FULL TITLE OF THE TRIAL:

A randomised crossover design study **comparing the pharmacokinetics and pharmacodynamics of two single Doses of ORal Aspirin** (75 mg v150mg) in pregnant women at risk of pre-eclampsia.

Short title of the trial: **DORA**

- **This protocol has regard for the HRA guidance and order of content**

RESEARCH REFERENCE NUMBERS

Protocol Version: V1.9 08.03.21

Trial Identifiers IRAS Number: 253665

EudraCT Number: 2021-000071-36

NHS REC Reference: 21/WA/0066

ISRCTN Number: ISRCTN14693054

Research Sponsor The Newcastle upon Tyne Hospitals NHS Foundation Trust

Sponsor Reference 8934

Research Funder Newcastle upon Tyne Hospitals NHS Charity

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the trial publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:

Signature:

.....

Date:
...../...../.....

Name (please print):

.....

Position:
.....

Chief Investigator:

Signature:
.....

Date:
...../...../.....

Name: (please print):

.....

KEY TRIAL CONTACTS

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I. LIST OF CONTENTS

CONTENTS

II. LIST OF ABBREVIATIONS

Define all unusual or 'technical' terms related to the trial. Add or delete as appropriate to your trial. Maintain alphabetical order for ease of reference.

AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EC	European Commission
EMEA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
IMP	Investigational Medicinal Product

IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials Number
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
MS	Member State
NHS R&D	National Health Service Research & Development
NIMP	Non-Investigational Medicinal Product
PD	Pharmacodynamics
PE	Pre-eclampsia
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
PK	Pharmacokinetics
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
RCT	Randomised Control Trial
REC	Research Ethics Committee
SA	Salicylic Acid
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics

SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reaction
Tbx B_2	Thromboxane B_2
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

iii. TRIAL SUMMARY

Trial Title	A randomised crossover design study **comparing the pharmacokinetics and pharmacodynamics of two single oral doses of aspirin** (75 mg v150mg) in pregnant women at risk of pre-eclampsia.
Internal ref. no. (or short title)	DORA
Clinical Phase	NA
Trial Design	A randomised 2 x 2 crossover design
Trial Participants	Pregnant women at risk of preeclampsia with clinical indication for aspirin prophylactic therapy.
Planned Sample Size	14
Treatment duration	Single dose in 24 hours on two occasions one week apart
Follow up duration	24 hours
Planned Trial Period	01/03/2021 to 31/08/2021
Primary objectives	To compare aspirin pharmacokinetics (plasma SA concentrations) and pharmacodynamics (serum TbxB2 concentrations) in pregnant women at 11-16 weeks gestation' following the administration of a single oral dose of either 75 mg or 150 mg aspirin.
Outcome Measures	Serum Thromboxane B_2 ($TbxB_2$) and salicylic acid (SA) concentration
Investigational Medicinal Product(s)	Aspirin
Formulation, Dose, Route of Administration	Dispersible oral aspirin 75 mg and 150 mg

I.V. ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

In accordance with the MHRA Good Clinical Practice Guide (page 167), NUTH (sponsor) does not see a need for a DMC/TSG committee for this study. The decision has been made by the sponsor where following aspect were considered:

1. **Safety profile of the IMP** – The IMP is aspirin used in dosages that are clinically acceptable and currently used.
2. **Size of the trial** – The sample size is low (14, with up to 18 patients to recruit to account to drop out) and short-term intervention (6 months or less). There is no complex flow-up and all procedures will be done in the Clinical Research Facility, which is a controlled environment.
3. **End points/data requiring regular review** – Due to the length of the intervention and follow-up there is little requirement to have regular review of the data. No interim analysis is required.
4. **Potential for high morbidity/mortality** – The risk of morbidity/mortality is low. The IMP has a well-known safety profile. Participants have a risk of hypertension during pregnancy, but it is not life threating.
5. **Vulnerable population** – Pregnant women with the risk of hypertension may be classified as vulnerable, however, due to the short time of the intervention and low-level risk of the IMP it is not deemed necessary to convene a DMC/TSC

The TMG will consist of the trial CI/PI, research sonographer, research pharmacist, project manager and sponsor representative. Due to the short duration of the trial the TMG will meet at agreed required times during the recruitment period. There will be no intermittent data for analysis due to the short timeline so it will not be beneficial to have a trial analyst or statistician to attend TMGs through recruitment period.

Responsibilities of the trial management group:

The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself. TMG meetings will occur at appropriate time points. Progress will be monitored proactively according to timelines and any issues addressed.

V. PROTOCOL CONTRIBUTORS

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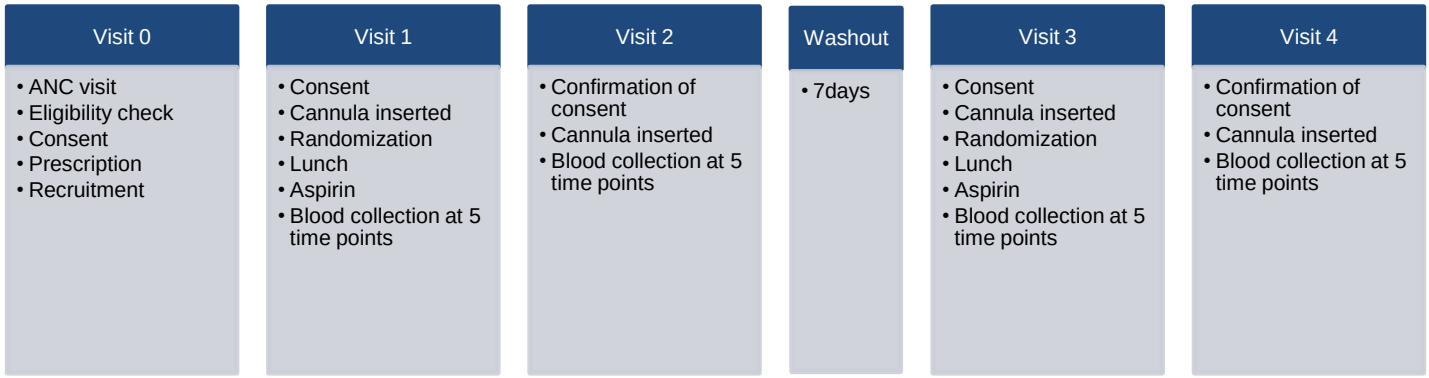
Public	Research sessions with Mother and a baby group	Advice regarding design and reimbursement	Janine Rudin janine@birthandbabyco.com

VI. KEY WORDS:	pharmacokinetics, pharmacodynamics, aspirin prophylactic therapy, preeclampsia, pregnancy

VII. TRIAL FLOW CHART:



TRIAL PROCEDURES FOR VISITS 1 AND 2 / 3 AND 4

Table 1: Schedule of activity

Time point Activity	Pre-ASA	0	1 hour	2 hours	3 hours	4 hours	15 hours	16 hours	17 hours	18 hours	19 hours
Eligibility	✓						✓				
Consent	✓						✓				
Cannula	✓						✓				
Food		✓					✓				
Aspirin		✓									
Blood sample	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓

1 BACKGROUND

Preeclampsia (PE), defined as pregnancy-induced hypertension and proteinuria, is a placenta-mediated disease (PMD) which affects over four million women worldwide each year with up to 1.7% maternal fatality rate (1). The severity of PE ranges from mild late onset disease (>37 weeks gestation) to severe early onset disease, progressing to eclampsia, hemolysis, elevated liver enzymes and a low platelet count (HELLP syndrome) and even maternal death. PE accounts for 6.3% of all stillbirths and substantially increases the risks of preterm delivery and small for gestational age (2, 3). Moreover, mothers affected by PE are more likely to develop cardiovascular disease later in life compared to unaffected mothers (4).

NICE guidance, issued in 2019 (5), recommends all women at increased risk of PE, based on clinical history, should be given aspirin 75 -150 mg daily at bed time, starting at 12 weeks optimally before 16 weeks of gestation. A new RCOG guidance for Care of Women with Obesity in Pregnancy is in agreement with NICE and recommends that women with more than one moderate risk factor should be prescribed 150 mg of aspirin daily(6). This is based on an overall reduction in the risk of PE of 10% (7). When aspirin is commenced before 16 weeks of gestation the risk reduction is greater (RR 0.47, 95% CI 0.36-0.62) (8, 9) although the number of subjects treated prior to 16 weeks in these reviews was small. Two recent larger trials have specifically addressed the effect of aspirin prophylaxis in high-risk women in early pregnancy. Odibo et al. (10) found no evidence that 81 mg/day aspirin started at 11-13 weeks of pregnancy prevented PE (RR 0.88, 95% CI 0.21-3.66) while Rolnik et al. (11) reported that 150 mg of aspirin reduced the rate of preterm PE (odds ratio 0.38, 95% CI 0.20-0.74) but not term PE.

A large body of evidence is available regarding the safety of aspirin in pregnancy. Use of low dose of aspirin has been well studied and considered to be safe in doses ranging from 60 to 300 mg(12). A recent large international randomised controlled trial of 150 mg aspirin found no difference in incidence of adverse events between aspirin and placebo treated groups (11). Moreover a recent systematic review and meta-analysis of low dose aspirin (50 to 150 mg) started <16 weeks showed a statistically significant reduction in the incidence of all maternal and neonatal adverse outcomes other than postpartum haemorrhage (RR=0.70, 95% CI=0.42-1.18; P=0.18)(13).

Aspirin (acetylsalicylic acid) is completely absorbed from the upper gastrointestinal tract and undergoes hydrolysis to salicylic acid (SA)(14). Aspirin inactivates cyclooxygenase (COX) by irreversibly acetylating a serine residue at the active site of COX-1 reducing the formation of thromboxane (Tbx) A2 for the lifespan of the platelet (8-9 days). In the normal circulation thromboxane acts as a platelet activator and contributes to vasoconstriction. These antithrombotic and anti-vasoconstrictor effects are believed to be central to aspirin's therapeutic effect in preventing PE. SA is more stable with a half-life of 6 h and undergoes hepatic metabolism by the microsomal enzyme system. With low dose aspirin 90% of SA metabolites undergo urinary excretion in the form of salicyluric acid (75%), SA (10%), a phenolic glucuronide (10%) an acyl glucuronide (5%) and other minor metabolites(15).

2 RATIONALE

Variability in aspirin response is widely recognised with sub-optimal response often referred to as aspirin resistance. A suboptimal platelet response is usually defined as a biochemical failure to inhibit platelet activation assessed by laboratory assay of the stable serum (TbxB2) or urinary (11-DTbxB2) metabolites of TbxA2 or by point-of-care tests (e.g. VerifyNow or PFA-100) (16). In women at high risk of PE, suboptimal platelet response has been identified in 29-39% of women taking 70-80 mg aspirin daily and was associated with increased rates of PE and other adverse outcomes (17, 18). A recent study conducted in Newcastle ('ASPIRE' study) confirmed that 27% of compliant women had a suboptimal response to aspirin 75 mg daily as assessed by platelet reactivity >550 ARU on VerifyNow testing(19). Further Rey et al.(17) assessed the impact of PFA-100 guided aspirin dose escalation from 81 mg to 162 mg daily; women that required escalation had a higher risk of PE (26% vs 9%). Thus there is accumulating evidence that the currently recommended dose of aspirin to prevent PE in high risk women may not inhibit platelet activation in a significant number of women.

Clinical practice in UK is transitioning from historical recommendation of 75 mg of aspirin to 150 mg of aspirin from 12 weeks of pregnancy in all high-risk women. However, there are no studies exploring platelet response after 75 mg and 150 mg aspirin daily dose in high-risk pregnant women.

To assess the clinical impact of suboptimal platelet response it is important to distinguish between non-responsiveness and non- or sub-optimal compliance (14). Several studies from patients with

cardiovascular disease report that, where platelet function tests suggest aspirin non-responsiveness, this is largely explained by suboptimal adherence (18). Comparative data is not available from high-risk pregnant women prescribed aspirin. Obstetric trials that have assessed aspirin compliance have mostly used semi-quantitative methods (e.g. pill counts) and reported suboptimal adherence in 3-37% (14). In the ASPIRE trial suboptimal compliance (defined as verbal report of taking <70% of prescribed aspirin was reported in only 5% of women at 20 weeks and 8% of women at 34 weeks.

Martin et al. [19] assessed the pharmacological effects of low dose aspirin in healthy third trimester pregnant women by measuring serum SA and urine prostacyclin (PGI_2) /thromboxane (Tbx) ratio in women taking daily placebo or 20 mg, 40mg or 80 mg of aspirin. Measurements were performed prior to, 4 hours and 7 days post start of the trial. The study showed an increase in PGI_2/Tbx ratio (due to decrease in Tbx with stable PGI_2) in higher doses. However SA was not detected at any time point in any of the 12 participants (20) which the authors suggested was because concentrations were below the limit of detection of the spectrophotometric assay (reported as 1.0 mg/dL) which was used in their study. Interestingly, our recent pilot data collected in healthy female volunteers (unpublished) confirms Martin et al findings in that the plasma SA concentrations [determined using high performance liquid chromatography (HPLC) technique] following a single oral dose of 75 mg are consistently below 1 mg/dL (with peak plasma SA concentration of 0.96 mg/dL reaching 1-2 h post aspirin ingestion). However, use of HPLC (which is ~100 times more sensitive than spectrophotometry), allows accurate measurement of serum SA concentration in relation to the ingestion time in women taking 75 mg and 150mg aspirin, and is clearly detectable at four hours post ingestion and SA concentration returns to baseline value at 24 hours. In our pilot healthy volunteer study sampling was performed at 0, 0.3, 0.6, 1, 2, 4 and 24 hours for both doses of aspirin. Recent PK study of 100 an 150 mg of aspirin in pregnant women has demonstrated to that SA can be still detected as 12 hours post injection and ceases towards 24 hour mark (21). Serum SA concentrations above baseline values could indicate recent ingestion of aspirin. Therefore, measurement of serum SA concentration could be used as a viable test to check patient adherence to treatment. However, we have no information available on serum SA concentrations between 12-24h post-aspirin doses. In real life the time period between pregnant women taking their aspirin daily dose and attending the clinic could be much longer than 4h perhaps as much as 19h. To devise a test for checking adherence that is more broadly applicable to the real-life situation we need to

demonstrate that serum SA concentrations remain above baseline values up to at least 19 h post-dose. The present study is designed to check for serum SA concentrations over 19 hours. Although 150 mg of aspirin is being increasingly used for prophylaxis there are no studies of the pharmacological effects of 75 mg and 150 mg aspirin in high-risk pregnancies. Further, there is no agreement on a gold standard test to assess aspirin adherence. Thus, there is a need to investigate aspirin dose dependent pharmacokinetics (PK) and pharmacodynamics (PD) further. Having completed a feasibility study involving healthy volunteers, we are ideally placed to conduct this study in a high-risk obstetric population in order to gather new valuable information regarding pharmacological (dynamics and kinetics) effects of suggested doses of aspirin.

2.1 ASSESSMENT AND MANAGEMENT OF RISK

This trial is categorised as:

- Type A = No higher than the risk of standard medical care

The use of aspirin in this trial is reflective of current recognised clinical practice (and approved for this indication by NICE and RCOG). As this is classed as standard of care within clinical practice, we consider that it therefore poses no greater potential risk than that of standard medical care.
See Appendix 1

3 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

3.1 PRIMARY OBJECTIVE

To compare aspirin pharmacokinetics (plasma SA concentrations) and pharmacodynamics (serum TbxB2 concentrations) in pregnant women at 11-16 weeks gestation' following the administration of a single oral dose of either 75 mg or 150 mg aspirin.

3.2 OUTCOME MEASURES/ENDPOINTS

Serum $TbxB_2$ and SA concentration

3.3 PRIMARY ENDPOINT/OUTCOME

Area under the serum Tbx concentration versus time curve (AUC_{Tbx}) and SA plasma concentration versus time curve (AUC_{SA}).

3.4 SECONDARY ENDPOINTS/OUTCOMES

Time taken for plasma SA concentration to reach baseline.

3.5 TABLE OF ENDPOINTS/OUTCOMES

Objectives	Outcome Measures	Time points of evaluation of this outcome measure (if applicable)
Primary Objective To compare aspirin pharmacokinetics (plasma SA concentrations) and pharmacodynamics (serum TbxB2 concentrations) in pregnant women at 11-16 weeks gestation' following the administration of a single oral dose of either 75 mg or 150 mg aspirin.	AUC for serum TbxB2 and plasma SA concentration in participants taking 75 mg and 150 mg of aspirin	Blood sampling on two occasions in accordance with 2 x 2 crossover design: Pre medicated,1, 2, 3, 4, 15, 16, 17, 18, 19 hours post medication
Secondary Objectives Time to baseline SA	SA concentration	Derived from the samples above

4 TRIAL DESIGN

Cross-over 2 x 2 design comparing PK/PD of a single oral dose of 75 mg aspirin with those of 150 mg of aspirin in pregnant women. Each of the participants will be given all the trial treatments in successive periods. The order in which the participants receive each treatment is determined at random.

The study aims to compare the plasma concentrations of SA and the pharmacological effects (by measuring serum Tbx concentration) of two doses of aspirin prescribed in clinical practice; it is not designed to compare the efficacy or safety of the medicine

5 TRIAL SETTING

This is a single site study. All recruitment and research activities will be conducted in Newcastle upon Tyne Hospitals Foundation Trust. Screening and face to face approach will take place in Antenatal Ultrasound and Clinic area, while all other study related procedures will be performed in Clinical Research Facility, the area with appropriate setup to conduct clinical trials.

6 PARTICIPANT ELIGIBILITY CRITERIA

Pregnant women identified as being at high risk of developing PE who have accepted but not started clinically prescribed aspirin therapy at 11-14 weeks' gestation.

6.1 INCLUSION CRITERIA

- Risk factors for PE as per NICE guidelines (2); specifically women with either 2 moderate or one high risk factor for PE shown below:

Moderate risk factors	High risk factors
First pregnancy	Hypertensive disease during prior pregnancy
Age 40 years or older	Chronic kidney disease
Pregnancy interval more than 10 years	Autoimmune disease such as systemic lupus erythematosis or antiphospholipid syndrome
BMI ≥35 kg/m2 at first visit	Type 1 or type 2 diabetes
Family history of PE	Chronic hypertension

- Participants capable of giving informed consent

- Women are only eligible for the study if, based on current clinical risk factors for PE, they have been recommended to commence aspirin after 12 weeks (but before 16 weeks) gestation.
- Age 18 – 50
- 11 to 14 weeks gestation at the time of the approach

Able to attend first study visit as soon as possible but no later than 14 weeks and 5 days gestation

6.2 EXCLUSION CRITERIA

Hypersensitivity to aspirin to salicylic acid compounds or prostaglandin synthase inhibitors (e.g. certain asthma patients who may suffer an attack or faint)

- Active, or history of recurrent peptic ulcer and/or gastric/intestinal haemorrhage, or other kinds of bleeding such as cerebrovascular haemorrhage
- Haemorrhagic diathesis; coagulation disorders such as hemophilia and thrombocytopenia
- Severe hepatic or renal impairment
- Gout
- Taken aspirin over preceding 4 weeks
- Current anticoagulant therapy
- Unable to give informed consent
- Multiple pregnancy
- Known fetal anomaly
- Vegetarian/vegan diet

7 TRIAL PROCEDURES

The duration of study participation for the prospective study will be 9 days. Participants will be asked to attend the Clinical Research Facility at Newcastle upon Tyne Hospitals NHS Foundation Trust. Following informed written consent, baseline blood (5 mL) collection participants will be given standardised meal. Each subject will then ingest a dispersible (non-enteric coated) oral dose of aspirin (75 mg or 150 mg determined at random). Serial (5 mL) blood samples will be collected at 1, 2, 3 and 4h hours (using venous cannula).

Participants will return on a following day and additional samples will be collected at 15, 16, 17, 18 and 19 hours.

This will be followed by a 7-day washout period. This is a modification from a traditional 10 day washout period and based on a current literature suggesting that platelet function recovers within 4 to 6 days following withdrawal from 100 mg of aspirin in healthy volunteers and surgical patient (22, 23).

Participant will be asked to return a week later for a second visit where the schedule of event will be replicated from the first visit, including confirmation of consent, base line blood test, standardised lunch and ingestion of an alternative dose to the one used at the firs visit, followed by a blood sampling as described in table 1 (schedule of activity).

7.1 RECRUITMENT

7.1.1 PARTICIPANT IDENTIFICATION

A member of the Reproductive Health Research Team at Newcastle upon Tyne Hospitals NHS Foundation Trust will review all antenatal booking proformas received in the antenatal clinic daily. Women at increased risk of developing PE (according to NICE guidelines) will be sent an approved patient information sheet and an invitation letter.

7.1.2 SCREENING

Face to face approach will be made following confirmation of fetal viability by a routine scan.

Review of the risk factors and eligibility to receive aspirin (will be confirmed by a medical team in Antenatal Clinic as part of their standard care).

7.1.3 PAYMENT

To reimburse participants for their time, at the time of the protocol completion, participants will be given an appointment to attend a 4D growth scan at 28 weeks gestation in Newcastle upon Tyne Hospitals NHS Foundation Trust (retail price approx. £90.00). Growth scan will be performed using local scan and reporting procedures.

7.2 CONSENT

During the consent procedure the research team must ensure that women:

- have had study printed information for at least 24 hours
- understand the purpose and nature of the research
- understand what the research involves, its benefits, risks and burdens
- understand the alternatives to taking part
- be able to retain the information long enough to make an effective decision
- be able to make a free choice
- given an opportunity to ask questions

Potentially eligible participants then will be asked to sign the study informed consent form. Consent procedure will be performed by a GCP trained member of a medical team.

The original consent form will be stored in the Investigator Site File. The participant will be provided with a copy and a copy will also be placed in the participant's medical records.

Following the consent procedure, a full eligibility assessment will be performed by a GCP trained doctor. Eligibility checklist and details of the consent process will be recorded in the woman's medical records along with a copy of the consent form.

7.2.1 ADDITIONAL CONSENT PROVISIONS FOR COLLECTION AND USE OF PARTICIPANT DATA AND BIOLOGICAL SPECIMENS IN ANCILLARY STUDIES.

At present no further studies are planned, however we will ask participants to donate remaining of the blood sample to the Newcastle Tissue Bank (REC reference 10/H0906/71).

Participants will be given an option to have remaining of the samples disposed (as per NUTH procedures) at the end of the research in case they would oppose to the donation.

7.3 THE RANDOMISATION SCHEME

7.3.1 METHOD OF IMPLEMENTING THE RANDOMISATION/ALLOCATION SEQUENCE

All participants will be randomised to a sequence of 75 mg – washout – 150 mg or 150mg-whashout-75 mg treatment. Sealed Envelope, an online software application, will be used for 1:1 randomization. The randomisation process will be administered by a member of the research team.

7.4 BLINDING

The laboratory team will be blinded to the dose taken by the participants. All samples sent to the laboratory will be labeled with unique participant number followed by a visit number and collection time point.

Clinicians, participants and research delivery team will not be blinded to the sequence randomization.

7.5 EMERGENCY UN-BLINDING

Emergency unbinding is not applicable in this study.

7.6 BASELINE DATA

Base line data collection will include: Age, Obstetric risk factors, Medical risk factors, Current medication(s), Height, Weight, Gestation period, Dietary habits, Combined screening results (if available), Smoking status

7.7 TRIAL ASSESSMENTS

- Screening for eligibility
- Invitation letter sent to eligible women
- Routine ultrasound
- Routine antenatal medical review
- Consent
- Eligibility checklist

Visit 1	Visit 2	*Wash out period 7 days* (no aspirin until visit 3)	Visit 3	Visit 4
Confirmation of consent	Assessment of AR/AE		Confirmation of consent	Assessment of AR/AE
Randomisation	Confirmation of consent		Compliance with the washout period check by the pill count	Confirmation of consent
Background data collection	Cannulation and sample at 15 hours		Cannulation and Sample 0	Cannulation and sample at 15 hours
Cannulation and Sample 0	Sample at 16 hours		First aspirin + meal	Sample at 16 hours
First aspirin + meal	Sample at 17 hours		Assessment of AR/AE	Sample at 17 hours
Assessment of AR/AE	Meal		Sample at 1 hour	Meal
Sample at 1 hour	Sample at 18 hours		Sample at 2 hours	Sample at 18 hours
Sample at 2 hours	Sample at 19 hours and discharge home		Sample at 3 hours	Sample at 19 hours and discharge home
Sample at 3 hours			Sample at 4 hours and discharge home	*End of trial*
Sample at 4 hours and discharge home				

7.8 LONG TERM FOLLOW-UP ASSESSMENTS

Trial participants will not be monitored after the active treatment phase has finished (24 hours post aspirin ingestion).

A letter informing the GP of the participation in the study will be sent explaining study procedures and highlighting a need to resume clinically recommended aspirin dose at the end of the trail.

7.9 WITHDRAWAL CRITERIA

Participants will be free to withdraw (discontinue his or her participation) from the study at any point of the trial without giving a reason. The investigator team will reserve the right to terminate participation where patient safety or trial integrity may be compromised.
Data collected prior to withdrawal from the trial will not be used and samples will be destroyed.
Considering time demands of the trial, anticipated withdrawal / attrition rate is 25% and we plan to recruit up to 18 participants to reach required sample size of 14 participants (see sample size section).

7.10 STORAGE AND ANALYSIS OF CLINICAL SAMPLES

At every collection time point one 5 mL sample of blood to be obtained using serum separator tubes (BDSST II Advance).

7.10.1 THROMBOXANE B_2 SAMPLE

Please see SOP for processing manual.
Remaining of samples will be transferred to the Newcastle Utero-placental Tissue bank in cases where participants gave consent to keep the samples. Alternatively, samples will be destroyed in line with organisational guideline for clinical waste incineration.

7.10.2 SALICYLIC ACID SAMPLE

Salicylic Acid samples will be processed in Institute of Cellular Medicine, Newcastle University. Tracked using an Achiever system and securely stored within the ICM freezers.

Please see SOP for processing manual.

Samples will be stored and analysed upon completion of the trial.

Remaining of samples will be transferred to the Newcastle Utero-placental Tissue bank in cases where participants gave consent to keep the samples. Alternatively, samples will be destroyed in line with organisational guideline for clinical waste incineration.

7.11 END OF TRIAL

End of trial is defined a last sample processed.

The sponsor will notify the MHRA of the end of a clinical trial within 90 days of its completion.

8 TRIAL TREATMENTS

8.1 NAME AND DESCRIPTION OF INVESTIGATIONAL MEDICINAL PRODUCT(S)

Aspirin 75mg dispersible tablets.

Each tablet contains 75 mg acetylsalicylic acid.

8.2 REGULATORY STATUS OF THE DRUG

Not licensed for use in pregnancy, however widely clinically accepted in doses 75 mg and 150 mg (6) .

8.3 PRODUCT CHARACTERISTICS

The SmPC for a generic common brand of aspirin (appendix 2) will be used for reference of safety data and product characteristics due to the large number of brands of aspirin stocked by the dispensing pharmacy.

8.4 DRUG STORAGE AND SUPPLY

As this is a Type A risk adaptive approach study there will be no accountability, segregated storage, temperature monitoring or labelling compliant with annex 13 performed for this study IMP.

8.5 PREPARATION AND LABELLING OF INVESTIGATIONAL MEDICINAL PRODUCT

As per 8.4, no labelling compliant with annex 13 will be expected for this IMP. Preparation and labelling is not applicable for this trial as participants will be obtaining clinically prescribed medication in line with the Trust's practice. This may take place before or after consent procedure to enter the trial.

8.6 DOSAGE SCHEDULES

Study participant will be expected to take 75 mg of aspirin (1 tablet) on one occasion and 150 mg of aspirin (2 tablets) on the other. Those doses will be taken 1 week apart to account to 7 day washout period.

8.7 DOSAGE MODIFICATIONS

Dosage modifications will not be permitted.

Participants will be advised to continue with clinically indicated therapy at the last study visit.

8.8 KNOWN DRUG REACTIONS AND INTERACTION WITH OTHER THERAPIES

Methotrexate at doses >15 mg/week is contraindicated to be taken with aspirin. However use of Methotrexate is contraindicated in pregnancy and we do not anticipate any pregnant participants on Methotrexate.

Use of aspirin in patients receiving uricosuria agents, other anticoagulants and anti-platelet agents, selective serotonin reuptake inhibitors, sulfonylureas, digoxin and lithium, diuretics, antihypertensives, NSAIDs, acetazolamide), systemic corticosteroids, ibuprofen, cyclosporine, tacrolimus, antacids, alcohol will be carefully considered by a medical team. Please note some of the above medications will be contraindicated in pregnancy.

8.9 CONCOMITANT MEDICATION

Pregnant women on anticoagulants and other anti-platelet agents will not be able to enter the trial.

8.10 TRIAL RESTRICTIONS

All participants who were prescribed and accepted aspirin therapy and do not fall in any of the exclusion category are permitted to enter the trial.

8.11 ASSESSMENT OF COMPLIANCE WITH TREATMENT

Trial participant will be observed by the research delivery team at the time of ingestion of both doses of aspirin during visit 1 and visit 3.

9 PHARMACOVIGILANCE

9.1 DEFINITIONS

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions. It is important to note that this is entirely separate to the known side effects listed in the SmPC. It is specifically a temporal relationship between taking the drug, the half-life, and the time of the event or any valid alternative etiology that would explain the event.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: results in death is life-threatening requires inpatient hospitalisation or prolongation of existing hospitalisation results in persistent or significant disability/incapacity consists of a congenital anomaly or birth defect Other ‘important medical events’ may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the reference safety information: In the case of a product with a marketing authorisation, this could be in the summary of product characteristics (SmPC) for that product, so long as it is being used within its license. If it is being used off label an assessment of the SmPC's suitability will need to be undertaken. in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

Detailed guidance can be found here:

http://ec.europa.eu/health/files/eudralex/vol-10/2011_c172_01/2011_c172_01_en.pdf

9.2 OPERATIONAL DEFINITIONS FOR (S)AES

Use of aspirin in pregnancy is outside of the licensed indication. Although it will be used in a clinically accepted doses with high safety profile, we will record all (S) AE's and (S) AR's. All (S) AE's and (S) AR's will be assessed by PI/CI prior to reporting.

All pre-existent conditions will be exempt from reporting.

9.3 RECORDING AND REPORTING OF SAES, SARS AND SUSARS

Safety monitoring will be performed during the trial visits and end at 24 hours post last study dose ingestion (i.e., end of the participation) due to short half-live of aspirin and fast elimination.

Long term follow up will not be performed as teratogenicity of a single low dose of aspirin is not recognized.

Safety reporting form will be completed by a member of the research team, assessed by PI/CI and reported to the Sponsor's team

Where a participant withdraws consent safety assessments will be performed at 24 hours post aspirin ingested at the research visit.

All SAEs occurring from the time start of trial treatment until 24 hours post cessation of trial treatment must be recorded on the safety assessment form and e-mailed to the Sponsor within 24 hours of the research staff becoming aware of the event. Once all resulting queries have been resolved, the Sponsor will request the original form should also be posted to the Sponsor and a copy to be retained on site.

For each SAEs the following information will be collected:

- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- causality (i.e. relatedness to trial drug / investigation), in the opinion of the investigator
- whether the event would be considered anticipated

Any change of condition or other follow-up information should be e-mailed to the Sponsor as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached."

All SAEs assigned by the CI/PI or delegate as both suspected to be related to IMP-treatment and unexpected will be classified as SUSARs and will be subject to expedited reporting to the Medicines and Healthcare Products Regulatory Agency (MHRA). The sponsor will inform the MHRA, the REC and Marketing Authorisation Holder of SUSARs within the required expedited reporting timescales.

9.4 RESPONSIBILITIES

Principal Investigator (PI):

Checking for AEs and ARs when participants attend for treatment / follow-up.

Using medical judgement in assigning seriousness, causality and whether the event/reaction was anticipated using the SmPC.

Ensuring that all SAEs are recorded and reported to the sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs are chased with Sponsor if a record of receipt is not received within 2 working days of initial reporting.

Ensuring that AEs and ARs are recorded and reported to the sponsor in line with the requirements of the protocol.

Chief Investigator (CI) / delegate or independent clinical reviewer:

Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.

Using medical judgement in assigning the SAEs seriousness, causality and whether the event was anticipated (in line with the SmPC) where it has not been possible to obtain local medical assessment.

Immediate review of all SUSARs.

Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.

Assigning Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all SAEs and SARs.

Preparing the clinical sections and final sign off of the Development Safety Update Report (DSUR).

Sponsor:

Central data collection and verification of AEs, ARs, SAEs, SARs and SUSARs according to the trial protocol onto a database.

Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.

Reporting safety information to the independent oversight committees identified for the trial (Data Monitoring Committee (DMC) and / or Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.

Expedited reporting of SUSARs to the Competent Authority (MHRA in UK) and REC within required timelines.

Notifying Investigators of SUSARs that occur within the trial.

Checking for (annually) and notifying PIs of updates to the Reference Safety Information for the trial.

Preparing standard tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the MHRA and REC.

Trial Management Group (TMG)

TMG will act as TSC and meet at agreed time points to review safety data to determine patterns and trends of events, or to identify safety issues (in accordance with the Trial Terms of Reference for the TSC).

9.5 NOTIFICATION OF DEATHS

Only deaths that are assessed to be caused by the IMP will be reported to the sponsor. This report will be immediate using safety report form.

9.6 OVERDOSE

No overdose expected over duration of this trial as participants will be observed taking their aspirin and will be asked to abstain from taking aspirin during the washout period.

In an unlikely event of an overdose please refer to SmPC.

9.7 REPORTING URGENT SAFETY MEASURES

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures.

9.8 THE TYPE AND DURATION OF THE FOLLOW-UP OF PARTICIPANTS AFTER ADVERSE REACTIONS.

Bedside observations will be performed for a duration of 4 hours post IMP ingestion.

Self-reported wellbeing check will be conducted at 20 hours post IMP ingestion.

In case of any (S)ARs, follow up care will be given until resolution.

For the duration of participation in the trial, any SUSAR will need to be reported to the Sponsor irrespective of how long after IMP administration the reaction has occurred until resolved.

9.9 DEVELOPMENT SAFETY UPDATE REPORTS

The Development Safety Update Report (DSUR) must be submitted to MHRA on an annual basis. A copy will also be provided to REC. The DSUR will be submitted within 60 days of the Developmental International Birth Date (DIBD) of the trial.

It is the responsibility of the CI to complete, review and submit the DSURs.

10 STATISTICS AND DATA ANALYSIS

10.1 SAMPLE SIZE CALCULATION

With a sample of 14 participants (7 participants in each group), we would have 80% power to detect a 1 SD difference in the area under the serum Tbx concentration curve (AUC) between two doses of aspirin. This is based on an Equivalence Test for Treatment Means in 2 x 2 Crossover Designs test with a common standard deviation of 109.7 (based on serum Tbx AUC data from healthy female volunteer study taking either 75mg or 150mg of aspirin) and alpha level of 0.05.

In this sample size calculation we have used common within the population SD as within-subject SD was not available. Considering that within-subject SD tends to be lower than between-subject SD, we will be able to achieve > 80% power.

After allowing for a 25 % dropout following study entry, we expect to recruit up to 18 participants to reach a sample size of 14 full data sets.

Sample size calculation was performed under supervision of David McGeeney, a Statistical Consultant, School of Mathematics, Statistics & Physics, Newcastle University.

10.2 PLANNED RECRUITMENT RATE

For the sample size of 14 participants we are planning to recruit up to 18 participants to account for potential withdrawals (25%). We anticipate a recruitment rate of 3 participants per month and thus expect to finish recruitment in 5-6 months with additional 2 months to complete laboratory assays and data analysis.

10.3 STATISTICAL ANALYSIS PLAN

Descriptive statistics will be used to describe the study population, Tbx2 and SA levels. Analyte levels in the 75 mg and 150 mg group will be compared at each time point by independent t-test or by nonparametric Wilcoxon tests depending of the nature of the data obtained. The area under the curve (AUC) for all analyses over the 24 hour period will also be analyzed using analysis of variance including sequence, period, and treatment effects. IBM SPSS version 21 statistical software will be used to analyse the data.

10.4 INTERIM ANALYSIS

Due to small sample size and short duration of the trial no interim analysis is planned.

11 DATA MANAGEMENT

11.1 DATA COLLECTION TOOLS AND SOURCE DOCUMENT IDENTIFICATION

Source Data Definition

ICH E6 section 1.51, defines source data as "All information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies)."

The basic concept of source data is that it permits not only reporting and analysis but also verification at various steps in the process for the purposes of confirmation, quality control, audit or inspection. A number of attributes are considered of universal importance to source data and the records that hold those data. These include that the data and records are:

- Accurate
- Legible
- Contemporaneous
- Original
- Attributable
- Complete
- Consistent
- Enduring
- Available when needed

Source Documents

ICH E6 1.52, defines source documents as "Original documents, data and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries of evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial)."

Case report forms (CRF)

A case report form (CRF) is a form on which individual patient data required by the trial protocol are recorded. CRF will be printed and used at the bedside to complete at each study visit. Only the data required by the protocol will be captured in the CRF.

Following the visit data to be transferred to the study specific database.

CRF forms are a source document and therefore will be filed in participants notes.

11.2 DATA HANDLING, RECORD KEEPING AND ACCESS TO DATA

Participant identifiable information will be handled in line with GDPR 2018 principles, will be stored on the Newcastle upon Tyne Hospitals NHS Foundation Trust's secure server under the Caldicott approval.

All participants will be given unique identifier to allow anonymization of the data and samples. Anonymized electronic research data will be transferred to Newcastle University secure server for analysis. No personal identifying information will be presented/published in the study outputs.

The research team and local R&D monitors may require access to the participant's clinical notes; participants will be informed of this in the participant information sheet, and permission to do so form part of the consent form.

11.4 Archiving

After the end of the study, data will be stored securely at a restricted access secure storage facility used by the Newcastle Hospitals NHS Foundation Trust. Research data generated by the study will be stored for 5 years.

12 MONITORING, AUDIT & INSPECTION

The trial will follow the Monitoring plan agreed with Sponsor.

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 ETHICAL CONSIDERATIONS

Before the start of the trial, approval will be sought from a REC for the trial protocol, informed consent forms, and invitation letters.

All substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the trial (note that amendments may also need to be reviewed and accepted by the MHRA and the sponsor.

All correspondence with the REC will be retained in the Trial Master File/Investigator Site File

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and at the end of the trial (we expect this study to be completed in less than 12 months therefor no annual report will be submitted). It is the Chief Investigator's responsibility to produce reports as required and to notify the REC of the end of the trial.

In case of premature end of the trial, the Chief Investigator will notify the REC, including the reasons for the premature termination

Within one year after the end of the trial, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

All recruitment will be conducted by an experienced member of the research team. Full, written consent will be obtained by a delegated member of the research team following eligibility assessment by a GCP trained obstetrician. At all stages, potential participants will be reminded that they are under no obligation to take part and that their decision will have no impact on any future care they may receive. It will be ensured that participants have the capacity to give consent, have a full understanding of the purpose of the research, the involvement required and the risks and benefits involved.

Every effort will be made to minimise potential discomfort or distress. There is a possibility that participants will experience some discomfort from the venipunctures at the time of cannulation, however, they will be offered the option of a local anesthetic, and the researcher is experienced in undertaking venipuncture. It is not anticipated that any unusual discomfort will be experienced. Neither patients nor clinicians will be given the $TbxB_2$ or SA results.

The study will be performed in time for patients to commence their planned prophylactic therapy in full i.e., participants will be seen by a research team as soon as feasible to allow treatment to be

recommenced not later than 16 weeks of gestation, therefore the washout period will not affect outcomes of preventative treatment.

13.2 Reimbursement

To reimburse participants for their time, at the time of the protocol completion, participants will be given an appointment to attend a 4D growth scan at 28 weeks gestation in Newcastle upon Tyne Hospitals NHS Foundation Trust (retail price approx. £90.00). Growth scan will be performed using local scan and reporting procedures.

Participants travel expenses will be reimbursed via the Trust process of claiming travel expenses, alternatively Taxis can be arranged by the Trust's Transport Team.

13.3 Public and Patient Involvement

Members of the public were involved in review of a scope (lay summary), design and incentives for this trial. High risk women viewed this research important to them and despite high demands on time would have expressed interest in participation considering trial would provide participants with a letter to the employer to justify absence from work.

Sampling time point are arranged to avoid busy time periods such as school drop offs and pick-ups.

Women also preferred to have a 4D scan rather than monetary reimbursement as though that a scan could be of a higher emotional value.

13.4 Regulatory Compliance

The trial will not commence until a Clinical Trial Authorisation (CTA) is obtained from the MHRA and Favourable REC opinion.

The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments

Before any site can enroll patients into the study, the Chief Investigator/Principal Investigator or designee will ensure that appropriate approvals are in place. Specific arrangements on how to gain approval from participating organisations are in place and comply with the relevant guidance. Different arrangements for NHS and non NHS sites are described as relevant.

For any amendment to the study, the Chief Investigator or designee, in agreement with the sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with sites (R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended.

13.5 PROTOCOL COMPLIANCE

It is the responsibility of the CI to ensure that the clinical trial is run in accordance with GCP and the protocol. This task may be delegated to a suitably qualified or experienced member of the research team but the CI will retain overall responsibility.

Protocol deviations, non-compliances or breaches are departures from the approved protocol.

Deviations from the protocol and GCP occur in clinical trials and the majority of these events are technical deviations that are not serious breaches. These events should be documented on the deviation tracking log (this will be provided as part of the ISF). The trial manger will ask sites to provide the research team of their deviation tracking log at intervals throughout the study and before any monitoring visits. If no deviations have been identified during a particular interval, site are required to send an email to the trial manager to confirm this.

If the deviation constitutes a violation, the site must complete a protocol violation form (again a blank template will be provided to the site as part of the ISF) and send a copy of this completed form to the Trial Manager within 3 working days. The violation must also be entered on to the deviation tracking log.

Deviations or violations that are found to frequently recur are not acceptable and could be classified as a serious breach.

13.6 NOTIFICATION OF SERIOUS BREACHES TO GCP AND/OR THE PROTOCOL

A serious breach is a breach which is likely to effect to a significant degree:

the safety or physical or mental integrity of the subjects of the trial; or

the scientific value of the trial

The sponsor must be notified immediately of any incident that may be classified as a serious breach. The sponsor will notify the MHRA and the NHS REC within the required timelines in accordance with the Sponsor SOP.

13.7 DATA PROTECTION AND PATIENT CONFIDENTIALITY

All identifiable data will be handled in line with GDPR 2018 and Caldicott principles.

Patient identifiable information will be accessed for screening purposes by a clinical research team using the Trust's policies and procedures for access of the data.

Once participants enrolled in the study, a unique identifier will be given to enable to store research samples and data to minimize access to identifiable information.

Participants' consent forms will be stored securely in the locked metal cabinet within secure research facility in the Trust.

Only clinical research team will be able to access identifiable information for safety assessment, clinical purposes and to monitor the trial.

Data generated by the trial will be stored for the duration of the data clearance and transferred in anonymised form to Newcastle University for statistical analysis.

13.8 FINANCIAL AND OTHER COMPETING INTERESTS FOR THE CHIEF INVESTIGATOR, PIS AT EACH SITE AND COMMITTEE MEMBERS FOR THE OVERALL TRIAL MANAGEMENT

Authors of the protocol declare no conflict of interest.

Funding

Costs related to the study will be supported by the Newcastle upon Tyne Hospitals NHS Charity

Some R&D system serum Thromboxane assays will be provided by Bio-Techne corporation.

The Newcastle upon Tyne Hospitals Foundation Trust Clinical Research Facility will be supporting the trial with provision of their facilities.

13.9 INDEMNITY

The Sponsor will provide indemnity in the event that trial participants suffer negligent harm due to the management of the trial. This indemnity will be provided under the NHS indemnity arrangements for clinical negligence claims in the NHS.

The substantial employers of the protocol authors will provide indemnity in the event that trial participants suffer negligent harm due to the design of the trial.

The study sites will provide indemnity in the event that trial participants suffer negligent harm due to the conduct of the trial at their site under the NHS indemnity arrangements for clinical negligence claims in the NHS. NHS Organisations must ensure that site staff without substantive NHS contracts hold honorary contracts to ensure they can access patients and are covered under the NHS indemnity arrangements. Study staff without NHS contracts e.g., General Practitioners or Dentists will provide their own professional indemnity.

This is a non-commercial study and there are no arrangements for non-negligent compensation.

13.10 AMENDMENTS

The trial manager will notify the REC of all required substantial amendments to the trial and those non-substantial amendments that result in a change to trial documentation (e.g. protocol or patient information sheet). Substantial amendments that require a REC favourable opinion will not be implemented until this REC favourable opinion is obtained.

All amendment to protocol to be recorded in Appendix 4.

Please note: All amendment to the other study related documents should be recorded in the ISF.

13.11 POST TRIAL CARE

Participants will take IMP for a maximum of 8 days while in this study. After this it is anticipated that the participant's should continue with the preventative treatment prescribed by an obstetrician.

13.12 ACCESS TO THE FINAL TRIAL DATASET

Upon completion of the trial, members of the TMG (including investigators and the statistician) will be able to access anonymized data set for review and analysis.

13.13 INTELLECTUAL PROPERTY RIGHTS

The study team recognise the value in exploiting its intellectual property rights (IPR) for societal benefit via improved health outcomes in the NHS and other healthcare providers, as well as contributing to the wider economy and the nation's wealth. Procedures are in place for the identification, management and exploitation of IPR and any arising IP from this study will be protected through Business Development Managers from Newcastle University and Newcastle upon Tyne Hospitals NHS Foundation Trust with relevant expertise in IPR and technology transfer.

14 DISSEMINATION POLICY

Final study reports will be disseminated to:

REC

Lay summary will be available on the project web page

Professional conferences and journals

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16. APPENDICIES

16.1 Appendix 1 -Risk

Risks associated with trial interventions

☐ A ≡ Comparable to the risk of standard medical care

Justification: Briefly justify the risk category selected and your conclusions below (where the table is completed in detail the detail need not be repeated, however a summary should be given):

The use of aspirin in this trial is reflective of current recognised clinical practice (and approved for this indication by NICE and RCOG). As this is classed as standard of care within clinical practice, we consider that it therefore poses no greater potential risk than that of standard medical care.

What are the key risks related to therapeutic interventions you plan to monitor in this trial?		How will these risks be minimised?		
IMP/Intervention	Body system/Hazard	Activity	Frequency	Comments
Aspirin 75 mg	Blood and lymphatic system disorders/ Increased bleeding tendencies.	4 hours observation 24 hours follow up	Once following aspirin ingestion	Emergency contacts will be provided
Aspirin 150 ng	Blood and lymphatic system disorders/Increased bleeding tendencies.	4 hours observation 24 hours follow up	Once following aspirin ingestion	Emergency contacts will be provided

Outline any other processes that have been put in place to mitigate risks to participant safety

Strict exclusion criteria will be applied to ensure patient safety. In addition 4 hour observation and 24 review will be contacted.

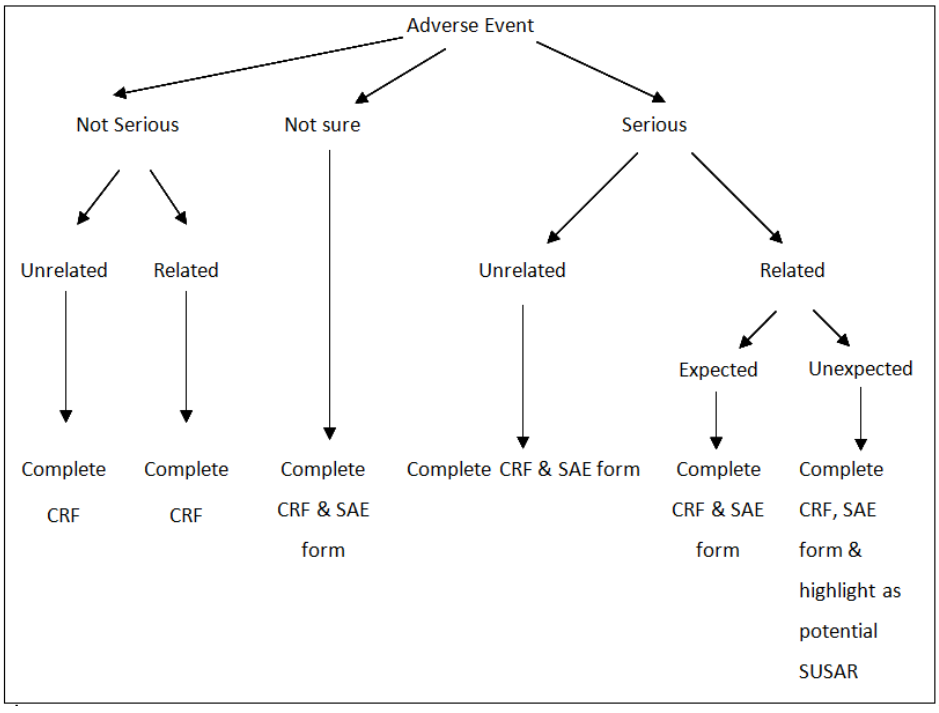
Routine TMG to meet regularly to discuss progress and safety.

Urgent call for TMG meeting will be created in case of safety concerns.
Outline any processes (e.g. IMP labelling +/- accountability +/- trial specific temperature monitoring) that have been simplified based on the risk adapted approach. As with the guidance issued by MHRA for risk-adaptive approaches within the scope of the Clinical Trials Directive it is therefore requested that labelling of the product be exempt from Annex 13 regulations (no need for clinical trial labelling or clinical trials specific content on labels) and that IMP management of the product is not required (tracking and accountability, storage). The latter under the proviso that sites are able to provide Sponsor with assurances for robust product recall procedures should this need occur within the duration of the clinical trial.

16.2 Appendix 2 – SmPC

https://www.medicines.org.uk/emc/product/2408/smpc

16.3 Appendix 3 – Safety Reporting Flow Chart



16.4 Appendix 4 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made

List details of all protocol amendments here whenever a new version of the protocol is produced.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee or MHRA.