compared with the previous trial; for a trial of repeat testing, women likely to deliver imminently might not have been recruited into the PARROT-2 trial. Additionally, the PARROT-1 trial presented geometric means, due to a log distribution of time to diagnosis, whereas arithmetic means are presented in the current trial, due to the distribution of data in this trial.

Strengths of this study include a robust evaluation of repeat PlGF-based testing, in a large population of women with suspected preterm pre-eclampsia. The trial was designed pragmatically to represent how repeat PlGF-based testing might be implemented in a real-world setting. This study was conducted to rigorous standards, with a prespecified, published protocol and statistical analysis plan, and it was registered prospectively. The trial participants were recruited by a network of research midwives, from maternity units from England, Scotland, and Wales, with pragmatic inclusion criteria and diverse representation, both in terms of demography and spectrum of disease, enhancing the generalisability of the study findings. A high proportion of eligible women participated in the study (88%), demonstrating high acceptability of the intervention and equipoise for the research question. Trials to assess effect of diagnostic tests on clinical outcomes are unusual, partly because a change in behaviour is needed as well as the novel diagnostic. The Patient-Centred Outcomes Research Institute recommend that process of care outcomes, such as time to diagnosis, should be used in evaluation, as well

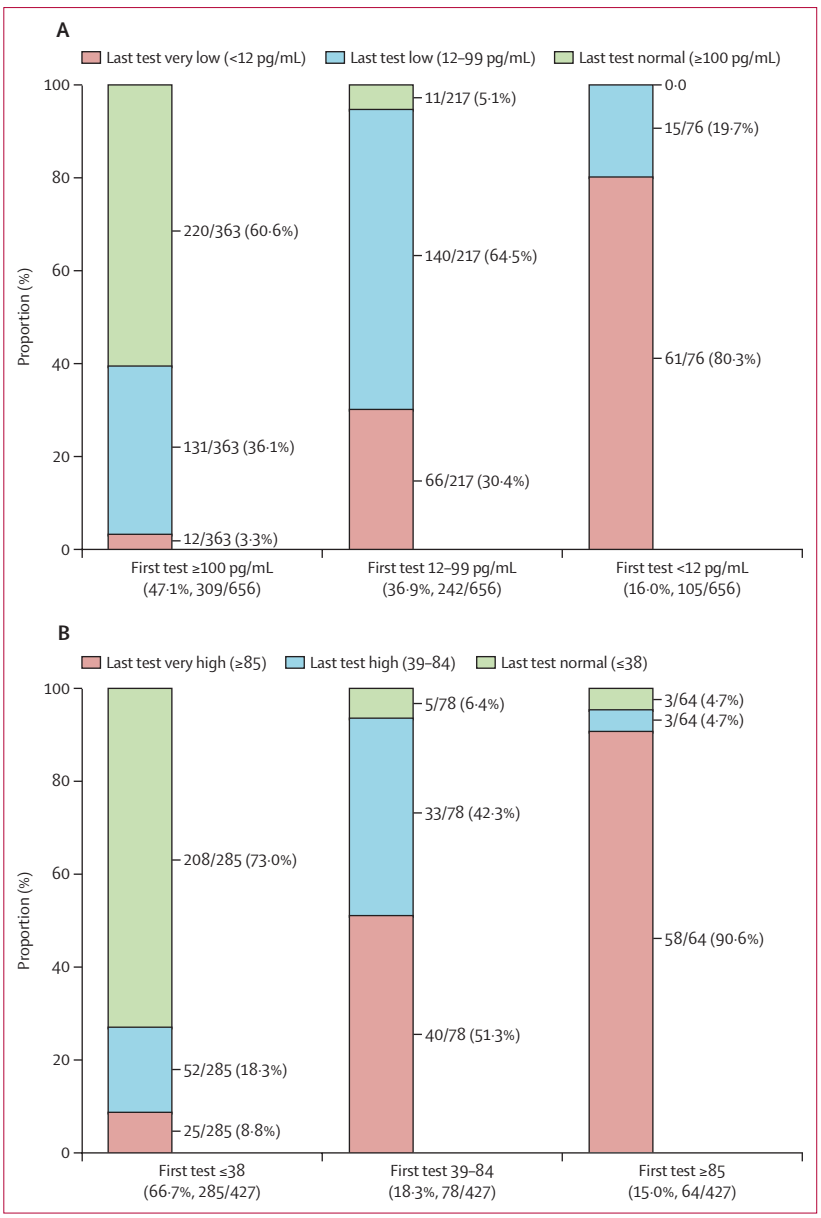

Figure 3: **Proportion of women changing PlGF category between first and last visit (in women who had at least one repeat test, revealed and concealed groups combined)**
(A) QuidelOrtho PlGF-based test results. (B) Roche sFlt-1/PlGF ratio test results. PlGF=placental growth factor.

as morbidity and mortality.[21] Our trial has shown a significant reduction in time to diagnosis, without improving downstream adverse clinical outcomes. This trial was a phase 3 effectiveness trial, and not a hybrid effectiveness-implementation trial. We have reported the trial according to the prespecified analysis plan in the published protocol, but this has not included evaluation of implementation of the management algorithm.

Limitations in this study include the challenge of finding an appropriate primary perinatal outcome. A composite of stillbirth, early neonatal death, or neonatal unit admission was selected with support of lay representatives; stillbirth and early neonatal death are uncommon adverse events of catastrophic severity, whereas neonatal unit admission involves physical separation of the mother and infant and is a more frequent event, capturing underlying neonatal morbidity. Clearly, the perinatal composite is driven by neonatal unit admission. The event rate of the perinatal composite exceeded that predicted in the sample size calculation; therefore, our trial is unlikely to be underpowered. However, it is possible that components of the composite might go in opposite directions, whereby a reduction in perinatal death occurs alongside an increase in neonatal unit admission. We additionally included a perinatal morbidity composite comprising major adverse outcomes, as used in recent studies of neonatal morbidity and agreed with co-investigators and lay representatives.[17]

When considering potential sources of bias, selection bias is unlikely as this was an individual-level randomised controlled trial. Despite adequate randomisation procedures, there was a chance imbalance in the PlGF test results between the revealed and concealed groups, which might have biased the results. Statistical analysis implies this is unlikely, but the post-hoc sensitivity analysis might be underpowered due to small numbers in subgroups. Performance or detection bias are possible, as it was not possible to mask the intervention allocation to clinicians, participants, or data collectors, due to the nature of the trial. Severe maternal adverse outcomes were verified by two members of the central research team and neonatal adverse outcomes were collected by routine clinical descriptors on the clinical discharge summary. There was very low attrition in both groups.

To our knowledge, there are no published randomised controlled trials of repeat PlGF-based testing in suspected pre-eclampsia. Repeat PlGF-based testing has been investigated in observational studies. A case series (n=289) showed that repeat PlGF-based testing retains high NPV (92·2% [95% CI 85·3–96·6]).[22] Our larger study demonstrates superior test performance for repeat testing, supports the use of pre-existing rule-in and rule-out thresholds, and shows that the diagnostic test used as the intervention had performance as expected. Another observational study of 652 women found that those who developed pre-eclampsia (n=42) had larger median differences in sFlt-1/PlGF ratios at 2 weeks (31·22 *vs* 1·45; p<0·001) and 3 weeks (48·97 *vs* 2·39; p<0·001) after the initial test compared with women who did not develop pre-eclampsia.[23] In a study of sequential sFlt-1/PlGF testing in 100 women admitted with suspected pre-eclampsia, those at risk for adverse pregnancy outcomes had higher sFlt-1/PlGF ratios, which continued to rise until delivery.[24] An international consensus on PlGF-based testing recommends to "re-test after 1–2 weeks or immediately if the clinical situation changes", but does not clearly identify the evidence base for this.[25] However, our trial questions the clinical value of such a policy, and demonstrates that routine repeat testing for all women presenting with suspected preterm pre-eclampsia confers no additional clinical benefit beyond the initial PlGF-based test. Further analysis might identify subgroups who could benefit from repeat testing, for example individuals with a normal initial result who present again with symptoms or signs of pre-eclampsia. However, our study does not support repeating PlGF-based tests if the initial test is abnormal.

Our planned future analyses (beyond those in the main trial protocol) will include a secondary analysis by test type, and separate interpretation of sFlt-1 and PlGF. Stratified analysis according to initial test result (normal or abnormal), or indication for repeat testing, might identify the impact of repeat testing on clinical outcomes. It might also be beneficial to explore test performance for stillbirth, or maternal or other perinatal adverse outcomes. PlGF is reported according to categories, but there might be additional benefit in using PlGF as a continuous measurement. Our trial evaluated use of PlGF-based testing with thresholds as recommended by national guidance. Multimodal algorithms are in use for combined first trimester screening for fetal aneuploidies; further research is awaited to provide an evidence-base for a similar approach for pre-eclampsia evaluation. At trial inception, NICE guidance specified two categories: normal (pre-eclampsia ruled out) and abnormal (pre-eclampsia not ruled out). This changed to three categories in 2022, including rule-in of pre-eclampsia, but clinicians typically interpret continuous variables (eg, blood pressure, kidney, and liver function results) alongside thresholds or categories. Finally, a recent study has suggested there might be ethnic differences in PlGF thresholds, with higher mean PlGF concentrations in Black women compared with White women, such that fixed thresholds might underestimate the proportion of Black women with an abnormal result;[26] this consideration should be interrogated in our large cohort.

As the first large, multicentre trial, to our knowledge, this has major implications for policy, practice, and guidelines. A policy of routine repeat PlGF-based testing for all individuals with suspected pre-eclampsia, as recommended by some international groups and being adopted into practice without an evidence base, is not supported by our findings. This study clearly delineates the limited value of repeat PlGF-based testing in women with suspected preterm pre-eclampsia. With an estimated 5% of women globally experiencing preterm pregnancy

hypertension, of 140 million births, there is now a clear evidence base for implementation of initial PlGF-based testing, but without the necessity of higher costs associated with repeat PlGF-based testing. These results should therefore lower the barriers to more widespread, equitable adoption of initial PlGF-based testing, improving maternal health outcomes globally.

PARROT-2 trial group collaborators
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Contributors
AHS and LCC conceived the study. LW, KED, JM, CB, PTS, KC, MG, AHS, and LCC were involved in securing funding for the study. AH, JS, LW, ZV, AB, CG, and LCC coordinated the study conduct and data collection. AH and PTS did the study analyses, supervised by LCC. RMH did the health economic analysis. AH, LW, and LCC wrote the Article, with assistance from JS, KED, PTS, JM, CB, and AHS. The corresponding author has full access to the complete data in the study and holds final responsibility for the decision to submit for publication. All authors approved the final version of the manuscript.

Declaration of interests
AHS has received funds from Perkin Elmer (Revvity) and QuidelOrtho for expenses to meetings and has received money from Roche as a consultant on strategy. All other authors declare no competing interests.

Data sharing
The dataset will be available to appropriate academic parties on request from the chief investigator (LCC) in accordance with the data sharing policies of King's College London, with input from the co-investigator group where applicable.

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