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An open-label randomized-controlled trial of low dose aspirin with an early screening test for pre-eclampsia and growth restriction (TEST): Trial protocol

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ABSTRACT

Objective: Pre-eclampsia remains a worldwide cause of maternal and perinatal morbidity and mortality. Low dose aspirin (LDA) can reduce the occurrence of pre-eclampsia in women with identifiable risk factors. Emerging screening tests can determine the maternal risk of developing placental disease, such as pre-eclampsia from the first trimester of pregnancy. The aim of this study is to determine if it is more beneficial in terms of efficacy and acceptability to routinely prescribe LDA to nulliparous low-risk women compared to test indicated LDA on the basis of a positive screening test for placental disease.

Methods: We propose a three armed multi-center open-labeled randomized control trial of; (i) routine LDA, (ii) no aspirin, and (iii) LDA on the basis of a positive first trimester pre-eclampsia screening test. LDA (75 mg once daily) shall be given from the first trimester until 36-week gestation. The primary outcome measures include; (i) the proportion of eligible women that agree to participate (acceptability), (ii) compliance with study protocol (acceptability and feasibility), (iii) the proportion of women in whom it is possible to obtain first trimester trans-abdominal uterine artery Doppler examination (feasibility) and (iv) the proportion of women with a completed screening test that are issued the screening result within one week of having the test performed (feasibility).

Conclusion: This will be the first clinical trial to determine the efficacy and acceptability in low-risk women of taking routine LDA versus no aspirin versus LDA based on a positive first trimester screening test for the prevention of placental disease.

1. Introduction

Ischemic placental disease (IPD) is an entity encompassing pre-eclampsia, fetal growth restriction (FGR) and placental abruption and has a combined incidence in pregnancy of 10–15% [1]. Pre-eclampsia is a serious systemic condition affecting 3–5% of pregnancies and is responsible for >50,000 of maternal deaths annually worldwide [2]. The International Society for the Study of Hypertension in Pregnancy defines pre-eclampsia as gestational hypertension with proteinuria of 300 mg or more in 24 h [3].

The use of low dose aspirin (LDA) prior to 16-weeks' gestation can prevent the pathological process causing placental disease by altering the balance of prostacyclin and thromboxane; hence preventing spiral artery thrombosis and widespread endothelial dysfunction [4].

There is extensive evidence, demonstrating the efficacy [5–9] and safety [10–13] of LDA for prevention of placental disease in high-risk pregnancies where there are clearly identifiable risk factors. However, there is a paucity of research into its efficacy in low-risk women. Administration of aspirin in pregnancy is associated with absolute risk reductions of 2% to 5% for pre-eclampsia, 1% to 5% for FGR 2% to 4% for

Abbreviations: LDA, low dose aspirin; FGR, fetal growth restriction; RCT, randomized controlled trial; FMF, fetal medicine foundation; MAP, mean arterial pressure.

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preterm delivery with no associated increase in perinatal or maternal morbidity [13].

Several screening tests have been devised to detect the risk of pre-eclampsia and FGR from the first trimester. One of the most notable is that of The Fetal Medicine Foundation (FMF), UK that have devised an algorithm encompassing uterine artery Doppler pulsatility indices, mean arterial pressure (MAP), the placental biomarkers PAPP-A and PLGF in addition to maternal characteristics, which can detect 96% of cases of pre-eclampsia requiring delivery before 34 weeks and 54% of all cases of pre-eclampsia at a fixed false-positive rate of 10% [14]. The FMF screening test is reserved as a research tool, pending validation within a low-risk population. Thus far it has been externally validated in other studies of unselected women with conflicting results as to sensitivity and specificity for placental disease prediction [15,16]. Following validation of the FMF screening test in low-risk nulliparous women, which is currently the topic of on-going research, the FMF pre-eclampsia screening test may potentially come into clinical practice in the future [17]. Current guidelines followed within the UK, set by The National Institute for Health and Clinical Excellence advocate screening through history taking and provision of LDA in the presence of one major risk factor or two moderate risk-factors [12]. The American College of Obstetricians and Gynecologists have a similar stance and do not recommend screening to predict pre-eclampsia beyond obtaining an appropriate medical history to evaluate for risk factors. They recommend that any further screening tests beyond this should undergo a cost-effectiveness analysis before being used in routine practice [18]. Such risk factors are demonstrated in Table 1.

It has been postulated that it is more cost-effective to use prophylactic medication, notably aspirin for the prevention of placental disease rather than screening and treating an entire low-risk population. The reason for this is because aspirin is felt to be an effective, affordable and safe treatment in pregnancy [19].

In light of such evidence, with an emerging novel screening test for pre-eclampsia and the efficacy of LDA for placental disease prevention we hypothesize that it may be more clinically effective and affordable to prescribe LDA routinely to all women in their first pregnancy as opposed to being upon the basis of a screening test. To assess this hypothesis a preliminary pilot study is required to determine feasibility, acceptability and statistical power required for such a study. Hence, we propose a three armed randomized control trial (RCT) in low-risk women to determine; (i) the efficacy and (ii) the acceptability of women to take routine LDA, versus no LDA versus LDA on the basis of a pre-eclampsia screening test in their first pregnancy. One anticipates that the use of such a three-armed study will aid in determining if it is more acceptable to women and feasible to prescribe LDA routinely compared to not at all, or based on results of a screening test.

Table 1
Major and moderate risk factors for pre-eclampsia as defined by the American College of Obstetricians and Gynecologists and the National Institute for Health and Clinical Excellence, UK [12,18].

Risk factors	ACOG major	NICE major	NICE moderate
Primiparity	✔		✔
Previous pre-eclamptic pregnancy	✔	✔	
Chronic hypertension, chronic renal disease or both	✔	✔	
History of thrombophilia	✔		
Multiple pregnancy	✔		✔
In vitro fertilization	✔		
Family history of pre-eclampsia	✔		✔
Diabetes mellitus type I/II	✔	✔	
Obesity			✔
Systemic Lupus Erythematosus (SLE) or Antiphospholipid Syndrome	✔	✔	
Advanced maternal age > 40 years	✔		✔
Pregnancy interval > 10 years			✔

2. Materials and methods

2.1. Overview

This protocol outlines the principles and methodology of a proposed three-armed multi-center open-labeled RCT which aims to assess if it is beneficial in terms of efficacy and patient acceptability to routinely prescribe LDA to low-risk women in their first pregnancy compared to test indicated LDA on the basis of a positive first trimester screening test for pre-eclampsia and FGR. Fig. 1 outlines the study methodology on the basis of the principle of Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) [20], and the Consolidated Standards of Research Trials (CONSORT) [21]. This trial is registered with ISRCTN Ref No ISRCTN15191778 EudraCT number 2013-004241-17 and has been approved by the Health Products Regulatory Authority January 2014.

2.2. Ethics

This clinical trial has obtained ethical approval from the National Maternity Hospital, Dublin Central Ethics Committee for Randomized Controlled Drug Trials.

2.3. Enrolment and eligibility

This will be a two-center RCT based in Dublin, Ireland in two of the main tertiary obstetric centers with approximately 9000 deliveries per annum respectively and managing a mixture of low- and high-risk obstetric populations with access to both midwifery and obstetric led antenatal care; The National Maternity Hospital and the Rotunda Hospital. The study is affiliated with the School of Medicine and Medical Science, University College Dublin, which shall act as trial sponsor. Pregnant women in their first pregnancy (nulliparous), between 11 and 14 weeks gestation, not already taking aspirin, with adequate English to understand the purpose of the study will be recruited at the time of their first routine hospital antenatal booking visit with their obstetrician/midwife. Subjects will be excluded if a fetal abnormality is detected at the time of the first trimester scan, if they have contra-indications to aspirin or are under 18-years of age. Data on all women approached for study participation (screened population) will be recorded to determine those that are non-eligible or decline taking aspirin in pregnancy.

Potentially eligible participants will be approached with both written and verbal information provided by a trained member of the research team. Following adequate time to decide on participation, a recruitment visit appointment will be organised, where written informed consent shall be obtained by the research clinician. Study participation will be highlighted in the patient records in addition to a letter to the general practitioner. At the recruitment visit (11 to 14 weeks gestation) subject demographics shall be entered, computerized randomisation performed, the components of the pre-eclampsia screening test are performed and aspirin prescribed where required.

2.4. Allocation of participants

Following assessment for study eligibility at the time of the antenatal booking visit, women will undergo computer-generated randomization using blocks of six to one of 3 antenatal management protocols: (i) aspirin therapy 75 mg daily commencing after a satisfactory first trimester assessment (routine aspirin arm), (ii) no aspirin therapy (control arm), and (iii) postponement of decision regarding aspirin therapy until availability of the FMF screening result for pre-eclampsia risk at the time of the first trimester assessment, with immediate commencement of LDA 75 mg daily in the screen positive subgroup (screen & treat arm). The study is open-label hence the participant and research team shall be aware of the allocation.

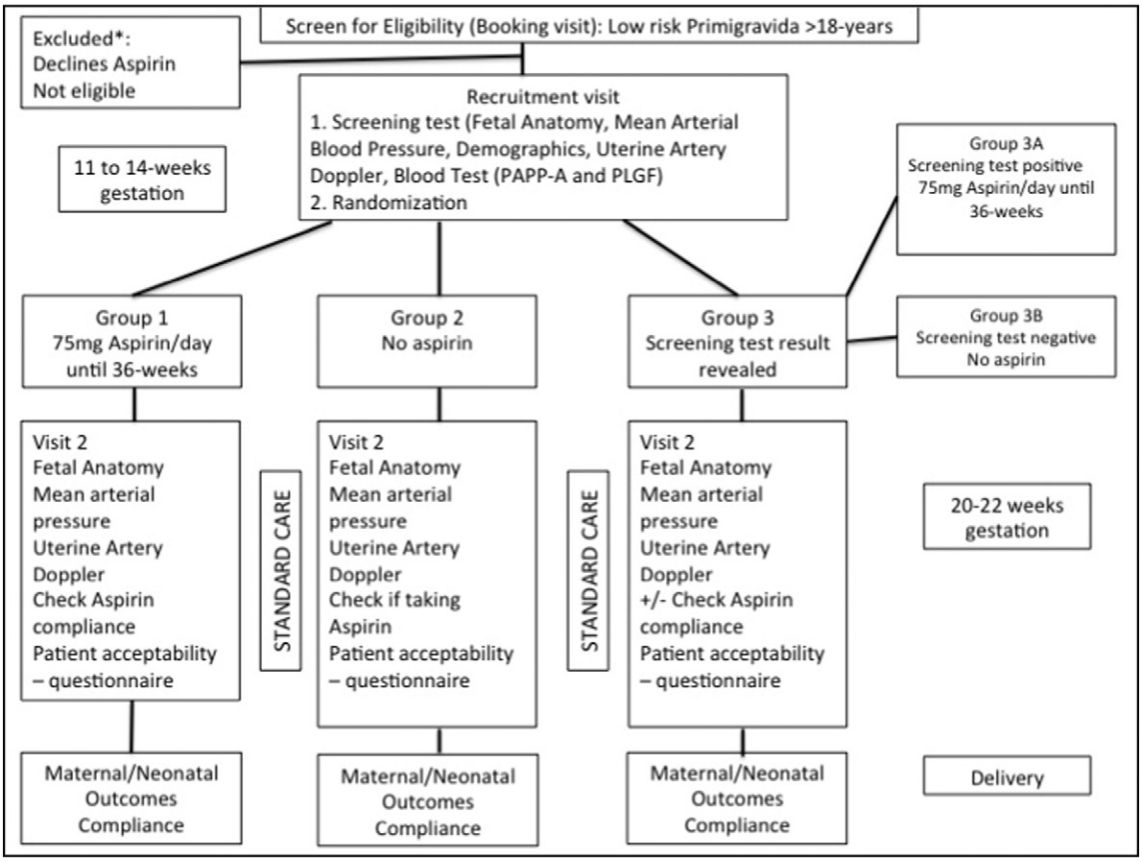

Fig. 1. Study flow diagram. *Excluded – multiparous, <11 weeks or >13 + 6 weeks at date of recruitment visit, non-English speaking, <18-years, fetal anomaly, contra-indication to aspirin or already taking aspirin or requiring aspirin as per major-risk factors NICE (Table 1).

2.5. Sample size

A statistician was consulted to determine the projected sample size for this RCT, which is 500 women. To determine pre-eclampsia as a primary outcome, the anticipated number of patients required is approximately 15,000 women. As the proposed study is determining the feasibility of such a study 500 subjects are more than adequate as literature dictates that 3% of the sample required for a substantive study with a primary outcome of reduction in pre-eclampsia ($n = 450$) [22]. Accounting for a drop-out/loss to follow-up rate of 10% ($n = 45$), 500 is an adequate number to determine primary outcomes of feasibility and acceptability. It is anticipated that a global proportion of patients shall develop placental disease, as a composite outcome of the pilot study which may then be used to formulate the overall power calculation, requiring fewer numbers than predicted for pre-eclampsia only. This pilot study shall inform us on the incidence of this entity in low-risk women. We aim to obtain all 500 patients across both centers over a two-year period under the presumption that 70% of women may decline taking aspirin in pregnancy, suggesting that over 850 eligible subjects must be approached.

2.6. Screening test methodology

The first trimester screening test will be performed at the time of the recruitment visit on all subjects. The results of the investigations are inputted by the research sonographer into the Viewpoint® Version 5.6.16 GE Healthcare, 2012 as per the patient unique study number. Investigations will include maternal demographics e.g. age, body mass index, type of conception. Mean arterial blood pressure (MAP) will be performed using an automated blood pressure monitoring device (3BTO-A2®; Microlife, Tapei, Taiwan) on both arms simultaneously as outlined by the FMF [23]. A first trimester trans-abdominal ultrasound shall be performed by a research sonographer with certification from the FMF to assess first trimester fetal anatomy including nuchal translucency, in addition to acquiring uterine artery Doppler waveforms bilaterally and determining the pulsatility index of each waveform to determine the average using a manual or automated tracing method as outlined from by the ISUOG guidelines (Fig. 3) [24]. Ultrasonography shall be performed on both sites using a Voluson Expert 730®, GE 2012 with standardized settings. A maternal blood sample will also be taken to determine the PAPP-A and PLGF level. These biomarkers will be quantified from maternal serum under standard conditions by the same biochemist using a 6000 DELFIA® Xpress, PerkinElmer, 2014 clinical random access screening platform. Following the input of all data, the risk of pre-eclampsia will be determined. The time frame from recruitment visit to test result availability will be recorded.

2.7. Study treatments

2.7.1. Group 1 — routine low-dose aspirin 'intervention'

Subjects randomized to Group 1 (routine LDA) shall receive standard antenatal care as well as taking LDA from booking until 36-week gestation orally once daily, as prescribed by the research clinician. As with all arms of the study, all subjects will undergo a recruitment visit involving the first trimester screening test, the results of which are only revealed for those in Group 3 (screen and treat).

2.7.1.1. Aspirin administration. 75 mg of Acetylsalicylic Acid (Nu-seals®) enteric-coated aspirin will be prescribed to women allocated to Groups

1 and to 3A (screen test positive). In Group 1 this will be at the time of the recruitment visit. In Group 3A this will be following the calculation of pre-eclampsia risk (see Section 2.7.3). All subjects within an aspirin-taking group will undergo a 20-minute education session with the research team and receive an instruction leaflet outlining potential benefits and risk as well as contact details and instructions around aspirin usage and compliance. 84 tablets shall be dispensed in blister packs with 14 tablets/sheet with one tablet to be taken daily, preferably at night with food. Subsequently at the 20–22 week visit any leftover aspirin is returned and a further 112 tablets dispensed to be taken from this time until the 36-week period. Blister packs shall be labeled by the research pharmacist with the patient study number with provision of the summary product characteristics.

2.7.1.2. Aspirin adherence. Aspirin adherence will be determined at the 20–22 week and the 36-week stage. Adherence will be endorsed by the specific instruction sheet in addition to a telephone call by a member of the research team one week following commencement. Compliance will be determined by one of two means; (i) tablet count and (ii) patient completed diary cards, the subject recording the days where they have taken the aspirin. Hence self-reported compliance and compliance from tablet counts can be determined at the 20–22 week and 36-week time point. Tablets will be counted by a member of the research team and counter checked with the research pharmacist. Patients that are entirely non-compliant with LDA will remain in the study on an intention-to-treat basis. Patients that are in the non-aspirin taking groups will be asked if they are taking LDA at the 20–22 week stage, which will be counter-checked retrospectively following delivery in addition to checking the prescription of concomitant medications. As 75 mg of aspirin can only be dispensed through prescription in Ireland, a record of prescription will be available in the patient's notes if it is not verbalized. The study participant's independent obstetrician and general practitioner will be made aware of their participation in the study through written correspondence with a study information leaflet and patient group information enclosed.

2.7.2. Group 2 — no aspirin group 'control'

Women randomized to Group 2 will, as with all arms undergo a recruitment visit involving the first trimester screening test, yet results will not be revealed. Due to the open-labeled nature of the study there will be no placebo.

2.7.3. Group 3 — screen and treat group 'test indicated aspirin'

In Group 3 that results of the FMF screening test will be prospectively revealed. Based upon the results of screening test components, the risk of developing any pre-eclampsia until 42-week gestation, set at a false positive rate of 5% will be used to determine a subject at high risk and hence allocated to Group 3A must have a risk > 1:8 and must start LDA immediately outlined as per Group 1 (see Fig. 2). Group 3B will have a < 1:8 risk of developing pre-eclampsia and will not take LDA.

2.8. Follow-up appointments

All participants will return at 20–22 weeks where MAP, fetal anatomy, uterine artery Doppler studies and PAPP-A and PLGF assessment will be repeated. Consent and compliance will also checked at this stage and aspirin with a repeat diary card issued where required (Groups 1 and 3A). Patients will also complete a questionnaire on their acceptability of taking LDA in pregnancy and of undergoing the screening test compared to standard care. Following this those patients on LDA will return leftover tablets and the diary card at 36-weeks. Maternal and neonatal outcomes shall be obtained for each participant one-month following delivery.

2.9. Outcome measures

The primary outcome measures of TEST include:

(i) The proportion of eligible women that agree to participate in the study – this will be reflected as a proportion of the number of

Screening test	FPR %	PE <34 weeks (n = 214)		PE <37 weeks (n = 568)		PE <42 weeks (n = 1,426)	
		risk cutoff	detection n (%)	risk cutoff	detection n (%)	risk cutoff	detection n (%)
Maternal characteristics	5.0	1:93	78 (35.5)	1:35	186 (32.7)	1:9	419 (29.4)
	10.0	1:143	108 (50.5)	1:51	246 (43.3)	1:12	574 (40.3)
Uterine artery PI	5.0	1:88	127 (59.3)	1:31	227 (40.0)	1:9	445 (31.2)
	10.0	1:164	161 (75.2)	1:52	313 (55.1)	1:12	602 (42.2)
MAP	5.0	1:88	125 (58.4)	1:31	250 (44.0)	1:8	532 (37.3)
	10.0	1:159	156 (72.9)	1:52	337 (59.3)	1:12	763 (53.5)
PAPP-A	5.0	1:88	93 (43.6)	1:33	212 (37.3)	1:9	449 (31.5)
	10.0	1:151	117 (54.7)	1:52	274 (48.2)	1:12	601 (42.1)
PLGF	5.0	1:95	127 (59.3)	1:33	232 (40.8)	1:9	415 (29.1)
	10.0	1:170	155 (72.4)	1:55	309 (54.4)	1:12	572 (40.1)
Uterine artery PI and MAP	5.0	1:96	171 (79.9)	1:31	310 (54.6)	1:7	498 (34.9)
	10.0	1:197	192 (89.7)	1:57	406 (71.5)	1:12	807 (56.6)
PAPP-A and PLGF	5.0	1:101	129 (60.3)	1:34	243 (42.8)	1:9	433 (30.4)
	10.0	1:181	159 (74.3)	1:56	317 (55.8)	1:12	582 (40.8)
Uterine artery PI, MAP and PAPP-A	5.0	1:105	175 (81.8)	1:26	298 (52.5)	1:7	514 (36.0)
	10.0	1:216	198 (92.5)	1:65	424 (74.6)	1:12	811 (59.9)
Uterine artery PI, MAP and PLGF	5.0	1:126	187 (87.4)	1:36	344 (60.6)	1:8	536 (37.6)
	10.0	1:261	205 (95.8)	1:67	439 (77.3)	1:12	755 (52.9)
Uterine artery PI, MAP, PAPP-A and PLGF	5.0	1:128	200 (93.4)	1:36	347 (61.1)	1:8	539 (37.8)
	10.0	1:269	206 (96.3)	1:67	435 (76.6)	1:12	764 (53.6)

Fig. 2. Table demonstrating estimated detection rates for pre-eclampsia at <34, <37 and <42 weeks gestation using the Fetal Medicine Foundation algorithm (final column) [14]. (Source: Reproduced with Permission of Karger Publishers®, 2012).

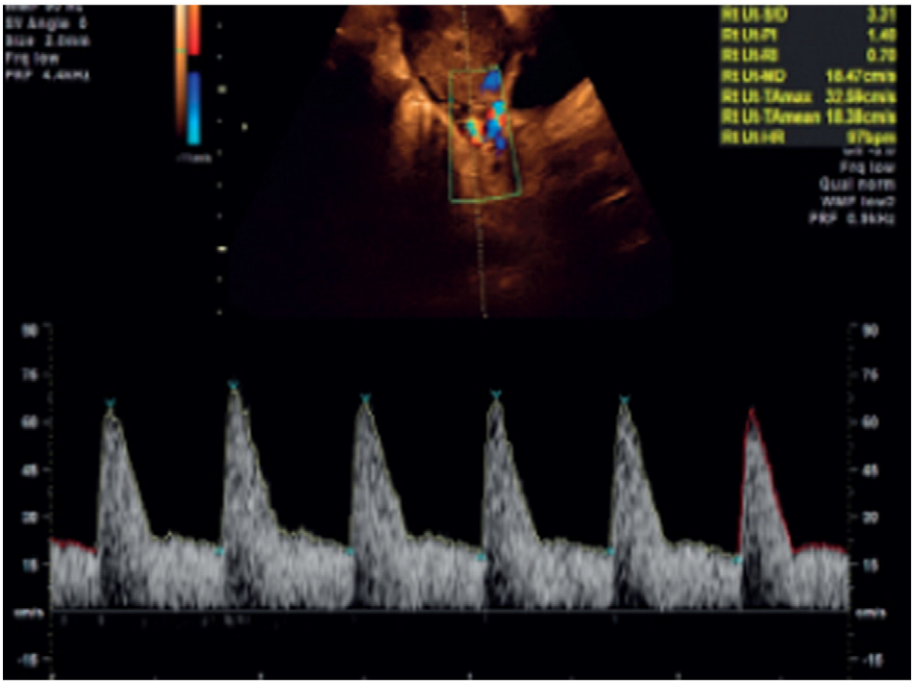

Fig. 3. Typical first trimester uterine artery Doppler waveform [24].
(Source: Figure reproduced with permission of John Wiley & Sons®, 2016).

women approached at the screening stage (feasibility).

(ii) Compliance with study protocol – this will be quantified as; (i) adherence to aspirin if prescribed (acceptability), (ii) attendance at study visits (acceptability), (iii) satisfactory collection of all data (feasibility), (iv) satisfactory collection of all endpoints and variables (feasibility), (v) any specific study protocol violations (feasibility).

(iii) The proportion of women in whom it is possible to obtain first trimester trans-abdominal uterine artery Doppler examination – this includes the subjectively recorded ease of acquisition (feasibility).

(iv) The proportion of women with a completed screening test who are issued the screening result within one week of having the test performed – also recorded will be the number of women within the screen and treat group that went beyond 16-weeks before receiving the screening test result as beyond this time LDA may not be effective (feasibility).

The secondary outcome measures include determining:

(i) The rate of pre-eclampsia as defined by the International Society for the Study of Pre-eclampsia in Pregnancy.

(ii) The rate of FGR.

(iii) Spontaneous or iatrogenic delivery prior to 34 and 37 completed weeks gestation.

(iv) The rate of admission to the neonatal intensive care unit,

(v) The rate of placental abruption, any reported death (stillbirth, neonatal or infant death) and small for gestational age infants.

(vi) Patient acceptability assessed with a questionnaire (acceptability).

Additional blood and urine samples and collection of placental tissue following delivery shall be obtained and stored to facilitate further research and sub-studies. A further aim of this study is to retrospectively assess the result of the screening tests in all participants and compare this to outcome to determine screening test sensitivity and specificity within our cohort.

2.10. Safety

Both Adverse (AEs) and Serious Adverse events (SAEs) will be prospectively recorded for all participants. Both will be recorded in terms of potential causality and severity. AEs shall be recorded on the case report form. SAEs will be formally reported to the sponsor and principal investigator, with further reporting to the HPRA should they be deemed a Serious Unexpected Serious Adverse Reaction (SUSAR). All AEs and SAEs shall undergo rigorous review by the independent Data Safety Monitoring Board (DSMB) who will meet quarterly.

2.11. Statistical analysis

Statistical analysis will be performed by a statistician using IBM SPPS version 20.0. Demographic characteristics will be outlined for each group. Two populations will used to describe the data (i) intention-to-treat: all subjects randomized to a treatment arm in the study and complete the full second trimester assessment and (ii) per-protocol: all subjects randomized who undergo all assessments up to and including post-partum and who do not violate protocol criteria (entry criteria).

3. Discussion

The purpose of this open-label multi-centre RCT is to determine if it is more beneficial in terms of efficacy and patient acceptability to routinely prescribe LDA to nulliparous low-risk women compared to test indicated LDA on the basis of a positive early pregnancy screening test for pre-eclampsia and FGR. In light of the development of novel screening tests for pre-eclampsia and a paucity of evidence on aspirin usage in low-risk women it is pertinent to generate evidence based on our outlined objectives before application of use of a screening test or routine LDA into routine clinical practice for low-risk patients. In this sense a cost-effectiveness analysis would also be of benefit. The study is novel in its assessment of LDA in low-risk patients in addition to the application of a pre-eclampsia screening test in an Irish population.

Conflict of interests

The authors declare that they have no competing interests.

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