Application for Institutional Review Board (I.R.B) Clearance

1.	Title of the Study	: **Low dose Aspirin in prevention of Preeclampsia**
2.	Principal Investigator (PI)/ Name of student:	: Dr. Shapla khatun
3.	Name of present course	: MS (Obs & Gynae).
4.	Joining date in phase B	: 1st September,2017
5.	Name of institute	: BIRDEM General Hospital
6.	Expected date of examination	: July, 2020.
7.	Guide/ Advisor	: Prof. Ferdousi Begum MBBS,FCPS(Obs & Gynae) Head of the Dept. of Obs & Gynae BIRDEM-II General Hospital .
8.	Place of study	: Department of Obstetrics and Gynaecology, BIRDEM-II General hospital. Shegunbagicha, Dhaka, Bangladesh.
9.	Type of study	: Randomized controlled trial.
10.	Duration of study	: 1 year from the date of IRB approval.
11.	Total cost	: Ninty six thousands
12.	Funding Agency (If Applicable)	: Self.

We agree to obtain approval of the Institutional Review Board of BIRDEM for any changes involving the rights and welfare of subjects or any changes of Methodology before making it.

Principal Investigator/Student Guide

To

The Chairman,

Institutional review Board (IRB),

BIRDEM General Hospital,

Shahbag, Dhaka-1000.

Subject: **Application for the ethical clearance**

Respected Sir,

With due respect I would like to state that I am Dr. Shapla khatun, Phase-B Resident of MS Course (Residency Program) of Obstetrics & Gynaecology at BIRDEM, Shegunbagicha, Dhaka. As a part of my MS Course, I have chosen my thesis title **'Low Dose Aspirin in prevention of pre-eclampsia'.** Prof. Dr.Ferdousi Begum, Department of Obstetrics and Gynaecology, BIRDEM-II has given her kind permission to be my thesis guide.

I am now seeking permission for the ethical clearance from IRB for my study. I agree to obtain approval of the Institutional review board for any changes involving the rights and welfare of subjects or any changes of the methodology before making any such changes.

Principal Investigator

Dr.Shapla Khatun

Resident, MS (Phase-B)

Dept. of Obstetrics and Gynaecology,

BIRDEM-II

Guide

Prof. Dr.Ferdousi Begum

Head of the department.

Dept.of Obstetrics and Gynaecology,
BIRDEM-II General Hospital.

To

The Chairman,

Institutional Review Board (IRB),

BIRDEM General Hospital

Shahbag, Dhaka - 1000.

Subject: Application for IRB clearance of thesis research protocol

Respected Sir,

With due respect I would like to state that I am Dr. Shapla Khatun, Phase-B Resident of MS Course (Residency Program) of Obstetrics & Gynaecology at BIRDEM, Shegunbagicha, Dhaka. As a part of my MS Course, I have chosen my thesis title **'Low dose Aspirin in prevention of Pre-eclampsia'.** Prof. Dr. Ferdousi Begum, Department of Obstetrics and Gynaecology, BIRDEM has given her kind permission to be my thesis guide.

Therefore, I pray that you would be kind enough to approve my thesis protocol.

Yours sincerely,

Dr. Shapla khatun

Resident, MS (Phase-B)

Department of Obstetrics and Gynaecology,

BIRDEM-II General Hospital

Shegunbagicha, Dhaka- 1000.

To

The Head of the Department,

Department of Obstetrics & Gynaecology,

BIRDEM-II, Shegunbagicha,Dhaka-1000.

Subject: Prayer for approval of thesis protocol on ethical issue.

Respected madam,

With due respect and humble submission, I would like to state that I am a Phase-B Resident of MS Course of Obstetrics & Gynaecology at BIRDEM –II, Shegunbagicha, Dhaka. As a part of the Course, I would like to conduct my thesis

'Low dose Aspirin in prevention of pre-eclampsia'.

Therefore I pray and hope that you would be kind enough to approve my thesis protocol and allow me to conduct this study after necessary formalities.

Yours sincerely,

Dr. Shapla Khatun

Resident, MS, Phase-B

Department of Obstetrics and Gynaecology,

BIRDEM-II General Hospital

Shegunbagicha, Dhaka-1000.

Contents

THESIS PROTOCOL

Title: Low dose Aspirin in prevention of pre-eclampsia

Investigator:
Dr. Shapla Khatun
MS (Obs and Gynae),
Resident,Phase-B
Department of Obstetrics and Gynaecology
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Supervisor:
Prof.Dr. Ferdousi Begum Professor & Head of department
Department of Obstetrics and Gynaecology BIRDEM-II,
Shegunbagicha,Dhaka-1000.

Place of study: Department of Obstetrics and Gynaecology
BIRDEM-II General Hospital,Shegunbagicha, Dhaka.

Protocol Proposal

1. **Project title:** **Low dose Aspirin in prevention of pre-eclampsia.**
2. **Investigator:** **Dr. Shapla Khatun**
   MS, Phase-B Resident
   Obstetrics & Gynaecocolgy.
3. **Guide:** **Prof.Dr. Ferdousi Begum**
   MBBS, FCPS, (Obstetrics and Gynaecology)
   Professor & Head of the Department
   Obstetrics and Gynaecology, BIRDEM-II,
   Shegunbagicha, Dhaka-1000.
4. **Place of Study:** Department of Obstetrics & Gynaecology, Bangladesh Institute of Research & Rehabilitation for Diabetes, Endocrine& Metabolic Disorders (BIRDEM), Shegunbagicha, Dhaka.
5. **Sponsoring/ Collaboration agencies:** Not applicable.
6. **Duration of study:** One (1) year.
7. **Date:** From the day of IRB approval.
8. **Total cost:** 96,000/- (Ninty six thousands taka only).
9. **Other supports for proposed research:** Not applicable.
10. **Date of joining (Phase B):** September, 2017.
11. **Proposed date of exam:** July, 2020.

We agree to obtain approval of the Institutional Review Board of BIRDEM-II for any changes involving the rights and welfare of the subject or any changes of the methodology before making it.

Name and Signature of the investigator:

Dr. Shapla Khatun

Student of MS (Obs. & Gynae),

Phase-B (Residency)

Department of Obstetrics & Gynaecology,

BIRDEM-II,Shegunbagicha,Dhaka-1000 **Signature:**

Name and signature of the guide:

Prof . Dr. Ferdousi Begum

MBBS, FCPS, (Obs & Gynae) Professor

& Head of the department Department of

Obstetrics & Gynaecology, BIRDEM-II,

Shegunbagicha,Dhaka-1000. **Signature:**

Abstract for IRB

Background

Preeclampsia is a pregnancy-specific multisystem disorder of unknown etiology. PE typically affects 2%–5% of pregnant women and is one of the leading causes of maternal and perinatal morbidity and mortality, especially when the condition is of early onset(FIGO‟2019)The exact nature of the primary event causing preeclampsia is not known. (Arias‟ 2015).There is now good evidence that intake of low dose aspirin during pregnancy reduces the risk of pre-eclampsia. Uncertainty remains, about whether some women(in terms of risks) benefit more than others, what dose of aspirin is best & when in pregnancy treatment should ideally start. Therefore this study is developed to find out the role of aspirin in preeclampsia, the knowledge of which expected to be used for prevention of preeclampsia .

Objective of the study:

Aim of study is to find out the effect of low dose aspirin in prevention of preeclampsia among pregnant women who are at high risk for developing preeclampsia.

Methodology

This Randomized clinical trial will be conducted in BIRDEM-II.Approval from Institutional Review Board will be taken. The study population will be pregnant women with risk factors for developing PE attending department of Obstetrics and Gynecology, BIRDEM-II. Pregnancy will be confirmed via USG.Then evaluation of risk factors of PE will be done by history taking, examinations & provided investigations.Those who will be eligibile according to inclusion & exclusion criteria will be enrolled in the study.Trial information will be provided verbally & with a written information sheet. Participants will be randomized by lottery in a closed envelope,which will determine who receive aspirin daily & who will not. A total of 200 women will be included in the study, of whom 100 pregnant women having risk factors of developing pre-eclampsia will be in intervention group & another 100 pregnant women having risk factors for developing PE will be in control group.Intervention group will be prescribed to take 75 mg Aspirin daily after lunch starting from 12-19 weeks of pregnancy.Control group will not be prescribed to take Aspirin. For each and every subject separate data collection sheet will be prepared. Data will be collected from the patients using the structured design by history, clinical examination, urine & haematological investigations, ultrasonography of the patients. Both group of patients will get the usual advices & medications of pregnancy.All patients will be followed up at 19-24 weeks, 32-34 weeks of gestation, 36 weeks of gestation and weekly up to delivery. During follow up SBP & DBP will be carefully measured. Urine analysis will be done. Aspirin will be stopped either 36 weeks of pregnancy or when delivery occurs or when PE is diagnosed. Primary & Secondary outcome will be observed in both experimental & control group separately.Then analysis will be done by comparison of outcome of this two groups. Data will be analyzed using SPSS software.

RESULT: Result will be incorporated after completion of study.

CONCLUSION: Will be incorporated after completion of study.

Introduction

Preeclampsia is a multi-organ diseases of unknown etiology characterized by de novo development of hypertension and proteinuria after 20 weeks of gestation, sometimes progressing into a multi-organ cluster of varying clinical features.(Arias,2015). PE typically affects 2%–5% of pregnant women and is one of the leading causes of maternal and perinatal morbidity and mortality, especially when the condition is of early onset. Globally, 76,000 women and 500000 babies die each year from this disorder.(Poon L et al.2019). WHO estimates incidence of pre-eclamsia, to be seven times higher in developing countries (2.4% of live birth) than in developed countries (0.4%) (WHO, 2005). In Bangladesh, the incidence of preeclampsia is alarmingly high, about 20% of maternal death associated with PE and eclampsia (Landscape analysis,2015).

The risk of preeclampsia is increased three-fold in nulliparous women (Duckitt et al.2005).Among parous women the risk of PE in subsequent pregnancies depends on a prior history of PE (Harnandez-Diaz et al.2009).Other risk factors have been identified-maternal age ≥35years,both short (<12months) & long interpregnancy intervals(>6years), ART, Family history of PE, obesity(BMI ≥30kg/$m^{\pm}$),comorbidities-hyperglycaemia in pregnancy, chronic HTN, renal disease, autoimmune disease-SLE,APS (FIGO,2019). In low socio economic status of women doubled the risk of pre -eclampsia and eclampsia (Ceron-Mireles et al. 2001).

Complication related to preeclampsia include preterm birth, intrauterine fetal growth restriction, placental abruption, maternal pulmonary edema, and eclampsia .The estimated incidence of eclampsia is 1-3 per 1000 preeclamptic patients. (CURRENT 2013).

In preeclamptic patients, prostacyclin synthesis is decreased & thromboxane production is increased, leading to vasoconstriction & platelet aggregation. Prostacyclin & thromboxane are products of the metabolism of Arachidonic acid by

the enzyme cyclooxygenase (Arias,2015).Aspirin (acetylsalicylic acid) is a nonsteroidal anti-inflammatory drug (NSAID) that works primarily through its inhibition of two cyclooxygenase isoenzymes (COX-1 and COX-2), which are necessary for prostaglandin biosynthesis. The effect of aspirin on COX-dependent prostaglandin synthesis is dose dependent. At lower dosages (60–150 mg/day) aspirin irreversibly acetylates COX-1, resulting in decreased platelet synthesis of TXA2 without affecting vascular wall production of prostacyclin (Clarke et al.1991 & Patrono C, 1994). At higher doses, aspirin inhibits both COX-1 and COX-2, effectively blocking all prostaglandin production.

Research is focusing on prevention rather than treatment.Cochrane meta analysis published in 2004 reported that the administration of antiplatelet agents in high risk women could reduce the rate of PE by 19%(Lowe et al. 2014). World Health Organization (WHO) and NICE and the US Preventive Services Task Force (USPSTF) currently recommend daily low-dose aspirin therapy beginning at 12 weeks of gestation in patients who are considered to be at “high risk for preeclampsia” according to medical and obstetrical criteria. FIGO also recommends that 150mg aspirin at night should be commenced at 11-14^{+6} weeks of gestation and continued until either 36 weeks of gestation or when delivery occurs, or when preeclampsia is diagnosed (FIGO,2019).It has an excellent maternal/fetal safety profile in pregnancy.Therefore we decided to conduct a RCT in BIRDEM-II General Hospital to evaluate the role of low dose Aspirin in prophylactic treatment for prevention of PE.

1.2 Rationale of the Study

Preeclampsia is a hypertensive disorder specific to pregnancy that remains a significant cause of maternal & neonatal morbidity & mortality. Because of the potential negative health consequences of PE for women & newborns & the lack of effective screening mechanisms, preventing PE is an important component of prenatal care. Bangladesh Maternal Mortality survey(BMMS) 2010 revealed that eclampsia is the second most common direct cause of maternal death in Bangladesh followed by PPH.Among 5000 to 6000 maternal deaths each year,1000 to 1,200 are due to Eclampsia.(Landscape report,2015). Preeclampsia should be detected and appropriately managed before the onset of convulsions (eclampsia) and other life-threatening complications.

Since there is no curative treatment other than delivery, an intervention that could prevent preeclampsia would have a significant impact on maternal and infant health worldwide. Researchers have documented that low dose aspirin during antenatal check- up can prevent the development of PE who are at high risk of developing PE and also reduce the incidence of pre-term birth & fetal growth restriction. The relevant evidence of Asian women is very limited. Its safety is sometimes questionable. BIRDEM is a center of excellence where majority patients are diabetic and so many high risk for developing PE. Therefore, this study has been designed to evaluate the role of aspirin in reducing the incidence of preeclampsia including its dose and duration of use & safety of the drug.

1.3 Hypothesis

Research question:

Can low dose aspirin prevent preeclampsia in the pregnant women who are at risk of developing pre-eclampsia?

Hypothesis:

Low dose aspirin can lower the development of preeclampsia in pregnant women who are at high risk of developing preeclampsia

1.4 Objectives

General objective

- To find out the effect of low dose aspirin in prevention of preeclampsia among pregnant women who are at high risk for developing preeclampsia.

Specific objectives

- To find out the socio-demographic characteristics (Age, Occupation,
- To find out the primary outcome (occurrence of Preeclampsia) among both intervention & control group.
- To detect the secondary outcome among both groups: Maternal- Gestational HTN, Oligohydramnios, Preterm labor, Placental abruption, APH, PPH ; Fetal- LBW, Preterm birth , Small for gestational age, IUD,Still Birth, NICU admission among both groups.
- To compare the outcome of two groups.
- To analyze the possible association between Aspirin & Pre-eclampsia.

1.5 Review of Literatures

YUECHONG CUI et al (2018) performed a systematic review and meta‑analysis of RCTs that evaluated the effect of aspirin intake during pregnancy was performed. Relevant citations from January 1979 until October 2017 were extracted from the Embase, PubMed, Cochrane Central Register of Controlled Trials and Web of Science databases. All 10 RCTs evaluated the effect of low‑dose aspirin for the prevention of preeclampsia irrespective of the time to delivery . As no heterogeneity was identified (P=0.51, I2=0%), the fixed‑effects model was used for the meta‑analysis. The results indicated that, compared with placebo or no treatment, low dose aspirin was associated with a 33% reduction in the relative risk of preeclampsia regardless of the time to delivery (RR=0.68, 95% CI=0.57‑0.80; P<0.0001). Next, the efficacy in the two subgroups of preterm and term preeclampsia was evaluated . Analysis of the data from 6 RCTs indicated that low‑dose aspirin, administered at ≤16 weeks of gestation, was associated with a 65% reduction in the risk of preterm preeclampsia. By contrast, no reduction in the relative risk of term preeclampsia by administration of low‑dose aspirin was obtained (RR=1.01; 95% CI=0.60‑1.70). (YUECHONG CUI et al .2018).

Rolnik, D.L.,et al (2017) conducted multicenter, double-blind, placebo-controlled trial among women with singleton pregnancies who were at high risk for preterm preeclampsia. 798 participants in the aspirin group and 822 in the placebo group. Preterm preeclampsia occurred in 13 participants (1.6%) in the aspirin group, as compared with 35 (4.3%) in the placebo group (odds ratio in the aspirin group,0.38; 95% confidence interval, 0.20 to 0.74; P = 0.004). (Rolnik,D.L.,et al.2017).

Michael l. et al (2014) on behalf of the USPSTF considered 19 RCTs (12 good-quality) and 2 good-quality observational studies to evaluate maternal,perinatal, and developmental harms. Studies of low- or average-risk pregnant women were included with trials of women at increased risk. Eleven RCTs (23 332 women) reported on the

outcome of placental abruption (6 trials in women with increased preeclampsia risk and 5 trials in women with low/average risk). Pooled analyses showed no statistically significant increase in abruption associated with aspirin (RR, 1.17 [95% CI, 0.93 to 1.48]; I2 =36.4%).Eighteen trials reported on the outcome of perinatal mortality (with 4 smaller studies reporting no events).Pooled analyses (n = 22 848) on perinatal mortality (RR,0.92 [95% CI, 0.76 to 1.11]; 14 studies; I 2 = 0%) suggested no harm from low-dose aspirin. Nine trials (6 in women at increased preeclampsia risk and 3 in women at low risk; 22 760 women in total) reported on the outcome of postpartum hemorrhage.There was no evidence of a treatment effect (RR, 1.02 [95% CI, 0.96 to 1.09]) No evidence demonstrated that low-dose aspirin affected blood loss. The pooled relative risk for intracranial hemorrhage in neonates (6 studies; n = 22 158) was 0.84 (95% CI, 0.61 to 1.16), with low heterogeneity (I2 = 27.1%; P = 0.23). Maternal death was a rare outcome and could not be evaluated.(Michael L. et al 2014).

Askie LM1 et al (2007) performed randomised trials of pre-eclampsia primary prevention. For women assigned to receive antiplatelet agents rather than control, the relative risk of developing pre-eclampsia was 0.90 (95% CI 0.84-0.97), of delivering before 34 weeks was 0.90 (0.83-0.98), and of having a pregnancy with a serious adverse outcome was 0.90 (0.85-0.96). Antiplatelet agents had no significant effect on the risk of death of the fetus or baby, having a small for gestational age infant, or bleeding events for either the women or their babies. (Askie LM1 et al (2007).

2. Materials and Methods

2.1 Study design

This will be a Randomized controlled trial.

2.2 Place of study

Department of Obstetrics & Gynaecology, BIRDEM-II General hospital, Shegunbagicha, Dhaka.

2.3 Study Period- one year

2.4 Study Population

Pregnant women with high risk for developing preeclampsia at gestational age 12 to 19 weeks will be divided into two groups-

Intervention (Patients with intake of aspirin) group:

Will be assigned to take 75mg aspirin after lunch in full stomach.

Control (Patients without intake of aspirin) group:

Will not assign to take aspirin.

3.5 Sampling technique

Simple randomization through lottery in a closed envelope. Randomization number will determine who will receive aspirin & who will not receive aspirin.

2.6 Study Procedure :

This Randomized clinical trial will be conducted in BIRDEM-II. Approval from Institutional Review Board will be taken. The study population will be pregnant women with risk factors for developing PE attending department of Obstetrics and Gynecology, BIRDEM-II. Pregnancy will be confirmed via USG.Then evaluation of risk factors of PE will be done by history taking, examinations & provided investigations.Those who will be eligibile according to inclusion & exclusion criteria will be enrolled in the study.Trial information will be provided verbally & with a written information sheet. Participants will be randomized by lottery in a closed envelope,which will determine who receive aspirin daily & who will not. A total of 200 women will be included in the study, of whom 100 pregnant women having risk factors of developing pre-eclampsia will be in experimental group & another 100 pregnant women having risk factors for developing PE will be in control group.Experimental group will be prescribed to take 75 mg Aspirin daily after lunch from 12-19 weeks of pregnancy.Control group will not be prescribed to take Aspirin. For each and every subject separate data collection sheet will be prepared. Data will be collected from the patients using the structured design by history,clinical examination,urine & haematological investigations, USG of the patients. Both group of patients will get the usual advices & medications of pregnancy. All patients will be followed up at 19-24 weeks, 32-34 weeks of gestation, 36 weeks of gestation and weekly up to delivery. During follow up SBP & DBP will be carefully measured. Urine analysis will be done. Aspirin will be stopped either 36 weeks of pregnancy or when delivery occurs or when PE is diagnosed. Primary & Secondary outcome will be observed in both experimental & control group separately.Then analysis will be done by comparison of outcome of this two groups. Data will be analyzed using SPSS software.

2.7 Sample size determination:

Sample size is calculated using the following formula

$$n = \left[\frac{\sqrt{2\bar{p}(1-\bar{p})}\,Z_{\alpha} + \sqrt{p_1(1-p_1) + p_2(1-p_2)}\,Z_{\beta}}{p_1 - p_2}\right]^2$$

Here, n= sample size

p_1 = 1.6% [Incidence of preeclampsia in experimental group (Rolnik et al., 2017)]

p_2 = 8.71% [Incidence of preeclampsia high risk group(Poon L.C et.al., 2019)]

$$p = \frac{\quad}{\quad} = \frac{\quad}{\quad} = 5.155$$

Z_{α} = 1.96 at a 95% confidence interval

Z_{β} = 0.84 at a 80% power

Putting the values in the above equation the sample size n is estimates as

$$n = \left[\frac{\sqrt{2\bar{p}(1-\bar{p})}\,Z_{\alpha} + \sqrt{p_1(1-p_1) + p_2(1-p_2)}\,Z_{\beta}}{p_1 - p_2}\right]^2 = 150.30 \approx 150$$

According to sample size determination it will be 150 in each group but 100 sample size in each group will be taken due to limitation of time.

2.8 Selection Criteria-Pregnant women have to fulfill any 1 of the following criteria to enroll the study

Inclusion criteria for both groups:

- Maternal age ≥18years
- Advanced maternal age (≥35 years)
- BMI ≥ 30 kg/m^2
- Live foetus at gestational age 12 weeks - 19 weeks.
- Pregnancy interval >10 years.
- Multiple pregnancy.
- Pregnancy assisted by Ovulation inducing drugs/ In vitro fertilization.
- Pregnant women with medical disorders-Chronic HTN,Hyperglycaemia in pregnancy,Thyroid disorder ,Autoimmune disease-APS,SLE.
- Previous history of Gestational HTN,PE, Eclampsia
- Previous history of IUGR, IUD, Still Birth.
- Family history of HTN, Gestational HTN, PE (mother and/or sister)

Exclusion criteria for both groups:

- Allergic to Aspirin.
- Peptic ulcer disease.
- Mental disease.
- Patient with treatment of antifolate drugs (antiepileptics, methotrexate)
- Patient who will not give consent to participate.

2.9 Main outcome variables

Dependent variable

Pre-eclampsia

Independent variables

- Age
- Parity
- BMI
- Educational status
- Monthly income
- Occupation
- Blood pressure
- Proteinuria
- Aspirin

2.10 Operational definitions:

Hypertension: According to ACOG hypertension is defined as: BP equal to or greater than 140/90 mm of Hg, rise of systolic BP 30 mm of Hg or rise of diastolic BP 15 mm of Hg or more. (Arias‟ 2015)

Chronic HTN: Hypertension that was present before pregnancy or it was diagnosed before 20th week of gestation.

Internationally agreed definition of PE is that of the International Society for the Study of Hypertension in Pregnancy (ISSHP) which is endorsed by FIGO.

Gestational hypertension: is defined as systolic blood pressure (sBP) at ≥140 mm Hg and/or diastolic blood pressure (dBP) at ≥90 mm Hg on at least two occasions measured 4 hours apart developing after 20 weeks of gestation in previously normotensive women.

Preeclampsia: is defined as gestational hypertension accompanied by ≥1 of the following new-onset conditions at or after 20 weeks of gestation:

1.Proteinuria (i.e. ≥30 mg/mol protein:creatinine ratio; ≥300 mg/l in 24 hour; or ≥2 + dipstick)

2.Other maternal organ dysfunction:

- Acute kidney injury (creatinine ≥90 μmol/L; 1 mg/dL)
- Liver involvement (elevated alanine aminotransferase or aspartate aminotransferase >40 IU/L) with or without right upper quadrant or epigastric pain)
- Neurological complications (including eclampsia, altered mental status, blindness, stroke, or more commonly hyperreflexia when accompanied by clonus, severe headaches, and persistent visual scotomata)
- Hematological complications (thrombocytopenia–platelet count <150 000/μL, disseminated intravascular coagulation,hemolysis) or

3. Uteroplacental dysfunction (fetal growth restriction, abnormal umbilical artery Doppler waveform or stillbirth).

Superimposed PE on chronic hypertension:

• Women with chronic essential hypertension develop any of the above maternal organ dysfunctions consistent with PE

• Increase in blood pressure per se is not sufficient to diagnose superimposed PE

• In the absence of pre-existing proteinuria, new-onset proteinuria in the setting of a rise in blood pressure is sufficient to diagnose superimposed PE.

2.11 Research instruments

Structured questionnaire will be prepared for this purpose, which will include all the variables of interests.

2.12 Data collection technique

a) Interviewing for risk factor evaluation

b) Examination including-

- Blood pressure measurement

- Height ,Weight & BMI

c) Investigation Reports

Measurement of blood pressure : After 10 minutes rest, BP will be measured following standard procedure. Korotkoff phase 1(first beat heard) an phase V (disappearance of sound) will be used to determine systolic (SBP) and diastolic blood pressure (DBP) (Hendler et al., 2005).

Measurement of proteinuria: Proteinuria is measured by dipstick test at least two midstream urine samples 6 hrs apart, in the absence of urinary tract infection. Test for

protein in urine by multiple reagent strip (dipstick) as follows: Trace = 0.1 gm/L; 1+ = 0.3 gm/L; 2+ = 1.0 gm/L; 3+ = 3.0 gm/L; 4+ = 10.0 gm/L (Haugen et al., 2006).

2.13 Data presentation and analysis plan

- Statistical analyses will be carried out by using Windows based Statistical Package for Social Sciences (SPSS-22.0).
- For continuous variables, distributions will be expressed by mean and standard deviation. Mean comparisons between two groups will be done by student‟s t-test.
- For qualitative variables, distributions will be expressed by frequency and their percentages. Chi square tests will be done to see the significance of differences between two groups.
- Relative Risk (RR) and 95% confidence interval will also be estimated for the outcome.
- The p value <0.05 will be declared as statistically significant.

2.14 Time table: (Activities with time schedule)

Activities	September-November 2017	December-May2018	1st Three months	2nd Three months	3rd Three months	4th Three months
Phase I Topic selection, Literature search, Protocol writing & submission, Pretesting						
Phase II Data collection & compilation						
Phase III Data entry, edit and analysis						
Phase IV Report writing and submission						

2.15 Sample Table

Table 1 : Socio demographic characteristics of study population (N=)

Characterstics	**Intervention** **n= n%**	**Control** **n= n%**	**P value**
Age			
≤18 years			
19-34years			
≥ 35 yrs			
Parity			
Nulliparous			
Multipara			

Socio demographic characteristics of study population (N=)

Educational status			
Illiterate			
Primary			
SSC			
HSC and above			
Occupation			
Housewife			
Service holder			
Others			
Monthly income (tk)			
<10,000			
(10,000-20,000)			
(20,000-40,000)			
>40,000			

Table 2: Distribution of study groups by BMI (kg/m2) (N=)

BMI (KG/ m2)	**Intervention**		**Control**		**P value**
	n =	**n%**	**n =**	**n%**	
<18.5 (underweight)					
18.5-24.9 (normal)					
25-29.9 (overweight)					
30-39.9 (obese)					
Mean ± SD					

P value will be reached from chi square test.

2.16 Ethical Consideration

There is minimum physical, psychological, social and legal risk during taking history, physical examination and investigations. Proper safety measures will be taken in every step of the study. Only researcher will be allowed to access the collected data. Ethical clearance will be obtained from Institutional Review Board (IRB) of BIRDEM to undertake the current study. According to Helsinki Declaration for Medical Research involving Human Subjects 1964, all the patients will be informed about the study design, the underlying hypothesis and the right of the participants to withdraw themselves from the research at any time, for any reason. Informed written consent will be obtained from each subject who will voluntarily provide consent to participate in this study.

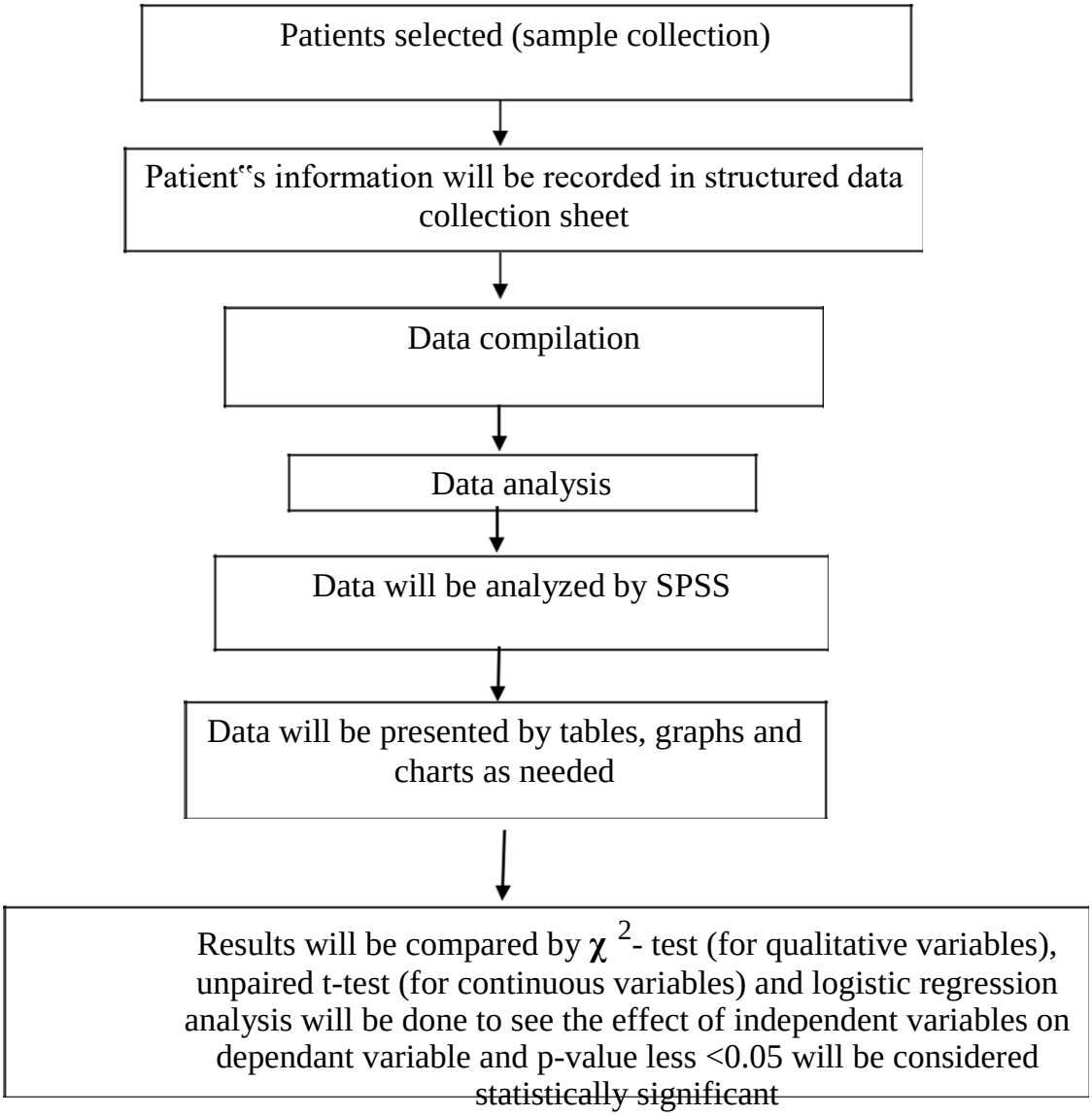
The following ethical issues will be addressed accordingly:

1. Strict confidentiality and security of data related to patient will be maintained. The presentation of data and information related to patient will be documented anonymously.
2. The data analysis will be completed on the subjects who complete the study according to protocol after recruitment of subjects with valid informed consent.
3. There is no additional risk or safety concern due to the research process to either patient or researcher.
4. There is no potential conflict of interest in this study and an entirely an academic research project.

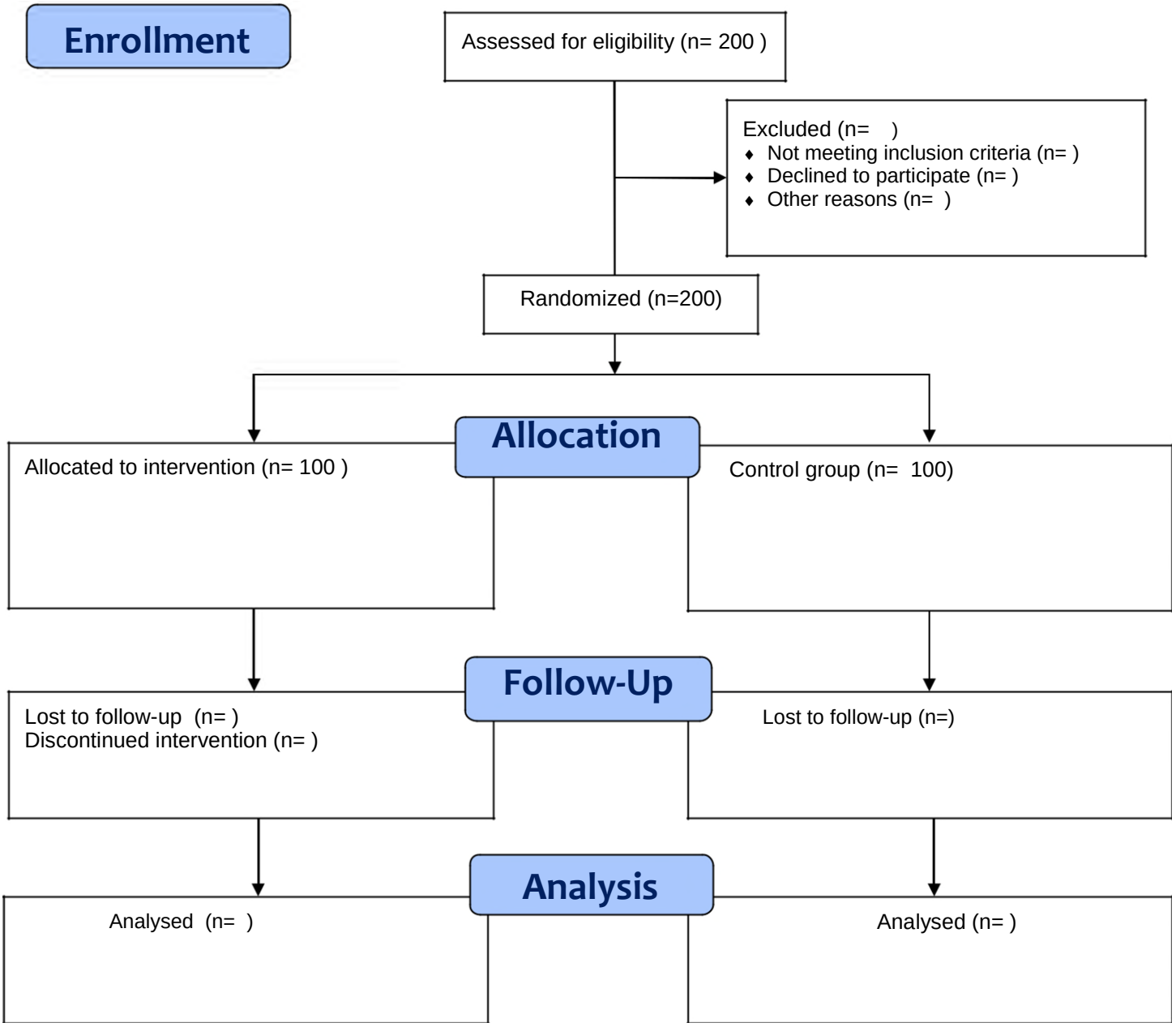
Procedure of maintaining confidentiality

1. For safeguarding confidentiality and protecting anonymity each of the patients will be given a special ID number which will be followed during examination and each and every step of the procedure.
2. A signed informed consent will be taken from the patient convincing that privacy of the patient will be maintained.
3. A data collection sheet will be enclosed for which a short interview will be required.
4. No experimental new drug will be administered.
5. No placebo will be used here.

2.17 Flow chart showing sequence of work



2.18 CONSORT Flow Diagram



3. Budget

Internet searching	2,000 Taka
Topic downloading	2,000 Taka
Books and literatures	2,000 Taka
Lab Investigation cost (400 x 200)	80,000Taka
Data analysis	3,000 Taka
Printing	5,000 Taka
Others	2,000 Taka
Total	**96,000 Taka**

4. References

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5.Appendices

DATA COLLECTION SHEET

Intervention /Control group

DATA COLLECTION FORMAT

Title: low dose Aspirin (75mg) in prevention of preeclampsia .

Principal Investigator: Dr. Shapla khatun

Sl. No: | | |

Name: _____

Husband Name: _____

Address: _____

Contact no: | | | | | | | | | | |

Mobile

Socio-Demographic Characteristics

1)Age : years

2)Occupation : Housewife/Service Holder/others

3)Socioeconomic condition

Monthly income(tk)	10.000	10,000-20,000	21,000-40,000	>40,000

3)Education :Illiterate/Primary/SSC/HSC/Graduate/Postgraduate

Obstetric history

Married for

Para

Gravida

ALC

Number of foetus in present pregnancy Singleton / Multiple fetuses

Method of conception- Spontaneous/ OID/ ART

Previous history of Gestational HTN/ PE/ Eclampsia

Previous history of IUGR/ IUD/Still birth

Menstrual History

Cycle Regular/irregular

LMP

EDD

Family history : HTN/PE/Gestational HTN

Medical history: GDM /DM/Chronic HTN/Hypothyroidism/APS/SLE

Drug history:

Hypersensitivity to Aspirin : Present /Absent

Levothyroxine sodium

Insulin

Others

Antenatal care Regular/Irregular

Clinical examination related informations

PHYSICAL EXAMINATION:

Date					
Height					
Weight					
BMI					
Anaemia					
Jaundice					
Edema					

Date					
Pulse (bpm)					
SBP (mmhg)					
DBP(mmhg)					
Proteinuria					

Proteinuria : trace,1=+, 2=++, 3=+++ / Nil

Morning urine sample

Per abdominal examination:

Date					
Maturity					
SFH (cm)					
FM					
FHR					

During Follow up:

Complications :

Maternal- No complication/GIT upset / Gestational HTN /APH /oligohydramnios /

Preterm labour/others

Fetal- No complication /SGA/IUGR/IUD/PTB/others

Investigations :

Blood group & Rh typing

CBC

Urine R/M/E

Blood Suger profile

HBsAg

VDRL

TSH

USG of pregnancy profile:

Mode of delivery: NVD/Caesarean section at weeks of gestation.

Outcome

Maternal: normal

PE - occurred /Not occurred

Gestational HTN

Oligohydramnios

PTL

APH

PPH

Fetal- Sex- weight- kg (Normal/SGA/LGA)

APGAR Score

PTB

NICU admission

IUD/ still birth

Others-

Date： **Signature of the investigator**:

INFORMED WRITTEN CONSENT

Title of the study: **Low dose Aspirin in prevention of preeclampsia**

Investigator's name: Dr Shapla khatun

Institution: BIRDEM-II General Hospital,Shegunbagicha, Dhaka, Bangladesh

Purpose of the study:75mg Aspirin will be given to the high risk pregnant women to prevent preeclampsia.

Selection of the participant: If you are a pregnant women fulfiling the criteria, you are eligible for this study.

Expectation from and involvement of the participant: You will be asked some questions according to a structured questionnaire to know that you are high risk for developing preeclampsia. Also some physical examinations and investigations will be done. We expect that you will give consent for physical examination, investigation and information given by you will all be correct.

Risk and benefits: There is no physical, psychological, social and legal risk during obtaining data or the information used for the study. However if any problem arises, it will be managed by us.

Privacy, anonymity and confidentiality: All information regarding your identity will be kept confidential. For safe guarding, confidentiality and protecting anonymity each of the patient will be given a special ID no. Research data will be coded with that ID no. and then data will be stored in a locked cabinet. Only reseach personnel will be allowed to access data. Personal information will not be used during data analysis or publication.

Right to withdraw: Your participation in this study is completely dependent upon your free will and it will not affect your current treatment process. You also reserve the right to withdraw your name anytime during this research procedure.

For any query or information about the rights or benefits of your involvement in this study, you are free to contact with:

Dr. Shapla khatun (MS, Phase-B Resident)

Department of Obstetrics and Gynaecology, BIRDEM-II General hospital, Shegunbagicha, Dhaka.

Phone No. 01645817279

If you agree to our proposal of enrolling in our study, please indicate this by putting your signature or your left thumb impression at the specified space below.

Thank you for your co-operation.

Signature or left thumb impression of the participant : Date……

Signature or left thumb impression of the attendant : Date…….

Signature of the investigator: Date……