[TETFund]

CLINICAL RESEARCH PROTOCOL

[PIPSICKLE TRIAL]

PROTOCOL NO.	01	VERSION NO.	04	DATE	21/05/2024
PROTOCOL NAME	PIPSICKLE				
FUNDING ORGANIZATION	Tertiary Education Trust Fund (TETFund)				
PRINCIPAL INVESTIGATOR name and contact information	Professor Bosede Bukola AFOLABI College of Medicine, University of Lagos. +2348023154064 bbafolabi@unilag.edu.ng				
Chairman DSMC/ Clinical MONITOR name and contact information	Prof Olayemi Oladapo Department of Obstetrics and Gynaecology, College of Medicine, University of Ibadan +2348023059558, +2348032197300 oladapo.olayemi@yahoo.com				
COORDINATING CENTER (if applicable)	College of Medicine, University of Lagos				

APPROVED BY:

Principle Investigator Signature and Title *Date*

SITE

PROTOCOL AGREEMENT

I have read and understood the protocol below. In my capacity as site coordinator, my duties include making sure of the safety of the study participants enrolled by supervising their care and providing **Prof. Bosede Afolabi** with complete and timely information. This information will be provided as outlined in this study protocol. All the information relating to this study will be held in strict confidence and these confidentiality requirements apply to all staff at this study site or involved with this study.

I agree to maintain the procedures required to perform this study in accordance with Good Clinical Practice principles and to abide by the terms of this protocol.

PROTOCOL DATE	21/05/2024
PROTOCOL VERSION NO	4
PROTOCOL TITLE	Low dose aspirin for preventing intrauterine growth restriction and preeclampsia in sickle cell pregnancy (PIPSICKLE): a randomised controlled trial.

Site Coordinator Signature *Date*

Name and Title (Print)

CONTACT INFORMATION	

TABLE OF CONTENTS

PROTOCOL SYNOPSIS

Brief summary in each category

STUDY TITLE	Low dose aspirin for preventing intrauterine growth restriction and preeclampsia in sickle cell pregnancy (PIPSICKLE): a randomised controlled trial.
FUNDING ORGANIZATION	Tertiary Education Trust Fund (TETFund)
NUMBER OF SITES	15
RATIONALE	Pregnancy in sickle cell disease is fraught with many complications including preeclampsia (PE), intrauterine growth restriction (IUGR) and several maternal complications. Low dose aspirin (LDA) has been shown to reduce the incidence of PE and IUGR in high-risk women due to its reduction of vasoconstrictor thromboxane whilst sparing prostacyclin. It has been found to be safe for use in pregnancy and has been suggested for use in sickle cell pregnant women, but all the studies were conducted in non-SCD pregnant women. To the best of our knowledge, there are no studies evaluating the role of low dose aspirin in prevention of preeclampsia and IUGR in pregnant SCD women in the scientific literature. As women with SCD have such a high incidence of morbidity and mortality in pregnancy, the results of this study could potentially save their lives and that of their babies.
STUDY DESIGN	Multicenter, randomized, placebo controlled, double blind, parallel trial designed to evaluate the efficacy, safety and tolerability of a daily dose of 100mg aspirin.
PRIMARY OBJECTIVE	To determine whether daily administration of 100mg LDA from 12-28 weeks of gestation till 36 weeks, reduces the risk of IUGR, miscarriages and perinatal deaths.
SECONDARY OBJECTIVE(S)	To determine the effect of the use of 100mg LDA during pregnancy in HbSS and HbSC women on the incidence of other maternal complications such as pre-eclampsia, preterm delivery, retained placenta, placental abruption, number of vaso-occlusive crises, blood transfusion needs, incidence of urinary tract infections, respiratory tract infections, acute chest syndrome and potential adverse effects such as vaginal bleeding, epigastric pain and heartburn.

NUMBER OF SUBJECTS	476 eligible pregnant HbSS and HbSC women
SUBJECT SELECTION CRITERIA	Age 18 years and above Singleton fetus, Hb genotypes are Haemoglobin SS or SC. 12-28 weeks gestation at recruitment, estimated from the last menstrual period or by an early ultrasound scan.
PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	Daily administration of 100mg Low Dose Aspirin, oral route.
(CONTROL) PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	Daily administration of Placebo, oral route.
DURATION OF SUBJECT PARTICIPATION AND STUDY DURATION	2 years. 18 months of active patient's study participation; 21 total months in the field including screening, enrollment, follow-up and data analysis.
FOLLOW-UP	2 weekly follow up visits from enrollment to 28 weeks gestation followed by weekly visits till delivery

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND ACRONYMS

AE	Adverse event
CRF	Case report form
CRA	Clinical research associate
CMUL	College of Medicine, University of Lagos
CI	Confidence interval
GCP	Good Clinical Practice
Hb	Haemoglobin
IUGR	Intrauterine growth restriction
LASUTH	Lagos State University Teaching Hospital
LBW	Low birth weight
LDA	Low dose aspirin
LUTH	Lagos University Teaching Hospital
ML	Machine learning
OR	Odds ratio
PACTR	Pan Africa Clinical trials Registry
PE	Preeclampsia
RCT	Randomised controlled trial.
SAE	Serious adverse event
SCD	Sickle cell disease
HbSS	Sickle cell Anaemia
HbSC	Sickle Hb C disease
SDG	Sustainable Development Goal
TETFund	Tertiary Education Trust Fund
WHO	World Health Organization
AE	Adverse Event
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
DSMC	Data and Safety Monitoring Committee

GCP	Good Clinical Practice
IRB	Institutional Review Board

GLOSSARY OF TERMS

Assessment	A procedure used to generate data required by the study
Control (Placebo) drug	A study drug used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug.
Investigational (Active) drug	The study drug whose properties is being tested in the study.
Study drug	Any drug (control or investigational) administered to the patient as part of the required study procedures; includes investigational drug and any control drugs
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Medication number	A unique identifier on the label of each medication package.
Study ID	A number assigned to each patient that is enrolled into the study. When combined with the center number, a unique identifier for each patient in the study is created. This is done automatically during the randomisation process.
Randomisation code	A unique identifier assigned to each randomised patient, corresponding to a specific treatment arm assignment
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned
Study drug discontinuation	Point/time when patient permanently stops taking study drug for any reason; may or may not also be the point/time of premature patient withdrawal
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points

1.0 INTRODUCTION

1.1 Background

Nigeria has the highest number of people living with sickle cell disease (SCD) in the world, amounting to 2-3% of the population (1). Sickle cell disease is a haemoglobinopathy fraught with complications as a result of vaso-occlusion, thrombosis and chronic anaemia. The red blood cells become abnormal and fragile when deoxygenated, forming polymers and adhering to vascular endothelial tissue with resultant obstruction of the vessels and haemolysis (2,3). These lead to the various clinical manifestations, which include splenic sequestration, susceptibility to infections, stroke, bone pain crises and acute chest syndrome. Vasoconstriction from nitric oxide depletion has also been postulated to be a pathophysiological mechanism for some of its adverse effects such as pulmonary hypertension and stroke (4).

Over 50% of females with SCD now achieve pregnancy due to increased survival into adulthood but they have a high incidence of complications during pregnancy including preeclampsia (PE) and intrauterine growth restriction (IUGR), infections, acute chest syndrome and more frequent crises (5,6,7). A number of pregnant women with sickle cell disease are thus more likely to die in pregnancy especially in low resource settings like ours (8); pregnancy-related studies in them should therefore be a priority.

Previously, we found a reversal in prostacyclin-thromboxane ratio in pregnant haemoglobin (Hb) SS women (9), a situation that is also found in non-sickle pregnancies with preeclampsia and unexplained IUGR (10). Low dose aspirin (LDA) has been shown to reduce the incidence of PE and IUGR in high-risk women due to its reduction of vasoconstrictor thromboxane whilst sparing prostacyclin, in effect correcting the ratio (11). It has been found to be safe for use in pregnancy (12) and has been suggested for use in sickle cell pregnant women (13), but all the studies were conducted in non-SCD pregnant women. To the best of our knowledge, there are no studies evaluating the role of low dose aspirin in prevention of preeclampsia and IUGR in pregnant SCD women in the scientific literature. As women with SCD have such a high incidence of morbidity and mortality in pregnancy, the results of this study could potentially save their lives and that of their babies.

1.2 Study Purpose:

The study is a multicentre, randomised, placebo controlled, double blind, parallel trial designed to evaluate the efficacy, safety and tolerability of a daily dose of 100mg aspirin, from 12-28 weeks gestation until 36 weeks. Pregnancy in sickle cell disease is fraught with many complications including preeclampsia (PE) and intrauterine growth restriction (IUGR). Low dose aspirin (LDA) has been found to reduce the incidence of PE and IUGR in high-risk women and has been found to be safe for use in pregnancy and is recommended in obstetric guidelines for this use, but has not been tested in sickle cell pregnancy.

Findings in this study may gain regulatory approval to recommend low dose aspirin for use in pregnant) women with SCD where it is expected to reduce the incidence of IUGR and PE.

2.0 STUDY OBJECTIVES

2.1 Aims

To determine whether daily administration of 100mg LDA from 12-28 weeks of gestation till 36 weeks, reduces the risk of IUGR, preeclampsia, perinatal deaths or miscarriages and other complications (sickling and non-sickling related) in pregnant women with SCD compared with the use of placebo.

2.2 Specific Objectives

1. To determine the effect of the use of LDA during pregnancy in HbSS and HbSC women on the risk of intrauterine growth restriction (IUGR), perinatal death or miscarriage.
2. To determine the effect of the use of LDA during pregnancy in HbSS and HbSC women on the incidence of other maternal complications including preeclampsia, preterm delivery, number of vaso-occlusive crises, need for blood transfusion, urinary tract infections, respiratory tract infections, acute chest syndrome, retained placenta, placental abruption and vaginal bleeding.

3.0 STUDY DESIGN

3.1 Sample size calculation

Assuming an incidence of intrauterine growth restriction (IUGR) of 20% in sickle cell disease (14) and expecting a 50% IUGR reduction with the use of LDA as detected by Bujold et al (15), we calculated that 198 women per group would be required to have a 90% power of detecting a decrease in IUGR at the 5% significance level, with a total of 396, using the formula for proportions in superiority parallel trials (16). Allowing for 20% attrition, this would become 476 in total.

3.2 Sample Population

A total of 476 eligible pregnant HbSS and HbSC women from 12-28 weeks gestation will be enrolled and followed until delivery. Two study groups will comprise of approximately 238 HbSS or HbSC pregnant women who are confirmed with Haemoglobin phenotype testing by HPLC randomly assigned to each arm.

3.3 Settings and locations

This will be a multi-center study with the coordinating center at the College of Medicine, University of Lagos (CMUL). Study sites will comprise 3 Teaching Hospitals, 12 General Hospitals and 1 Federal Medical Centre within and outside Lagos State.

The study sites will include:

Site Code No.	Name of Study Site	Site Investigator/Coordinator
01	Lagos University Teaching Hospital, Lagos State	Dr. Opeyemi Akinajo, Dr Babah O.A
02	Lagos State University Teaching Hospital (LASUTH), Ikeja, Lagos State	Dr. Yusuf Oshodi
03	Alimosho General Hospital, Igando, Lagos State	Dr. Ogungbe O.Y
04	General Hospital, Gbagada, Lagos State	Dr. Ojo Oluwole O, Dr Kaka A.A .

05	General Hospital, Ikorodu, Lagos State	Dr. Aletan O.B.
06	General Hospital, Ifako Ijaiye, Lagos State	Dr. Awobusuyi Omotayo R.
07	Randle General Hospital, Surulere, Lagos State	Dr. Aderolu Monsurat B.
08	Island Maternity Hospital, Lagos State (LIMH)	Dr. Agbetoba H.A
09	Federal Medical Centre, Ebute Metta, Lagos State	Dr. Uchendu I.A, Dr Olusi A.M
10	Ajeromi General Hospital, Ajegunle, Lagos State	Dr. Idowu Adewale, Dr Azie Kingsley
11	General Hospital, Isolo, Lagos State	Dr. Ajayi Akinola B.
12	General Hospital, Shomolu, Lagos State	Dr. Inofomoh Aloysus
13	General Hospital, Orile-Agege, Lagos State	Dr. Olodeoku Kayode .O, Dr Omodigbo
14	Mother and Child, Amuwo-Odofin, Lagos State	Dr. Alokha Mercy
15	General Hospital, Ibeju-Lekki, Lagos State	Dr. Bamisebi A.O, Dr. Hassan Khadijah. O
16	Obafemi Awolowo University Teaching Hospital, Ile-Ife	Dr. Awowole Ibraheem, Dr Adeniyi, Dr Allen

3.4 Randomisation (Interventions: Investigational and placebo therapy)

This study will employ a randomised, patient and investigator-blinded, multi-centre, parallel-group, placebo controlled design to assess efficacy, safety and tolerability of Low dose aspirin for preventing intrauterine growth restriction and preeclampsia in sickle cell pregnancy (PIPSICKLE).

At the baseline visit, a pregnant woman who is referred or is found to have sickle cell disease (HbSS or HbSC) on routine haemoglobin genotype testing, meets the eligibility criteria and gives informed consent will be enrolled and randomised to one of the two treatments groups (Blinded)

Randomisation and allocation concealment will be done with the use of a web-based randomisation software known as 'Sealed envelope' in a 1:1 ratio in blocks stratified according to centre. Only an unblinded pharmacist will be aware of the actual codes and the pharmacist will not be in contact with any of the study participants or investigators.

A total of 476 eligible pregnant HbSS and HbSC women will be randomly assigned to either group.

Those in the LDA group will receive 100mg aspirin daily while those in the placebo group will receive a tablet that looks like the active drug in terms of diameter, thickness and colour.

The drugs will be started between 12 and 28 weeks' gestation and continued till 36 weeks or delivery, whichever comes earlier.

The study drugs will be prepared in sachets and dispensed in 2 weekly doses (*3 weeks dosage at enrollment)*. The women will be sent daily reminders by text message, questioned on compliance at each visit and asked to bring in their used sachets for sighting. All the women will be followed from enrollment till delivery.

The study drugs will be packed in boxes labelled with codes and each box will have sufficient study drugs for one patient for 24 weeks with 4 extra weeks' worth of drug in case the patient loses some pills. The drug boxes will be delivered to each centre in batches of 8 (4) and 4 (2) more boxes will be sent to the centre whenever a message is received from the centre that there are 4 boxes left.

In the unlikely event that a woman loses all her drugs, the unblinded pharmacist will be asked to label another batch for the woman, based on the code list that she holds. If all the relevant drugs have been used up, the trial pharmaceutical company Emzor Pharmaceutical Ltd, will be asked to produce a new pack of study (investigational or control) drug.

Investigational (active) and control (placebo) therapy:

- Formulation A: LDA; The investigational drug (Aspirin) 100mg aspirin taken once at about same time daily

- Formulation B: The placebo (control); tablet that looks like the active drug in terms of terms of diameter, thickness and colour, also taken once at about same time daily.

3.5 Patient numbering

Each patient will be uniquely identified in the study by a combination of her study site code and a three digit number to make a study ID. The study site code has been pre-assigned by the PI. Upon signing the informed consent form, the patient is assigned a Study ID as soon as she is randomised on the web based randomisation form.

3.6 Measures to minimize bias

3.6.1 Randomization and allocation concealment.

This will be done remotely by "Sealed envelope", an on-line randomization service. Sealed envelope will generate a randomization code list and share it ONLY with the unblinded pharmacist, Mrs Edet, by email. The code list will be in blocks of four and the drugs will be sent out in blocks of four to each site by the unblinded pharmacist. Once the drugs are received by each site, they will let the PI know and she will alert Sealed Envelope so they can load the appropriate codes onto the system. As each new patient is recruited in a particular site, her details are entered into a tablet and a code is generated, which will be one of the codes that were sent to the site. She is then given tablets from the box of drugs that carries the generated code. Only the unblinded pharmacist will have the code list that shows the group that the code is assigned to i.e. whether active drug or placebo.

The number of blocks sent to a site will correspond to the expected recruitment frequency at the site, based on the average number of sickle cell patients seen in the site. So for Alimosho and LASUTH for example, two blocks will be sent initially i.e. 8 packs of drugs, while for Federal Medical Centre, Ebute Metta, one block will be sent i.e. 4 packs of drugs.

3.6.2 Blinding

Our goal is to blind: 1) Participants, 2) Site coordinators, PIPSICKLE research team. The only person that will know the codes will be the un-blinded pharmacist. The appearance of the trial drug

aspirin and placebo are identical and will be packaged and labelled the same way. There will only be unblinding if there are serious adverse events and the PI will be told the correct allocation, after the DSMC/External Monitoring Committee (EMC) have agreed that unblinding is necessary.

3.6.3 Randomization and decoding procedures

The PIPSICKLE randomisation manager, who in this case is the unblinded pharmacist, will maintain the trial treatment randomisation codes. The manager will provide the code to the DSMC/EMC during meetings to review the interim data. The manager will provide the code to the DSMC/EMC statisticians when they are prepared to unblind the code to review interim data.

3.7 Physical examination

Full physical examinations will be performed at baseline, and at each visit .The initial evaluation will also include measurement of the patient's weight, blood pressure and oxygen saturation.

Information about the physical examination must be entered into the source documentation at the study site. Significant findings that are present prior to receiving study medication must be included in the relevant medical history/current medical conditions in the Case Report Form (CRF).

3.8 Laboratory evaluations

Standard clinical laboratory evaluations will be performed as follows:

Haematology:

- Full blood count (at enrollment and delivery)
- Hb fraction by HPLC (enrollment)
- Haemoglobin concentration with the Hemocue haemoglobinometer every 2 weeks from 20 weeks' gestation till delivery.

Urinalysis:

- Measurements will be performed by dipstick at every visit.

- Random/Spot urine protein to creatinine ratio (UPCR) will be ordered on a random urine sample if there is evidence of significant protein (≥ 1+) in the urine by dipstick.

Blood specimen will be collected in serum separator tubes for storage and use for future research. All samples will be processed and analyzed at Synlab (an internationally accredited medical laboratory). Complete the ***laboratory tests request form (Appendix i)*** to accompany the sample to the lab, document date and time samples were taken in participant's case-note. Call courier services for sample pickup preferably within 6 hours of sample collection. Store samples at 4-8^{0}C (refrigeration) immediately after collection before pickup; for not more than 12 hours. If any results are of clinical concern, a repeat sample will be collected at the next scheduled visit.

3.9 Outcome measures

Primary outcomes:

- Birth weight below 10th centile for gestational age on the WHO INTERGROWTH- 21st birthweight charts
- Stillbirth
- Fetal death
- Miscarriage.

Secondary outcomes:

Pregnancy complications: Pre-eclampsia, Preterm delivery, retained placenta, placental abruption;

Maternal complications: Maternal death, frequency of crises, no of blood transfusions, incidence of urinary tract infection, respiratory tract infection, acute chest syndrome, and potential adverse effects such as vaginal bleeding, epigastric pain and heartburn.

Preeclampsia will be diagnosed based on ISSHP classification (17) if there is development of hypertension (either systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg on two occasions at least 4 h apart) after 20 weeks gestation plus one of the following: proteinuria, thrombocytopenia or any multisystem complication.

Proteinuria will be defined as a dipstick test with ≥1+ proteinuria (≥30 mg dl^{-1}) on two occasions at least 4 hours apart, without any evidence of a urinary tract infection. Or UPCR >300mg/g Cr.

Thrombocytopenia will be defined as platelet count < 100,000/Ul.

4.0 SELECTION OF PARTICIPANTS

The target population is sickle cell pregnant women who are either HbSS or HbSC.

Eligibility

4.1 Inclusion criteria

- Age 18 years and above
- Singleton fetus
- Hb genotypes are Haemoglobin SS or SC.
- 12-28 weeks gestation at recruitment, estimated from the last menstrual period or by an early ultrasound scan.

4.2 Exclusion criteria

- Women with associated medical conditions in pregnancy e.g. HIV infection, diabetes mellitus, chronic hypertension, renal disease, sickle nephropathy.
- Hb genotype other than HbSS & HbSC
- Gestational age greater than 28 weeks
- Multiple pregnancy
- History of hypersensitivity to aspirin
- A vaso-occlusive crisis in the last 4 weeks
- Blood transfusion in the last 3 months
- Women who participated in the PIPSICKLE trial during their previous pregnancy

Once a participant is enrolled, she will be assigned a study ID and a randomisation code, which will be entered into the database and written on the patient's case record. An electronic enrollment CRF will be completed using REDCap software installed on electronic tablets.

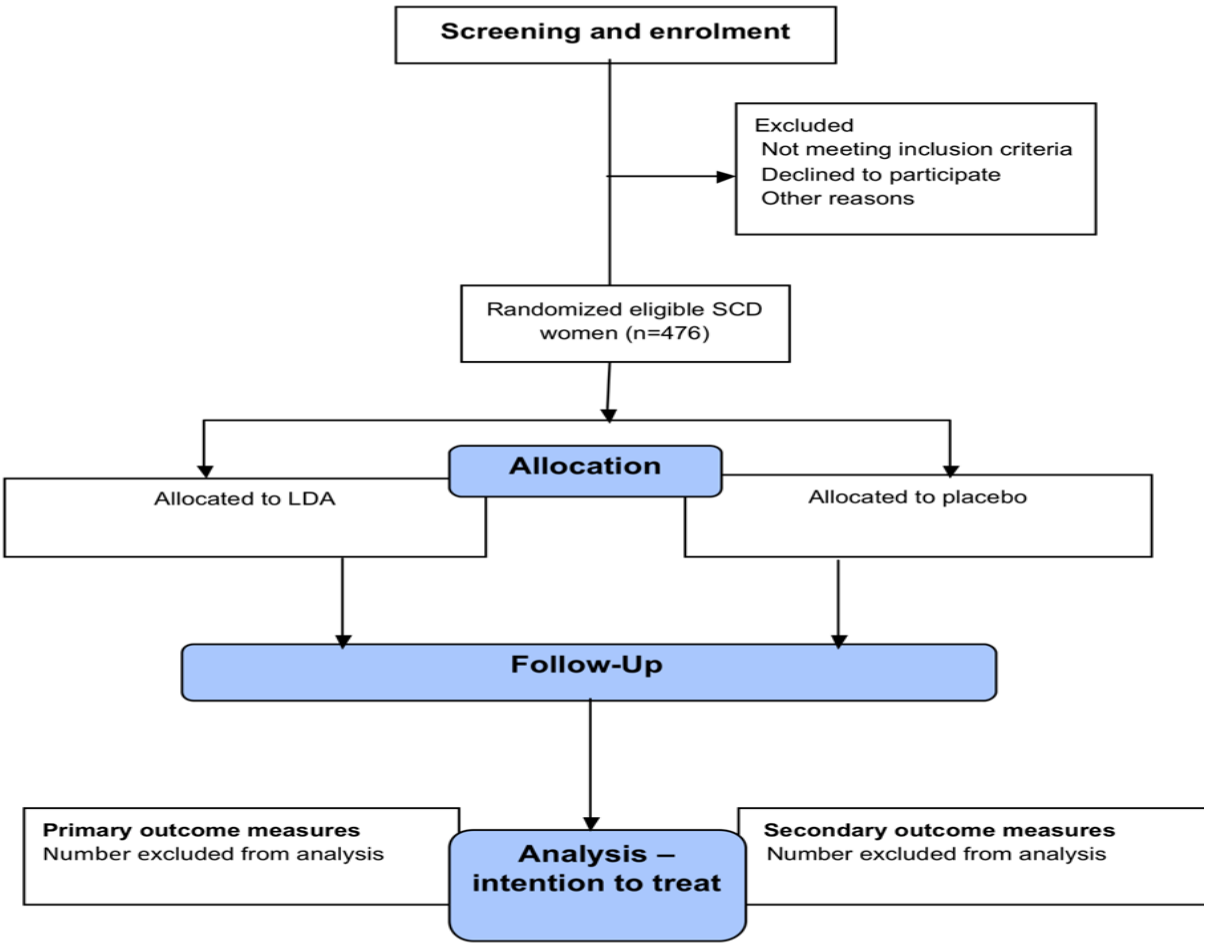

Figure 1. PIPSICKLE Trial flowchart

5.0 VISIT SCHEDULE AND ASSESSMENTS

5.1 Screening visit (visit-0)

All prospective participants will be evaluated to determine their eligibility according to the study eligibility criteria. Information will be completed for all prospective participants as required in the ***screening log* (*Appendix ii*).**

The following additional steps must be taken during the screening visit:

- An interview/information disclosure/discussion and interaction with the participant to make sure she comprehends the nature and purpose of the study, duration of participation and number of participants, procedures to be followed, investigations; if any to be performed, foreseeable risk and discomfort, other study requirements and schedule and is willing to comply.
- Acceptance/rejection to participate
- Agreement to participate (Consent). Must be recorded (written)/witnessed. Each participant will be asked to sign (or provide other mark if need be) an ***informed consent document* (*Appendix iii*)** and will be given a signed copy to take home. If the participant cannot read, a witness will be present at the time of the study explanation and consent process and will witness the signature or mark of the participant.
- The women may be asked to return in 2-4 weeks for the enrollment visit if she met all eligibility criteria. ***However screening (visit-0) and enrollment (visit-1) may take place during the same visit.***

Contact information

For each participant the research staff will obtain contact information. The study site will develop its own ***Patient locator form* (*Appendix iv*)** and determine the best way to collect this information for its own study site participants. In the event that a participant misses a scheduled appointment (enrollment or follow-up or end of study visit), the research staff will try to establish communication with the participant through authorized possible means (e.g telephone if this is possible, emails or visiting the participant's home or workplace). The need to return for all scheduled follow up visits will be emphasized to all study participants at every visit.

5.2 Enrollment visit (visit 1- GA 12-28 weeks)

Screening (visit-0) and enrollment (visit-1) may take place during the same visit.

Once the participant is screened and determined to meet study eligibility criteria and consent to the study, she will be randomised to one arm of the study and assigned a study ID and randomisation code.

The following additional steps will be taken in the enrollment visit

- Study ID and randomisation code will be written on her case-notes
- Complete study ***enrollment log (Appendix v).***
- Do a physical examination & take relevant medical history and concomitant medications
- Complete ***enrollment e-CRF (Appendix vi).***
- The box corresponding to her randomisation code will be opened and she will be given a three-week pack of the drugs from the parcel and scheduled for a follow-up visit in 2 weeks.
- Take blood for full blood count and Hb fraction by HPLC – 4ml each into 2- EDTA bottles.
- Take spot urine sample for urinalysis by dipstick. UPCR if significant proteinuria by dipstick.

If a patient is screened but does not get enrolled, the reason for not being enrolled must be entered into the screening log.

5.3 Follow- up visits (visit 2- 28-36 weeks to delivery)

Each participant will have a follow up visit at the study site. The research staff will be responsible for interviewing and re-supplying the participants with the trial drugs.

The following will be done at follow up visits

- Physical examination
- Evaluate compliance & ADR
- Counselling
- Complete follow-up visit e-CRF ***(Appendix vii)*** and relevant source documents
- Re- supply of trial drugs in an amount sufficient to last until the next follow up visit.

- ❖ Haemoglobin concentration with the Hemocue haemoglobinometer every 2 weeks till delivery.
- ❖ Take spot urine sample for urinalysis by dipstick. UPCR if significant proteinuria by dipstick.

5.4 Interim contacts and unscheduled visits

The participant or the investigator may request an interim contact or an unscheduled visit at any time during the study. All interim contacts and unscheduled visits will be documented in the participants study records and visit e-CRFs.

Interim or unscheduled visits are AE-related visits in that health related reaction, effect, or abnormality is reported. Other examples of reasons for an interim or unscheduled visit not in response to an AE are:

- To get more trial drugs in cases of loss or misplacement.
- To ask questions and discuss problems with study compliance
- Interim examination - examination requested but no complaints or symptoms

5.5 Study Completion visit (Pregnancy loss or delivery)

A participant will be considered to have completed the study once there is a pregnancy loss or delivery at any time after randomisation and all relevant data is captured into the appropriate study completion CRF.

The following steps will be taken at the end of study visit

- ❖ Physical examination
- ❖ Evaluate compliance & ADE
- ❖ Complete all relevant documents
- ❖ Complete delivery e-CRF ***(at delivery- Appendix viii)*** and end of study visit e-CRF at completion of all study visits and data entry ***(Appendix ix)*** and other relevant source documents.

- ❖ Counselling and necessary referral (e.g Postpartum and family planning clinics)

Tables below lists all of the assessments and indicates with an "X" the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation. The Table indicates which data are entered into the database (D) or remain in source documents only (S) or both (SD).

Assessments that generate data for database entry and which are recorded on CRFs are listed using the CRF name (Enrollment, Visit, Study completion). Assessments that are transferred to the database electronically (e.g. laboratory data) are listed by test name.

Table 1: Study Visit Schedule

	Pre-treatment	Treatment (Enrollment and follow-up)																Delivery			
Study Visit	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
GA in weeks	6-11	12	14	16	18	20	22	24	26	28	29	30	31	32	33	34	35	36	37	38	39	40
Screening	X	X	X	X	X	X	X	X	X	X												
Enrollment		X	X	X	X	X	X	X	X	X												
Follow-up			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
End of study			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 2: Assessment schedule for study participants

Phase	Pre-Treatment	Treatment (Enrollment and follow-up)																Delivery			
Study visit	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
GA in weeks	6-11	12	14	16	18	20	22	24	26	28	29	30	31	32	33	34	35	36	37	38	39	40
Inclusion/exclusion criteria (S)	X	X	X	X	X	X	X	X	X	X												
Written informed consent (S)	X	X	X	X	X	X	X	X	X	X												
Demographics/ PMH (SD)	X	X	X	X	X	X	X	X	X	X												
Concomitant medication (SD)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight (SD)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination (SD)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory (SD) Hb +Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Obstetric Scan (SD)						X																
Study Drug (SD)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Adverse Events (SD)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
End of study form (D)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

6.0 PARTICIPANTS WITHDRAWAL & STUDY DISCONTINUATION

6.1 Premature patient withdrawal

Patients must be withdrawn from the study for any of the following reasons:

- Withdrawal of informed consent
- Use of any of un-prescribed medications
- Patients who discontinue study drug

Patients could also be withdrawn at any time if the investigator concludes that it would be in the patient's best interest for any reason. Protocol violations should not lead to patient withdrawal unless they indicate a significant risk to the patient's safety.

Patients may voluntarily withdraw from the study for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, or fail to return for visits, or become lost to follow up for any other reason.

If premature withdrawal occurs for any reason, the investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information on the Study Completion CRF.

Patients who are prematurely withdrawn from the study will not be replaced by newly enrolled patients.

6.2 Loss to follow up

If a participant fails to appear for a scheduled visit, at least three attempts to contact her will be made over the subsequent 30 days. These attempts will be documented in the participant study file. Her file will remain open until the study close out.

For patients who are lost to follow-up (i.e. those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc.

If the participant does not return to the study before the study is closed, the end of study form will only be completed at the time of study closeout. The form will indicate that the participant was lost to follow up. The "lost to follow up" designation cannot be made for any participant until the closing date of the study

7.0 STUDY PRODUCTS AND TREATMENTS

7.1 Study products:

- Aspirin
- Placebo

7.2 Study drug supply and resupply, storage, and tracking

Study drugs must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Upon receipt, all study drugs should be stored according to the instructions specified on the drug labels. Clinical supplies are to be dispensed only in accordance with the protocol.

The investigator must maintain an accurate record of supplies and dispensing of study drug in a drug accountability ledger. Monitoring of drug accountability will be performed by the field monitor during site visits and at the completion of the trial. Patients will be asked to return all unused study drug and packaging at the end of the study or at the time of study drug discontinuation.

7.3 Treatment assignment

At enrollment visit, all patients who fulfill all the inclusion/exclusion criteria will be given the lowest available number on the randomisation list. This number assigns them to one of the treatment arms. The investigator will enter the randomisation number on the enrollment log/CRF.

Each participant will receive a supply of the trial drugs. Participants will receive supplies in quantities anticipated to last until next visit. Research staff will show the participants how the drugs are to be taken. A participant will be instructed to return between scheduled visits to obtain more supplies if needed. A product dispensing log will be maintained by the clinic and field staff to track distribution of the trial drugs.

7.4 Treatment blinding

The trial is a double-blinded RCT study. Both treatments will be identically packaged and the pharmacist or an independent study site personnel will prepare and give the medication to the patient after randomisation. The investigator should remain blinded.

7.5 Dispensing the study drug and labeling

Each study site will be supplied by the unblinded study pharmacist with the study drugs in identically-appearing boxes. There will be a label with a unique randomisation code affixed to each of the boxes. Each unique code will correspond to a treatment arm. When the batch of study drug is delivered to a site, the receiving investigator (site coordinator), will notify the PI of receipt with a list of the randomisation codes received. The PI then notifies Sealed Envelope. Once a patient at a particular site is randomised, the code generated will correspond to the code on one of the boxes at that site. The investigator or research assistant will identify the study drug to dispense to the patient using the randomisation code on the label. Immediately before dispensing study drug to the patient, investigator staff will copy the code onto the source document ***(Appendix x: Drug Accountability Form)*** containing that patient's unique Study ID.

7.6 Other concomitant treatment

Use of the following treatments is NOT allowed after the start of study drug:

- Any drug not prescribed.
- Herbal medications

7.7 Study drug discontinuation

Study drug must be discontinued for a given patient if the investigator determines that continuing it would result in a significant safety risk for that patient. The following circumstances require study drug discontinuation:

- Emergence of severe adverse events: severe nausea/vomiting, allergy, severe pruritus, life threatening symptoms
- Persistent or heavy vaginal bleeding
- Abnormal laboratory values: Platelet count $\leq 50 \text{ X } 10^9$/ml
- In addition to these requirements for study drug discontinuation, the investigator should discontinue the study drug for a given patient if, on balance, he/she thinks that continuation would be detrimental to the patient's well-being.

Patients who discontinue study drug will be followed for the whole study duration until 36 weeks or delivery at which time all of the assessments listed for the final visit will be performed.

Reasons for Study Drug discontinuation should be completed, giving the date and primary reason for stopping the study drug under the relevant portion of the CRF.

7.8 Emergency unblinding of treatment assignment

- As aspirin is a tried and tested commonly used drug, we do not foresee any need for emergency unblinding. However, in the event of an acute hypersensitivity reaction, we will have to perform emergency unblinding. -- Any other reason as determined by the DSMC/External monitoring committee.

7.9 Treatment exposure and compliance

All medication (other than study drug) and significant non-drug therapies administered after the patient starts treatment with study drug will be documented under concomitant medications/Significant non-drug therapies in the CRF after start of study drug.

Records of study medication used and exact dosages administration and compliance will be kept during the study. Drug accountability will be noted by the field monitor during site visits and at the completion of the study.

8.0 ADVERSE EVENTS AND REPORTING REQUIREMENTS

8.1 Adverse Events (AEs)

- An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Study drugs include the investigational drug/placebo under evaluation that is given during the treatment phase of the study.
- *Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug*.
- Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, or are considered clinically significant, or require therapy.

Clinical signs and symptoms will be assessed at baseline, before dosing and all follow-up visits, and recorded on the CRF. Any symptom that worsens or starts after baseline will be recorded as a new adverse event on the e-CRF.

The occurrence of adverse events, such as weakness, chills/rigors, headache, myalgia, dizziness, epigastric pain, abdominal pain, anorexia, nausea, vomiting, diarrhea, palpitations, insomnia, pruritus, coughing, tinnitus, abnormal gait, tremor, clonus or dyskinesia, will be sought by the investigator (or designee) at each study visit and recorded in the e-CRF.

Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments.

8.2 Relationship of AE to study product

The investigator must determine the relationship of the AE to the product under investigation and document in the appropriate section of the e-CRF. For each AE, an assessment of the relatedness to the study drugs should be made using the following scale:

- **Unrelated:** Onset of the AE had no reasonable temporal relationship to administration of the study product or a causal relationship to administration of the study product is biologically implausible or the event is attributed to an alternative etiology.

- **Possibly Related:** Onset of the AE has a reasonable temporal relationship to study product administration and a causal relationship is not biologically implausible.
- **Probably Related:** Onset of the AE has a strong temporal relationship to administration of the study product that cannot be explained by the participant's clinical state or other factors and a causal relationship is not biologically implausible.
- **Definitely Related:** Onset of the AE shows a distinct temporal relationship to administration of the study product that cannot be explained by the participant's clinical state or other factors or the AE occurs on re-challenge or the AE is a known reaction to the product or chemical group or can be predicted by the product's pharmacology.

These criteria in addition to good clinical judgement should be used as a guide for determining the causal assessment. If it is felt that the event is not related to study drug therapy, then an alternative explanation should be provided.

8.3 Reporting Adverse Events

Study site coordinators will document on the appropriate study e-CRF all AEs reported by or observed in enrolled study participants regardless of severity and presumed relationship to study product. The study clinician must provide on this form information on symptoms, time of onset, severity, frequency, product-relatedness, actions taken and participant outcome. The PI may request additional information from the site if it is needed to evaluate the AE. Site coordinators will report information on SAEs to the local Ethics committee in accordance with the local committee requirements.

All adverse events must be recorded on the e-CRF with the following information:

1. the severity grade (mild, moderate, severe)
2. its relationship to the study drug(s) (see section 8.2)
3. its duration (start and end dates or if continuing at final exam)
4. whether it constitutes a serious adverse event (SAE)

- All adverse events recorded at any time after baseline on the CRF will be summarized at analysis.

8.4 Serious Adverse Events (SAEs)

A SAE is defined as an event which:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements.

All adverse events should be treated appropriately. Treatment may include one or more of the following:

- No action taken (i.e. further observation only);
- Study drug dosage adjusted/temporarily interrupted;
- Study drug permanently discontinued due to this adverse event;
- Concomitant medication given;
- Non-drug therapy given;
- Patient hospitalized/patient's hospitalization prolonged.

The action taken to treat the adverse event should be recorded on the adverse event section of the e-CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.5 Reporting SAEs

All SAEs should be reported to PIP-SICKLE administrative core & steering committee as soon as possible after the SAE is identified by site personnel. It is strongly recommended that site personnel report SAEs within 24 hours of the study site becoming aware of the problem. The investigator should complete ***SAE report form (Appendix xi)*** and forward to the DSMC/EMC. The investigator may report the SAE via telephone or email; however a SAE report form must be completed as soon as possible after the informal report.

8.6 Safety

Adverse events will be monitored throughout the study to assess the general safety and tolerability of the two treatment groups.

Safety assessments will consist of:

- monitoring and recording all adverse events
- the monitoring of hematology and urinalysis
- regular measurement of vital signs
- physical examinations as indicated

9.0 STATISTICAL SUMMARY

9.1 Data collection

Designated investigator or staff must enter the information required by the protocol onto the electronic CRFs on REDCap and source documents as indicated. Field monitors will review the e-CRFs for completeness and accuracy and instruct site personnel to make any required corrections or additions.

9.2 Data Management and Analysis

DATA ANALYSIS; POPULATIONS FOR ANALYSIS

The assignment of patients into analysis populations will be performed prior to database lock and any data analysis.

Randomised – all patients who receive a randomisation number.

Intention-to-treat (ITT) – all randomized patients with at least one relevant post-baseline efficacy assessment, and who had at least one dose of study drug. Following the intention-to-treat principle, patients will be analyzed according to the treatment they were assigned to at randomization.

Primary Analysis (PA) – all ITT patients that completed 36 weeks or delivery

Per Protocol (PP) – all PP patients that meet all of the following:

- Took at least 80% of scheduled study drug

Safety – all patients that received at least one dose of study drug and had at least one post-baseline safety assessment. Patients will be analyzed according to treatment received.

9.3 Data analysis plan

Data analysis will be by intention-to-treat. Categorical variables will be expressed as frequencies and percentages. For continuous variables, a Shapiro–Wilk test of normality will be performed and normally distributed data will be presented as means ± SD, while non-normally distributed data will be presented as median and interquartile range (IQR). The risk of occurrence of IUGR, perinatal death and other key outcome variables will be computed and compared in both groups. A multivariate regression analysis will be performed to determine the odds of each of the key outcomes among women who received the intervention with respect

to those who did not, after controlling for common confounders. This will be presented as regression coefficients and their 95% confidence intervals. Level of significance will be set at 5%. Post-regression analysis will be performed to determine the goodness-of-fit of the final model. STATA version15.0 (StataCorp LP, College Station, TX, USA) will be used for statistical analysis.

9.4 Quality control and data management

The data file will be accessible by the PI and the statistician. Data will be captured in electronic case report forms (CRF) at various patient visit types and uploaded real time to the central server after being checked by the site coordinator. They will follow the guidelines specified in the SOP developed by the Data handling and communications committee for data collection, data entry, and transmission, data compilation and management and data quality and security.

10.0 MONITORING PLAN SUMMARIES

10.1 Monitoring and Evaluation Mechanism

The Project monitoring and evaluation mechanism will help to determine progress being made towards achievement of study outcomes and will provide constructive recommendations to address key problems identified. It will review the effectiveness, efficiency and timeliness of project implementation; analyse effectiveness of implementation and partnership arrangements; identify issues requiring decisions and remedial actions; analyse whether the project is on track with respect to achieving the expected results; and propose any mid-course corrections and/or adjustments to the Work Plan as necessary.

The project M &E mechanism will include

i. An Administrative Core- this will be the essential infrastructure that will enable synergy and coordination of the project, scientific core and the collaborating sites of PIPSICKLE. The administrative core will consist of the PI and Ms Rachel Quao, a full time project coordinator. They will provide administrative oversight and management of the research study and coordinate all internal and external meetings of investigators and staff.

ii. Steering committee – this will ensure a successful delivery of the project, maximizing the benefits from the projects and ensuring the approved methodology is followed. This committee will provide Cross-functional leadership and direction, provide Project Management Governance, and accept responsibility for the project strategy and the overall benefit realization of the project. The steering committee will comprise the PI, all co-investigators and project site coordinators as may be appointed. A patient representative and an external monitor, an Obstetrician with clinical trial experience will also be included. The steering committee will monitor project progress by holding a bi-weekly on-line meeting (Zoom/Skype) to evaluate enrolment rate, challenges and issues as they arise. The committee will also hold a bi-annual face to face meeting to monitor and evaluate progress and ensure compliance with regulatory, fiscal and reporting requirements.

iii. Clinical Trial Monitors – The Clinical monitor will be responsible for trial monitoring. To verify that: (a) the rights and well-being of human subjects are protected. (b) The reported trial data are accurate, complete, and verifiable from source documents. (c) The conduct of the trial is in

compliance with the currently approved protocol/amendment(s), with Good Clinical Practice (GCP), and with the applicable regulatory requirement(s). Clinical trial monitors will conduct:

i. Pre-Trial Monitoring visit: to ensure feasibility in the centre and interest of the investigator.
ii. Trial Initiation visit: to deliver study material, documents, products and make sure the investigational team understands the protocol and GCP requirements.
iii. Routine Monitoring visit: Make sure the study is conducted according to the protocol and GCP and help the investigational team in solving problems.
iv. Close-out visit: Make sure the investigator file is archived properly and collect back all unused material, documents or products. Appointed site coordinators will be trained in GCP and research monitoring to perform the duties of clinical monitors in sites other than theirs.

10.2 Clinical Monitoring plan

Site visits by the external clinical monitors will be made in accordance with the policy drafted and SOPs. The purpose of the monitoring is to ensure the quality and accuracy of data collected on the e-CRF and entered in the database and to determine that all regulatory requirements surrounding clinical trials are met.
The investigator will allow the clinical monitors and designated persons to inspect study documents (e.g consent forms, drug distribution forms, CRF and pertinent clinic records for confirmation of the study data).

Various authorized individuals may visit the study site to audit the progress of this study (e.g monitoring committee). ***A site monitoring visit log (appendix xii)*** will be maintained at the study site in which all visits made by authorized individuals are recorded. All clinical records and the e-CRFs for all the participants enrolled in this study will be made available for review to authorized individuals.

Before the study begins, the clinical monitors will conduct an evaluation visit at each site to determine the suitability of the site for the research study. In addition there will be a study initiation visit (study start-up), quarterly monitoring visits (to track study progress) and a close out visit. The overall responsibility of the monitors is to ensure that the study is being conducted according to the protocol, SOPs, GCP and applicable regulatory requirements.

A detailed monitoring plan will be developed for this study and will be used by all clinical monitors. This plan will specify responsibilities and qualifications of the identified clinical monitors, back-up provisions, in house monitoring procedure and site monitoring visit procedures. All monitoring visits will be documented.

10.3 Data and safety monitoring committee

The steering committee will assemble an independent DSMC/External Monitoring Committee made up of at least three members; which will include one clinician and one statistician. Members are Prof Olayemi UCH – Chairman, Prof Akanmu and Dr Kamma Okafor. The DSMC/EMC will meet at a minimum once before the study begins and twice during the study. The details for the operation and responsibilities of the DSMC will be provided in the DSMC/EMC Operational protocol No 2

11.0 PROTOCOL VIOLATIONS & DEVIATIONS

11.1 Protocol violations

Any deviation that may affect the subject's rights, safety, or welfare, and/or the completeness, accuracy and integrity of the study data. This is considered a major, more serious, variance from an approved protocol than a deviation.

Emergency departures from protocol that eliminate an apparent immediate hazard to participate and are deemed crucial for the safety and well-being of that participant may be instituted for that participant only by the investigator. The investigator will notify the EMC & Ethics committee in writing as soon as possible and document on the ***Protocol Deviation/Violation Form (appendix xiii)*** the reasons for violation and ensuing events. Protocol violations may also be identified by the clinical monitors during the periodic and closeout monitoring visits as well as during in house monitoring. The reporting procedures will be specifically detailed in the monitoring plan.

Examples of Protocol Violations

1. Omission or inadequate administration of informed consent.
2. Inclusion/exclusion errors including gestational age limit.
3. Treatment errors: no treatment or incorrect treatment (including dose or regimen, expired product), participant compliance problems.
4. Missing or incorrectly timed study procedures and assessments
5. Forcing a participant to enter or remain in the study, failure to withdraw a subject meeting withdrawal criteria;
6. Inadvertent loss of samples or data;
7. Participants who should have been discontinued from the study due to protocol criteria, but were not
8. Working under an expired professional license/certification, debarred or disqualified status
9. Frequent minor deviations

11.2 Protocol Deviation

Any change, divergence, or departure from the approved study design or procedures of a research protocol that is under the investigator's control and that has not been approved by the IRB, and ***does not affect*** the participant's safety, rights, or welfare and/or the completeness, accuracy and integrity of the study data.

Examples of Protocol deviation

1. implementation of unapproved recruitment procedures;
2. use of an incorrect informed consent version;
3. Missing original signed and dated consent form or missing pages from executed consent form;
4. Inappropriate documentation of consent, including missing signatures
5. Individual obtaining consent not listed on IRB approved application
6. Subject visit/procedure falls outside of the window of time indicated by the protocol, or is not done per protocol, and there is no increased potential for risk to the subject or any damage to the integrity or completeness of the data.

11.3 Serious Noncompliance

Failure to comply with federal regulations, state laws, institutional policies, requirements or determinations of the Ethics committee, and/or provisions of the approved research study, where the occurrence involves substantive potential or actual increased risk to the safety, rights and welfare of participants.

11.4 Reporting Protocol violation and deviations

- The Trial clinical monitors must report deviations and violations to the PI.
- It is the principal investigator's responsibility to report protocol violation/deviation to the steering committee upon discovery. Protocol violations which may be considered serious noncompliance and are to be reported to the ethics committee within 5 business days on the Protocol Violation Report. The Principal investigator must develop a corrective action plan to present to the committee for review and approval. This corrective action plan will outline what steps the investigator has taken or will take to resolve the event and to prevent such events from occurring in the future.

11.5 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by the Ethics committee. Only amendments that are required for patient safety may be implemented prior to ethics committee approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the ethics committee at the study site should be informed within 10 working days.

12.0 STUDY DOCUMENTS

12.1 Study initiation

The following documents will be in place and monitored by a clinical monitor at the study site before any potential participants are contacted.

1. Investigators file: Signed Study protocol, screening log, enrollment log, informed consent form, protocol violation form, SAE report form, Sample CRFs

2. Information given to participants: consent form, other written information, advertisements

3. Financial records

4. Signed agreement between involved parties

5. Ethics committee approval

6. CV for investigator, Co-Investigator and Site coordinators, research nurses and other staff

7. Laboratory test normal values

8. Instructions for handling investigational product and trial related materials, drug label form

9. Site Monitoring visit log

12.2 Study conduct

During the study the following documents will be in place and periodically monitored by a clinical monitor at the study site. Revision of documents will be made if relevant.

1. Revision to the investigators file

2. Revision to protocol and amendments

3. Revision to the CRFs

4. Revision of information given to participants: consent form, other written information, advertisements

5. Ethics committee updated approvals

6. Ethics committee composition changes

7. Updated CV for investigator, Co-Investigator and Site coordinator

8. Update on laboratory test normal values

9. Documentation of investigational product and trial related materials

10. Relevant communication other than site visits

11. Signed consent forms.

12 Sample of e-CRFs

13. Copies of documentation of CRF corrections

14. Notification of Principal investigator on SAEs

15. Notification on SAE, protocol; violations by investigator to local Ethics committee

16. Interim or annual report to Ethics committees

17. Participant screening log

18. Participant randomisation code list

19. Investigational products accountability documents

20. Staff signature list

21. Site Monitoring visit logs

22. Progress reports

12.3 Study completion

After completion of the study, all of the documents in 12.1 and 12.2 should be in the file together with the following:

1. Investigational products accountability documents

2. Documentation of product destruction (if destroyed at site)

3. Complete participant ID code list

4. Final report by investigators to IRB.

12.4 Site record retention and access to documents at the site

The signed original informed consent documents for each participant, original and copies of CRFs and original copies of study documentation (e.g drug inventory forms, participant clinic records, original laboratory reports, e.t.c) will be retained by the Principal investigator for a minimum of 10 years. At study completion at various study sites, all study documents will be moved and stored at the College of Medicine, University of Lagos and retained by the PI for a minimum of 10 years.

The investigators may be subject to a field audit by the sponsor to validate the participation of study participants and to verify the data reported on the CRFs. This audit could occur while the study is in progress or several years after the study is completed. All of the participants' records and other study documentation must be filed and accessible on short notice (3-5 days) during the study and subsequent retention period.

13.0 LABORATORY QUALITY ASSURANCE

All study laboratory tests will be conducted by Synlab Nigeria. The steering committee will put in place a QA plan and transportation logistics before initiation of the study. The detailed QA plan will be finalized when the sites and the reference laboratories have finalized logistics. Synlab Nig laboratory services has been chosen based on the international accreditation and recognition, experience and facilities which comply with Good Laboratory practices (GLP) and ISO certification.

14.0 ETHICS AND RESEARCH INTEGRITY

14.1 Administrative procedures: Ethical and Environmental Considerations

This trial has been registered with the Pan African Clinical Trials Registry (PACTR). Ethical approvals by the Health Research and Ethics committees of the Lagos University Teaching Hospital, Idi-Araba, Lagos State University Teaching Hospital, Ikeja, Federal Medical Centre, Ebute Metta and the Health Service Commission of Lagos State for the use of Lagos State University Teaching Hospital (LASUTH) and the general hospitals listed above under the section on study sites have been obtained.

The purpose of the study will be duly explained to all eligible participants prior to recruitment. They will be informed of their right to withdraw or refuse to partake in the study without prejudice to the usual standard of care given to them at the health facility. All participating women will sign the study's informed consent form prior to entry into the study. The personal data of each participant will be kept strictly confidential. The site coordinator of each center will collect all data at his/her facility and send same to the principal investigator at periodic intervals. This will be stored securely in a central electronic database by the principal investigator who will be the only one who will have access to the data of all participants collated centrally. The statistician will be granted access to the electronic database during statistical analysis or at any other time the principal investigator might require her to review the data.

None of the women will be made to pay for any aspect of the study as the medication for the research will be given at no cost all through the pregnancy. All investigations pertaining to this research will also be conducted at no cost to the participants.

This proposed research poses minimal or no risk to both mother and baby. Blood specimen collection might cause minimal discomfort in form of pain. For this reason all the blood sample collection will be made as comfortable as possible for the women. The intervention drug (Aspirin) is known to be safe in pregnancy and we will be using a low dose of 100mg, which is not expected to have significant adverse effects on participants. All participants will receive other routine medication (malaria prophylaxis, tetanus toxoid prophylaxis and folic acid supplementation) as normally prescribed. Malaria prophylaxis and folic acid will be provided to the participants all through pregnancy. The participants will enjoy equal rights and quality care all through the duration of the research.

Leftover blood specimen will be stored for future research if participant consents. Ethical approval has been obtained for this (LUTH HREC Approval Number: ADM/DSCST/HREC/APP/3301).

Environmental issues are not applicable to this study.

14.2 Informed consent

No participant may be admitted into this study until the investigator has obtained her legally effective informed consent. An investigator shall seek such consent only under circumstances that provide the prospective participant with sufficient opportunity to consider whether or not to participate in the study. Informed consent must be obtained without coercion, undue influence or misrepresentation of the potential benefits or risks that might associated with participation in the study

Informed consent encompasses all oral or written information given to the participants about the study and study materials. This includes the consent from signed by the participant, recruitment advertising and any other information provided to the participant. All such information that is given to the participant will be in a language that is understandable to her. The information will not include any language in which the participant is made to waive any of her rights or which releases or appears to release the investigator or the investigators institution.

Informed consent will be documented by the use of a written consent form that is signed by the participant (or participant's mark if she cannot sign). A copy of the signed consent form will be given to each participant. The consent form includes each of the basic elements of an informed consent document and describes each of the risks or discomforts to the participant that have been identified as reasonably foreseeable.

14.3 Participant confidentiality

The confidentiality of all participants enrolled in the study will be protected to the fullest extent possible. Study participants will not be identified by name on any document sent or in any report or publication resulting from data collected in this study.

14.4 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations and with the ethical principles laid down in the Declaration of Helsinki.

14.5 Responsibilities of the investigator and IRB

The protocol and the informed consent form have been reviewed and approved by a properly constituted Independent Ethics Committee/Research Ethics Boards (IRB) before study start. Signed and dated statements that the protocol and informed consent have been approved by the IRBs have been obtained by the investigator before study initiation.

Prior to study start, all investigators are required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to monitors, auditors, IRBs, and regulatory authorities as required.

15.0 DISSEMINATION STRATEGIES

This indicates the steps that will be taken to ensure the project outcomes are brought to the attention of stakeholders. The findings of the study will be presented at conferences (both international and local) so as to disseminate them to a large body of professionals in the field of Obstetrics and Gynaecology. We will also publish them in high impact peer reviewed journals for wider dissemination of information. The findings will be used in counselling pregnant women with sickle cell disease at the various antenatal clinics on complications associated with the disease and preventive measures that may be employed. Charts will be created to facilitate counselling at the various antenatal clinics. We will issue press releases about the findings of the study.

16.0 REFERENCES

1. WHO. Sickle-cell Anaemia Report by the Secretariat. World Health Organisation. Fifty-ninth World Health Assembly; 2006a. Report No.: A59/9 Contract No.: Provisional agenda item 11.4.
2. Chakravorty S, Williams TN. Sickle cell disease: a neglected chronic disease of increasing global health importance. Arch Dis Child. 2015;100(1):48-53.
3. Yawn BP, Buchanan GR, Afenyi-Annan AN, Ballas SK, Hassell KL, James AH, et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. JAMA. 2014;312(10):1033-48.
4. Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. Lancet. 2010;376(9757):2018-31.
5. Oteng-Ntim E, Ayensah B, Knight M, Howard J. Pregnancy outcome in patients with sickle cell disease in the UK-a national cohort study comparing sickle cell anaemia (HbSS) with HbSC disease. Br J Haematol. 2015;169(1):129-37.
6. Villers MS, Jamison MG, De Castro LM, James AH. Morbidity associated with sickle cell disease in pregnancy. Am J Obstet Gynecol. 2008; 199(2):125 e1-5.
7. Afolabi BB, Iwuala NC, Iwuala IC, Ogedengbe OK. Morbidity and mortality in sickle cell pregnancies in Lagos, Nigeria: a case control study. J Obstet Gynaecol. 2009;29(2):104-6.
8. Say L, Souza JP, Pattinson RC. Maternal near miss--towards a standard tool for monitoring quality of maternal health care. Best Pract Res Clin Obstet Gynaecol 2009; 23: 287–296.
9. Obilade OA, Akanmu AS, Broughton Pipkin F, Afolabi BB. Prostacyclin, thromboxane and glomerular filtration rate are abnormal in sickle cell pregnancy. PLoS One. 2017;12(9):e0184345.
10. Lewis DF, Canzoneri BJ, Gu Y, Zhao S, Wang Y. Maternal levels of prostacyclin, thromboxane, ICAM, and VCAM in normal and preeclamptic pregnancies. Am J Reprod Immunol. 2010;64(6):376-83.
11. Duley L, Henderson-Smart DJ, Meher S, King JF. Antiplatelet agents for preventing pre-eclampsia and its complications. Cochrane Database of Systematic Reviews. 2007. Issue 2. Art. No.:CD004659

12. Moore GS, Allshouse AA, Post AL, Galan HL, Heyborne KD. Early initiation of low-dose aspirin for reduction in preeclampsia risk in high-risk women: a secondary analysis of the MFMU High-Risk Aspirin Study. J Perinatol. 2015;35(5):328-31.
13. RCOG. Management of Sickle Cell Disease in Pregnancy. Royal College of Obstetricians and Gynaecologists Green-top Guideline. 2011:1-20.
14. Al Jama FE, Gasem T, Burshaid S, Rahman J, Al Suleiman SA, Rahman MS. Pregnancy outcome in patients with homozygous sickle cell disease in a university hospital, Eastern Saudi Arabia. Arch Gynecol Obstet. 2009;280(5):793-7.
15. Bujold E, Roberge S, Lacasse Y, Bureau M, Audibert F, Marcoux S, et al. Prevention of preeclampsia and intrauterine growth restriction with aspirin started in early pregnancy: a meta-analysis. Obstet Gynecol. 2010;116 (2 Pt 1):402-14.
16. Sealed Envelope Ltd. Power calculator for binary outcome equivalence trial. [Online]. 2012. Available from: https://www.sealedenvelope.com/power/binary-equivalence/.
17. Brown MA, Lindheimer MD, de Swiet M, Assche AV, Moutquin J-M. The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the international society for the study of hypertension in pregnancy (ISSHP). Hypertens Pregnancy 2001;20 (1):ix–xiv.

APPENDICES

i. Laboratory Request form
ii. Screening Log forms
iii. Informed consent form
iv. Patient locator form
v. Enrollment log
vi. Enrollment e-CRF
vii. Follow-up visit e-CRF
viii. Delivery e-CRF
ix. End of study visit e-CRF
x. Drug Accountability Form
xi. SAE report form
xii. Site monitoring visit log
xiii. Protocol deviation/ violation form

APPENDIX 01

Laboratory Request form

Study ID:		Hospital number:	
Participant's name:			
Date of birth:		Age:	

Test	**Date of request**	**Time sample collection**
FBC		
UPCR		
Other tests:		

Requesting Clinician

Name of requesting clinician: ……

Sign: ……..

Date: ……

Site Name & Code: ……....

Phone number: …….

Email: ……

APPENDIX 02

PIPSICKLE TRIAL

SCREENING LOG

S/N	Date	Name (Initial and Surname)	DOB	Eligible (Yes or No)	Consent (Yes or No)	Reason for non-eligibility / Non- Consent	Hosp. No	Phone No
1.								
2.								
3.								
4.								
5.								
6.								
7.								
8.								
9.								
10.								
11.								
12.								
13.								
14.								
15.								
16.								
17.								
18.								
19.								

APPENDIX 03

REPLACE WITH STUDY SITE NAME

INFORMED CONSENT DOCUMENT

TITLE OF RESEARCH: Low dose aspirin for preventing intrauterine growth restriction and preeclampsia in sickle cell pregnancy (PIPSICKLE): a randomized controlled trial.

HREC APPROVAL NO.

NAME & AFFILIATION OF RESEARCHER: The study is being led by the Principal Investigator; Professor Bosede B. Afolabi of Dept. of Obstetrics and Gynaecology, College of Medicine of University of Lagos/Lagos University Teaching Hospital, Idi-Araba, Lagos.

INTRODUCTION: Preeclampsia and intrauterine growth restriction are common complications in pregnancy that affect the health of the mother and baby adversely or cause death in them. Preeclampsia is a complication in pregnancy in which the woman develops hypertension and starts excreting larger amount of protein in her urine and it usually starts after the pregnancy is at least 20 weeks. Intrauterine growth restriction is a condition in which a baby does not grow at the expected rate while in the womb, that is, the growth of the baby is abnormally slow. The risk of these complications is more in women with sickle cell disease because of the underlying problems associated with sickle cell disease. Low dose aspirin, which is safe in pregnancy have been tried in pregnant women who do not have sickle cell disease to reduce the risk of these complications and they have been found to be beneficial. For this reason we have decided to conduct this trial in pregnant women with sickle cell disease to ascertain if it will be worthwhile to use this medication in preventing preeclampsia, intrauterine growth restriction and other complications. You are invited to participate in this research because you have been confirmed to have sickle cell disease and currently pregnant.

PURPOSE OF THE RESEARCH: This study is to determine if low dose aspirin will be beneficial in preventing preeclampsia, intrauterine growth restriction and other complications in pregnant women with sickle cell disease.

PROCEDURE OF THE RESEARCH: The research involves obtaining information from you directly by asking certain questions and using your answers to complete a proforma designed for this study. This initial assessment will take approximately 10 minutes of your time. We will also retrieve additional information from your case note where necessary. Subsequently 4mls of blood sample will be drawn from your vein at your first antenatal visit and sent to the laboratory for full blood count assessment and confirmation of your genotype and your haemoglobin fraction. Your urine specimen will also be collected for urinalysis and urine culture to rule out infection. These tests will be repeated after you have delivered. You will be followed up until you deliver. We will update your records each time you come for your antenatal clinic and also take your blood for haemoglobin concentration to know your blood level and your urine to know if there is protein or glucose in it. We will also follow up whenever you are on admission to monitor your progress and update your records.

POTENTIAL BENEFITS: By participating in this study, you will have the opportunity of having some of your investigations, the test drugs and your routine drugs free at no cost to you all through pregnancy. You will have the opportunity of enjoying one-on-one contact with your health care providers as phone numbers will be exchanged. You will have the benefits of getting regular reminders of your appointments either via phone calls or text messages in order to minimize you missing antenatal visits. Generally, you will enjoy a closer monitoring of your health all through pregnancy and delivery until discharge from the hospital. The result of this research might enable us review our current protocol for management of sickle cell pregnancy, in order to reduce the rate of pregnancy complications. The findings will be presented at a conference in order to disseminate the findings to other health workers. The findings of this study will be published in a reputable journal for wider dissemination of information.

POTENTIAL RISKS: This study involves filling a questionnaire designed for the study and collection of blood specimen from your veins using a syringe and needle only. Therefore the harm it poses to participants is minimal. The trial drugs are well known and have been found to be safe in pregnancy. Call the investigators immediately (see contact details at the end of this pamphlet) if you notice any delay in stopping bleeding from minor cuts or pain in your upper tommy, asthma-like symptoms such as difficulty in breathing.

CONFIDENTIALITY: All information obtained in this study will be kept strictly confidential by the principal investigators. The blood specimen collected will also be labelled using the code assigned to each participant only to conceal the identity from the laboratory scientists. The principal investigator will have the key to the codes and will use them in tracking records when necessary. All

data will be stored in an electronic database which will be in the possession of the principal investigator until analyzed.

WILLINGNESS TO PARTICIPATE: Your participation in this research is entirely voluntary and if you choose not to participate, no punishment will be attached to your decision. You will not be paid any fees for participating in this research. You can choose to withdraw from the research at any time.

WHAT HAPPENS TO RESEARCH PARTICIPANTS AND COMMUNITY WHEN THE RESEARCH IS OVER: The researcher will inform you of the outcome of the research if you so wish. There is no conflict of interest whatsoever.

For further enquiry, please contact:

Principal Investigator Contact:
Prof. Bosede B. Afolabi
Mobile Contact: +2348023154064
E-mail: bbafolabi@unilag.edu.ng
Dept. of Obstetrics and Gynaecology,
College of Medicine, University of Lagos/
Lagos University Teaching Hospital,
Idi-Araba, Lagos

Thank you for participating in this research.

REPLACE WITH STUDY SITE NAME

INFORMED CONSENT FORM

STATEMENT OF PERSON GIVING INFORMED CONSENT:

I have read the description of the research. I understand that my participation is voluntary. I know enough about the purpose, methods, risk and benefits of the research to judge that I want to take part in it. I give consent for the following to be done on me:

Tick which is applicable

[ ] All information concerning my health and pregnancy to be collected by the investigator

[ ] My blood samples to be taken for various tests relating to this research

[ ] My urine samples to be collected for tests relating to this research

[ ] The whole placenta to be collected and sent for testing (histology)

[ ] Only a little portion of my baby's placenta to be collected for testing (histology)

[ ] I am not willing to release any portion of the placenta for testing (histology)

I understand that I may freely stop being part of the study at any time. I have received a copy of this consent form to keep for myself.

Name of (print legal name): ……..

Signature: …… Thumb Print

Date of signature: …….

Study ID/ Hospital Number: ……

Witness Name: ……..

Signature: ……

Date: ……..

STATEMENT OF PRINCIPAL INVESTIGATOR (OR DESIGNEE):

I have fully explained this research to the respondent and given sufficient information, including the risk and benefit to make an informed decision.

Name: ……..

Title: ……

Signature: ……

Date of Signature: ……

Thank you for participating in this research.

APPENDIX 04

PATIENT LOCATOR FORM

DATE _____ INTERVIEWER Initial_____

STUDY ID# _____

On this form we collect information that will help us reach you when it's time for your follow-up visit. The information you give us will be kept in a separate and secured place from health records.
It will be used only to locate you for your follow-up if you persistently miss your appointment, and it will not be given to anyone else. We will not tell any contact anything except that you are participating in a health study.

1. Full name:_____ (_____)
   First Middle Last (Maiden)
2. Other names or nicknames: _____
3. Where were you born? _____ (City, State)
4. Residence address: _____

   _____

   (Apartment#, Street address, Major Landmark)

   _____
   (City) (State)
5. How long have you lived there? _____
6. Do you plan to move anytime soon? Yes ☐ No ☐
7. Do you know where to? _____
8. Who else lives there?

   a. Full Name: _____Relationship_____

   Phone no: _____

   b. Full Name: _____ Relationship_____

   Phone no: _____
9. What is your own Home Phone Nos: (i)_____; (ii)_____
10. Your Mobile Phone Nos: (i)_____; (ii)_____
11. Your Work phone No: _____

12. Work Address & Company name: _____; _____

13. Your e-mail address: _____

14. Best Contacts: Do you have friends or relatives who usually know how to reach you if you should move or leave the program?

(1) Full Name: _____

(First, Middle, Last)

Address: _____

Phone No: _____ Relationship: _____

E-mail address: _____

Work phone No: _____ Name of Company _____

APPENDIX 05

PIPSICKLE TRIAL

ENROLLMENT LOG

S/N	Enrollment Date	Study ID	Randomization Code	Name	Hospital Number	Phone No	Next Appointment Date
1.							
2.							
3.							
4.							
5.							
6.							
7.							
8.							
9.							
10							
11							
12							
13							

APPENDIX 06 – e-ENROLLMENT

Confidential

Enrollment

Record ID _____

Study Site _____

SECTION A: GENERAL INFORMATION

Date of Enrollment _____

Study ID _____

Randomization Code _____

Hospital Number _____

Patient Name

_____

(First Name)

_____

(Middle Name)

_____

(Surname)

Date of Birth

_____

(Best Estimate)

Age

_____

Marital Status

- ○ Married
- ○ Single
- ○ Widow
- ○ Divorced
- ○ Separated
- ○ Cohabiting

Phone Number

_____

Phone Number of Husband/Partner

_____

Phone Number of Other Close Relative

Place of Residence Urban Rural

Address ○ ○

Landmark

(Nearest Popular Landmark)

Ethnicity Hausa Igbo Yoruba

○ Others ○ ○

Others

Highest Level of Education
- No formal education
- Completed Primary
- Completed Secondary
- Completed Tertiary
- Postgraduate

Occupation
- Unemployed
- Self-Employed
- Government Employment
- Private Employment

Estimated Monthly Income
- Less than N20,000
- N21, 000 - N50,000
- N51, 000 - N100,000
- N101, 000 - N200,000
- GREATER THAN N200,000

Haemoglobin Genotype ○ Hb SS ○ Hb SC

SECTION B: OBSTETRIC HISTORY

No. of Pregnancies

_____

Parity

_____

No. of Miscarriages

_____

(including VTOP & Ectopic)

No. of Children Alive

_____

Last Menstrual Period

_____

Last Menstrual Period Given? ○ By Known Date ○ By Scan Date

Expected Delivery Date

_____

Estimated Gestational Age at booking by LMP

_____

(weeks)

_____

(days)

SECTION C: HISTORY OF CHRONIC MEDICAL CONDITION

Have you been diagnosed as having diabetes?	Yes	No	Don't Know
Have you been diagnosed as being HIV positive?	Yes	No	Don't Know
Have you been diagnosed as having hypertension?	Yes	No	Don't Know
Have you been diagnosed as having renal disease?	Yes	No	Don't Know

Have you been diagnosed as having sickle cell nephropathy?

○ Yes ○ No ○ Don't Know

Do you have any other chronic medical condition?

○ Yes ○ No

Specify

_____

(Other Medical Conditions)

SECTION D: DRUG USE AND ALLERGY HISTORY

Do you react to aspirin?

○ Yes ○ No

What is the nature of reaction?

_____

Do you have Penicillin Allergy?

○ Yes ○ No

What is the nature of reaction?

_____

Are you on any of the following drugs?

- [ ] None
- [ ] Paludrine
- [ ] Hydroxyurea
- [ ] Folic Acid
- [ ] Penicillin V
- [ ] Multivitamin
- [ ] Ciklavit
- [ ] Astymin
- [ ] Jobelyn
- [ ] Vitamin B
- [ ] Vitamin C
- [ ] Others

Other Drugs

_____

SECTION E: PHYSICAL EXAMINATIONS

Weight

_____

(kg - 2 Decimal Places)

Weight

_____

(g)

Height

_____

(cm - 2 decimal places)

BMI

_____

Fundal Height

_____

(corresponding to week size)

BP

_____

(Systolic)

_____

(Diastolic)

Pulse Rate

_____

Pulse Oximetry (SpO2)

_____

(%)

Respiratory Rate

_____

Temperature _____

LABORATORY

Sample for Haemoglobin Fraction Taken ○ Yes ○ No

Sample for Full Blood Count ○ Yes ○ No

Haemoglobin Level (At Today Visit) _____ (g)

URINALYSIS TODAY

Leukocyte - ± + ++ +++

Nitrite - ± +

Urobilinogen Negative Positive

Protein - ± + ++ +++ ++++

Random Urine Sample Sent for UPCR Yes No

pH _____

Blood Negative Positive

Specific Gravity _____

Ketones	○ Negative ○ Positive
Bilirubin	○ Negative ○ Positive
Glucose	○ - ○ ± ○ + ○ ++ ○ +++ ○ ++++

ULTRASOUND

Date of Result

_____

Ultrasound Report

_____

Ultrasound result

STUDY DRUG

Patient Given Study Drug? ○ Yes ○ No

Name of Clinician _____

APPENDIX 07 e-follow up visit

Confidential

Visit

Record ID

_____

Date of Follow-up Visit

_____

_____

Gestational Age at FollowUp Visit

_____

(weeks)

_____

(days)

FollowUp Visit Type	Scheduled	Unscheduled

Reason for Unscheduled Follow-Up Visit	Sickle Cell Crisis
	Pregnancy Complications
	Adverse Event Report

	○ Others
Sickle Cell Crisis	○ Vaso-occlusive ○ Haemolytic ○ Sequestration ○ Acute Chest Syndrome (ACS) ○ Anaemia/Haemolytic ○ Others (Specify)
Others	_____
Pregnancy Complications	_____ (Specify)
Other Reason for Unscheduled Followup	_____ (please specify)

ADVERSE EVENTS REPORT

Is there an Adverse Event (AE)?	Yes No
Adverse Event (AE) - 1	_____ (Brief description of the nature of AE)
Start Date	_____ (dd-mm-yyyy)
Stop Date	_____ (dd-mm-yyyy)
Severity	Mild Moderate Severe (SAE)
Category of AE	Life Threatening Hospitalization Congenital anomaly Required intervention to prevent permanent impairment Persistent Disability / Incapacity Other
Other (Category of AE)	_____
Relationship of AE to Study Drug	Unrelated Possibly Related Probably Related

☐ Definitely Related

Action Taken

☐ No action taken (i.e. further observation only)

☐ Study drug dosage adjusted/temporarily interrupted

☐ Study drug permanently discontinued due to this adverse event

☐ Concomitant medication given

☐ Non-drug therapy given

☐ Patient hospitalized/patient's hospitalization prolonged

Add Another Adverse Event (AE)?

○ Yes ○ No

Adverse Event (AE) - 2

_____

(Brief description of the nature of AE)

Start Date

_____

(dd-mm-yyyy)

Stop Date

_____

(dd-mm-yyyy)

Severity	Mild Moderate Severe (SAE)
Category of AE	Life Threatening Hospitalization Congenital anomaly Required intervention to prevent permanent impairment Persistent Disability / Incapacity Other
Other (Category of AE)	_____
Relationship of AE to Study	Unrelated Possibly Related Probably Related Definitely Related
Action Taken	No action taken (i.e. further observation only) Study drug dosage adjusted/temporarily interrupted Study drug permanently discontinued due to this adverse event Concomitant medication given Non-drug therapy given Patient hospitalized/patient's hospitalization prolonged
Add Another Adverse Event (AE)?	Yes No
Adverse Event (AE) - 3	_____ (Brief description of the nature of AE)

Start Date	_____ (dd-mm-yyyy)
Stop Date	_____ (dd-mm-yyyy)
Severity	Mild Moderate Severe (SAE)
Category of AE	Life Threatening Hospitalization Congenital anomaly Required intervention to prevent permanent impairment Persistent Disability / Incapacity Other
Other (Category of AE)	_____
Relationship of AE to Study Drug	Unrelated Possibly Related Probably Related Definitely Related

Action Taken	No action taken (i.e. further observation only) Study drug dosage adjusted/temporarily interrupted Study drug permanently discontinued due to this adverse event Concomitant medication given Non-drug therapy given Patient hospitalized/patient's hospitalization prolonged
Any Admission since last visit?	Yes No
if yes: Specify reason	_____
Duration	_____
	Day(s) Week(s) Month(s)
Have you had blood transfusion since last visit?	Yes No
Date of blood transfusion?	_____
How many units of blood?	_____
Are you on any of the following drugs?	None Paludrine Hydroxyurea Folic Acid Penicillin V

☐ Multivitamin

☐ Ciklavit

☐ Astymin

☐ Jobelyn

☐ Vitamin B

☐ Vitamin C

☐ Others

Others

_____

PHYSICAL EXAMINATIONS

Weight

_____

(kg - 2 Decimal Places)

Weight

_____

(g)

Fundal Height

_____

(corresponding to week size)

BP

_____

(Systolic)

_____

(Diastolic)

Pulse Rate

_____

Pulse Oximetry (SpO2)

_____

Respiratory Rate

_____

Temperature

_____

LABORATORY

Haemoglobin Level (At Today Visit)

_____

(g)

Urinalysis Today

Leukocyte - ± + ++ +++

Nitrite - ± +

Urobilinogen Negative Positive

Protein - ± + ++ +++ ++++

Random Urine Sample Sent for UPCR Yes No

pH _____

	Negative	Positive
Blood	○	○
Specific Gravity		_____
Ketones	○	○
Bilirubin	○	○

Glucose ○ - ○ ± ○ + ○ ++

○ +++ ○ ++++

Full Blood Count

Date of Full Blood Count Result

_____

PCV

_____

(%)

Haemoglobin

_____

(g/dl)

Total WBC

_____

(cells/ml)

Neutrophils

_____

(%)

Lymphocytes

_____

(%)

Basophils

_____

(%)

Eosinophils

_____

Monocytes

_____

(%)

Platelet Count

_____

(cells/ml)

FBC Result

Is Urine M/C/S Result Available? Yes No

○ ○

Urine M/C/S Result Date

_____

Urine M/C/S Result

_____

Haemoglobin Fraction

Date of Haemoglobin Fraction

_____

☐ Hb S

☐ Hb F

☐ Hb A2

☐ Hb A1C

☐ Hb C

☐ Other

Hb S

_____

Hb F

_____

Hb A2

_____

Hb A1C

_____

Hb C

_____

Hb Other

_____

Haemoglobin Fraction Result

Date UPCR Done

_____

UPCR Result

_____

(Last Sample Collected)

ULTRASOUND

Date of Ultrasound Result

_____

Ultrasound Report

_____

Ultrasound Result

Clinical Plan

☐ Stable continue present management

☐ Change in clinical plan

☐ Change in other co-medication

☐ Additional Medication or Discontinuation

☐ Others

Change in Clinical Plan

_____

(Specify)

Change in Medication

_____

(Specify)

Additional Medication or Discontinuation

_____

(Specify)

Other

_____

Referrals Made

- ☐ None
- ☐ Hospitalization
- ☐ Blood Transfusion
- ☐ Nutritional Support
- ☐ Psychosocial counseling
- ☐ Social support
- ☐ Other

Other

_____

STUDY DRUG

Patient Given Study Drugs? ○ Yes ○ No

Pill Count from Last Visit

_____

(Pill Remaining)

Study Drug Adherence (Since Last Visit)

_____

(%)

Name of Clinician

_____

Delivery

Record ID

_____

Pregnancy Outcome

- Miscarriage
- Pre-term Delivery
- Term Delivery

Date of Miscarriage / Delivery

_____

Gestation Age at Miscarriage / Delivery

_____

_____

(weeks)

_____

(days)

BABY'S CONDITION AT BIRTH

Foetal Outcome

- Alive
- Still Born
- Early Neonatal Death - Within 7 days of birth
- NNU Admission after 24 hrs Initial Observation
- Congenital Abnormality

Indication for Admission / Diagnosis

_____

Congenital Abnormality

(Describe or Diagnosis)

_____

Baby's Birth Weight

_____

(g)

Head Circumference

_____

(cm - 2 decimal places)

Baby's Length

_____

(cm - 2 decimal places)

Apgar Score

	_____ (at 1 minute)
	_____ (at 5 minutes)
	_____ (at 10 minutes)

MATERNAL CONDITION AT MISCARRIAGE / DELIVERY

Maternal Complications	Pre-Eclampsia Eclampsia Sepsis Pneumonia Sickle Cell Crisis Maternal Death Others
Others	_____ (Specify)
Sickle Cell Crisis	Vaso-occlusive Haemolytic Sequestration Acute Chest Syndrome (ACS) Severe Anaemia Others

Others

_____

(Specify)

Estimated Blood Loss

- < 500 ml
- 500 - 1000 ml
- > 1000 ml

Mother Physical Examination Within 1 Hour of Delivery

Maternal Weight

_____

(kg - 2 Decimal Places)

BP

_____

(Systolic)

_____

(Diastolic)

Pulse Rate

_____

Pulse Oximetry (SpO2)

_____

Respiratory Rate

_____

Temperature

_____

LABORATORY

Haemoglobin Level

_____

(At Today Visit)

Urinalysis Today

Leukocyte - ± + ++ +++

Nitrite - ± +

Urobilinogen Negative Positive

Protein - ± + ++ +++ ++++

Random Urine Sample Sent for UPCR Yes No

pH _____

	Negative	Positive
Blood	○	○
Specific Gravity	_____	
Ketones	○	○
Bilirubin	○	○

Full Blood Count

Sample Taken for FBC ○ Yes ○ No

PCV

_____

(%)

Haemoglobin

_____

(g/dl)

Total WBC

_____

(cells/ml)

Neutrophils

_____

(%)

Lymphocytes

_____

(%)

Basophils

_____

(%)

Eosinophils

_____

Monocytes

_____

(%)

Platelet Count

_____

(cells/ml)

Full Blood Count Result

Name of Clinician

_____

APPENDIX 09 – e-End of study

Confidential

End of Study

Record ID	_____
Please enter the date this form is completed	_____
End of Study Category	Normal Withdraw Death LTFU
Date of death	_____
Cause of Death	_____
	_____
Gestational Age At Death	_____ (weeks)
	_____ (days)
Outcome of Severe Adverse Event (SAE)	Never had SAE SAE Resolved

Recovered with minor sequelae

Recovered with major sequelae

○ Ongoing treatment

○ Condition worsening

○ Death

○ Unknown

APPENDIX 09 – DRUG ACCOUNTABILITY FORM

PIPSICKLE TRIAL

INVESTIGATIONAL DRUG ACCOUNTABILITY RECORD

Study site Name:	
Site Code:	**Total Quantity Received/Date:** (including Replacement kits)
Site Investigator:	**Test Drug:**
Study Title:	**Batch No. :**
	Mfg Date :
	Expiry Date :

Subject initials	Subject ID	Drug Kit Number/ RC	Visit type (E or F)	Date dispensed	Dispensed By/Initials	Date Returned	Amount of Drug present	Site personnel Signature	CRA/Monitor Signature

RC- Randomisation code E= Enrollment F- Follow-up

APPENDIX 11– SAE REPORT FORM

SEVERE ADVERSE EVENT (SAE) REPORT FORM

STUDY TITLE	Low dose aspirin for preventing intrauterine growth restriction and preeclampsia in sickle cell pregnancy (PIPSICKLE): a randomised controlled trial.		
Site No.			
SITE Name			
PATIENT ID		DATE OF REPORT	dd-mm-yyyy

1.	SAE Date of Onset:	dd-mm-yyyy	
2.	SAE Date Stopped:	dd-mm-yyyy	
3.	Location of SAE:		
4.	Was this an unexpected adverse event?	☐ Yes ☐ No	
5.	Brief description of participants (do not include personal identifiers):	Age	
		Diagnosis for study participation	
6.	Brief description of the nature of the SAE: *attach description, if applicable*		
7.	Category of SAE:	☐ Date of Death: dd-mm-yyyy ☐ Life threatening ☐ Congenital anomaly, birth defects ☐ Life threatening ☐ Required intervention to prevent impairment (permanent) ☐ Hospitalization ☐ Disability	

		☐ Other:
8.	Describe study intervention	
9.	Relationship of event to intervention:	☐ Unrelated ☐ Possible ☐ Definite
10.	Was the study intervention discontinued due to the event?	☐ Yes ☐ No
11.	What steps were taken to treat the SAE?	
12.	List relevant tests, lab data, history, and pre-existing medical conditions:	
13.	Report type:	☐ Initial ☐ Follow-up ☐ Final

Print Name of Site Investigator

Signature of Principal Investigator *Date*

Print Name of Principal Investigator

Signature of Principal Investigator *Date*

APPENDIX 12 – STUDY MONITORING LOG

PIPSICKLE TRIAL STUDY INITIATION CHECKLIST

STUDY TITLE	**Low dose aspirin for preventing intrauterine growth restriction and preeclampsia in sickle cell pregnancy (PIPSICKLE): a randomised controlled trial.**
SITE NAME ; CODE	
SITE INVESTIGATOR	
MONITOR NAME	
DATE OF VISIT	
METHOD OF VISIT	☐ On-Site ☐ Teleconference ☐ Other, specify:

List personnel in attendance from site, below. Attach attendance sheet.

NAME, TITLE	ROLE

Verify each document or activity required below. Attach any supporting documentation.

NO.	DOCUMENT OR ACTIVITY (DISCUSSED/VERIFIED)	YES	NO	N/A	COMMENTS
1	Staff CVs signed/dated	☐	☐	☐	
2	Staff trained on protocol	☐	☐	☐	
3	Staff read investigator brochure for product	☐	☐	☐	
4	Check required number of forms delivered to site (i.e. consent forms, case forms).	☐	☐	☐	
5	PI and site have agreed to study contract and budget.	☐	☐	☐	
6	HREC/IRB approval granted/renewed for study.	☐	☐	☐	
7	Staffing allocation complete.	☐	☐	☐	
8	Specific staff responsibilities discussed with staff	☐	☐	☐	
9	Required facilities are available/functional.	☐	☐	☐	
10	Study drugs stored appropriately.	☐	☐	☐	
11	Materials/equipment for study available/received.	☐	☐	☐	
12	Materials/equipment for study stored and maintained appropriately	☐	☐	☐	
13	Investigator's file prepared and maintained	☐	☐	☐	
14	Final contract and budget signed and filed.	☐	☐	☐	
15	e-case forms available (if applicable)	☐	☐	☐	
16	Drug shipment received (if applicable)	☐	☐	☐	

NO.	DOCUMENT OR ACTIVITY (DISCUSSED/VERIFIED)	YES	NO	N/A	COMMENTS
17	Other supplies received (if applicable)	☐	☐	☐	

Name of Monitor (Print)

Monitor Signature *Date*

Name of Principal Investigator (Print)

Principal Investigator Signature *Date*

APPENDIX 13-

PROTOCOL DEVIATION TRACKING LOG

NO.	SUBJECT ID NO.	DEVIATION DATE	DEVIATION DESCRIPTION	DEVIATION REASON AND CORRECTIVE MEASURES	IRB / IEC NOTIFICATION Yes / No	INVESTIGATOR INITIALS	INVESTIGATION DATE