Government of the People's Republic of Bangladesh
Office of the Principal
Chittagong Medical College
Chattogram, Bangladesh.

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To
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Subject: Clearance of Research Protocol.

With reference to your application in the above subject, this is to inform you that your research proposal corrected entitled **"COMPARATIVE EFFICACY OF PROPRANOLOL, FLUNARIZINE AND THEIR COMBINATION IN MIGRAINE PROPHYLAXIS: AN OPEN-LABEL, PARALLEL-ARM RANDOMIZED CONTROLLED TRIAL"** has been reviewed and approved by the Institutional Review Board (IRB) of Chittagong Medical College.

08.06.2026
Professor (Dr.) Md. Abdus Sattar
Professor & Head
Department of Medicine, CMC.
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THESIS PROTOCOL

TITLE

Comparative Efficacy of Propranolol, Flunarizine, and Their Combination in Migraine Prophylaxis: An Open-label Parallel-arm Randomized Controlled Trial

INVESTIGATOR:

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Session: March 2025

PART-C

Summary

Background: Migraine is a prevalent neurological disorder with a significant global burden, affecting approximately 12% of the population, with a higher incidence among women. In Bangladesh, migraine contribute substantially to reduced quality of life and productivity, with limited access to effective prophylactic therapies. Propranolol and flunarizine are widely used for migraine prevention, but comparative studies evaluating their efficacy, including combination therapy, in Bangladeshi population are scarce.

Objective: The primary objective of this study is to compare the efficacy of propranolol, flunarizine, and their combination in reducing the number of monthly migraine days. Secondary objectives include comparing the ≥50% responder rate, headache severity, duration, MIDAS score, and the safety profile of each treatment approach.

Materials and Methods: This open-label, parallel-arm randomized controlled trial will be conducted at the inpatient and outpatient departments of Neurology and Medicine at Chittagong Medical College Hospital, Bangladesh. A total of 177 patients aged 18–55 years, diagnosed with migraine based on the IHS criteria, will be enrolled. Participants will be randomly assigned to one of three groups (59 per group) using block randomization. Treatment involves dose titration over 1 week, with follow-up visits at 6 and 12 weeks. Headache diaries will be maintained by participants, and clinical safety monitoring will be performed.

Data Analysis Plan: Statistical analyses will be performed using SPSS software. Descriptive statistics, ANOVA/Kruskal-Wallis tests for continuous variables, Chi-square tests for categorical variables, and repeated measures analysis will be employed. Intention-to-treat analysis and Per-protocol analysis will be conducted with a significance level set at $p < 0.05$.

Conclusions: The findings from this study will provide valuable evidence for optimizing migraine prophylaxis in Bangladesh and inform decisions regarding the rational selection of monotherapy versus combination therapy.

Keywords: Migraine Prophylaxis; Propranolol; Flunarizine; Combination Therapy; Randomized Controlled Trial; Bangladesh.

PART-D

1. Introduction:

Migraine is a prevalent and disabling neurological disorder affecting 1.16 billion people worldwide. It ranks first in disability-adjusted life years among children and adolescents and second among adults aged under 60 years (Peres et al., 2024). Bangladesh is no exception to this growing public health problem with migraine accounting for about 25% of all headache disorders (Ahmed et al., 2019). It primarily affects the productive 15–34 years age group (Ahmed et al., 2019), causing substantial loss of work hours, reduced efficiency, and absenteeism, thus imposing a heavy socioeconomic burden (Masurkar et al., 2025). Despite its substantial impact, migraine often lacks proper attention because of its non-fatal nature, invisibility and historical neglect of neurological disorders (Peres et al., 2024).

While acute therapies such as triptans provide relief during attacks, preventive therapies are essential for reducing the number of migraine days, frequency and severity of attacks, and associated disability. Propranolol, a non-selective beta-blocker, and flunarizine, a calcium channel blocker, are two of the most commonly used prophylactic agents for migraine. Both medications have shown efficacy in reducing the frequency of migraine in various populations (Deligianni et al., 2023; Jackson et al., 2015). However, there is limited evidence comparing the efficacy of these two agents in our population and even fewer have investigated their combined use in migraine prophylaxis, particularly in resource-limited settings such as Bangladesh.

Numerous studies have evaluated the efficacy of propranolol and flunarizine in migraine prophylaxis. Propranolol has been extensively studied and is considered one of the most effective treatments for reducing migraine frequency and severity (Jackson et al., 2019). Propranolol's mechanism of action in migraine prevention is believed to be related to its ability to reduce the excitability of neural pathways involved in migraine pathophysiology, likely through its effects on beta-adrenergic receptors (Versijpt et al., 2024).

Flunarizine, a calcium channel blocker, has also been found to be effective in preventing migraine by reducing the frequency and intensity of attacks (Stubberud et al., 2019). Its action is thought to be related to its ability to block calcium influx into neurons, thereby stabilizing vascular tone and reducing neuronal excitability.

Recent single center randomized controlled trials (RCTs) provided mixed results regarding the comparative efficacy of the two drugs: one Bangladeshi trial found greater improvement and higher responder rate with flunarizine than propranolol (Alam et al., 2024), whereas another Bangladeshi trial suggested propranolol is more effective than flunarizine in migraine without aura (Hasan et al., 2019). Some RCTs report no significant efficacy difference between the two (Bhat et al., 2017, Diener et al., 2002). Moreover, evidence on the combined use of propranolol and flunarizine is limited. Despite optimal monotherapy, 30-40% patients fail to respond. In such cases, combining treatments with different pharmacodynamic profiles presents a potential strategy to enhance outcomes by targeting multiple pathways involved in migraine. 62% of studies involving combination therapy shows improved outcomes compared to monotherapy. Moreover, 90% of studies found no significant increase in adverse effects with combination therapy, suggesting that this approach may offer enhanced efficacy without compromising tolerability (Pellesi et al., 2024).

A few studies have hypothesized that combination therapy of propranolol and flunarizine might offer enhanced efficacy by targeting multiple mechanisms involved in migraine pathophysiology, such as beta-adrenergic and calcium channel modulation. An indian study (Raybarman et al., 2016) found a low dose combination of propranolol and flunarizine to be highly effective in patients who did not respond to flunarizine monotherapy. The study recommended robust trials for head to head comparison of combination therapy against monotherapy. A classic double blind trial (n=45) comparing propranolol, flunarizine, and their combination found all three regimens significantly reduced migraine index and attack frequency vs baseline, with a numerical but not statistically significant trend favoring the combination (Bordini et al., 1997). Another observational randomized study (four arms) found propranolol 40 mg + flunarizine 10 mg more effective than low dose amitriptyline at 3 months, but not clearly superior to each monotherapy at earlier time points (Dixit et al., 2024). An Indian study versus valproate reported that both valproate and the propranolol+flunarizine combination were “highly effective,” with very similar reductions in headache days and disability scores (Panigrahi et al., 2022). Combination therapy in these trials did not show substantially more adverse events than monotherapy (Bordini et al., 1997; Dixit et al., 2024; Panigrahi et al., 2022).

In this context, present study aims to provide rigorous evidence on the comparative efficacy and safety of these treatments in a real-world clinical setting. By doing so, it will contribute

to the growing body of knowledge on migraine prophylaxis and help guide clinicians in selecting the most appropriate treatment for their patients.

2. Rationale

The rationale for this study stems from the high burden of migraine in Bangladesh, where the condition significantly impairs quality of life and productivity, yet effective migraine management remains suboptimal due to limited access to evidence-based treatments. While propranolol and flunarizine are established prophylactic agents with proven efficacy, there is insufficient comparative data on their effectiveness in the Bangladeshi population, particularly in resource-limited settings. Moreover, the potential benefits of combination therapy, which could theoretically offer enhanced outcomes by targeting different mechanisms involved in migraine pathophysiology, remain unexplored. This study aims to fill this critical gap by evaluating the comparative efficacy and safety of propranolol, flunarizine, and their combination in a randomized controlled trial at a tertiary care hospital in Bangladesh, providing much-needed local evidence to guide clinical decision-making and optimize migraine management in the country.

3. Research questions and Hypothesis

3.1 Research question: How do propranolol, flunarizine and their Combination therapy affect the prevention of episodic migraine in adult patients?

3.2 Research hypothesis:

Null Hypothesis:

There is no difference in efficacy among propranolol, flunarizine, their Combination therapy in preventing episodic migraine in adult patients.

Alternative Hypothesis:

At least one treatment group (propranolol or flunarizine or combination of both) is more effective in preventing episodic migraine in adult patients.

4. Objectives

4.1 General objective: To compare the efficacy and safety of propranolol, flunarizine, and their combination in the prophylactic treatment of episodic migraine in a tertiary care setting in Bangladesh.

4.2 Specific objectives

i. To assess the difference in the number of monthly migraine days among patients treated with propranolol, flunarizine, and their combination.

ii. To compare the ≥50% responder rate (reduction in migraine days) between propranolol, flunarizine, and their combination.

iii. To evaluate the impact of propranolol, flunarizine, and their combination on headache severity and headache duration.

iv. To compare the change in MIDAS (Migraine Disability Assessment) scores between the three treatment groups.

v. To assess the safety profiles of propranolol, flunarizine, and their combination by evaluating adverse events during the trial period.

5. Materials and method:

5.1. Type of study: Open-label, parallel-arm randomized controlled trial.

5.2. Place of Study: Chittagong Medical College Hospital (CMCH), Chattogram, Bangladesh.

5.3. Study period: One year from acceptance of protocol.

5.4. Study population: The study population will consist of adult patients with episodic migraine attending or admitted to CMCH. Participants will be recruited from both outpatient and inpatient department of Neurology and Medicine.

5.5 Study groups: The study will consist of three treatment groups, each receiving one of the following interventions: Propranolol, Flunarizine, or a combination of both. The allocation will be conducted using block randomization to ensure an equal distribution of participants across the three treatment arms.

1. **Propranolol Group (Group 1):** This group will receive propranolol as the sole prophylactic treatment.
2. **Flunarizine Group (Group 2):** Participants in this group will receive flunarizine as the sole treatment for migraine prophylaxis.
3. **Combination Group (Group 3):** This group will receive a combination of propranolol and flunarizine.

5.6. Sampling Technique: A consecutive sampling approach will be applied, whereby all patients who fulfill the screening criteria during the recruitment period will be approached sequentially until the required sample size is achieved.

5.7. Sample size: The sample size for this study will be calculated by a statistical power analysis. The calculation is based on Cohen's effect size framework, where the noncentrality parameter is related to total sample size and effect size as follows:

$\lambda = N \times f^2$

For equal allocation across k treatment groups, the required sample size per group can be expressed as:

$n = \lambda \div (k \times f^2)$

Where:

N= Total sample size

n = Sample size per group

λ = Noncentrality parameter

k = Number of groups

f = Cohen's effect size

Power analysis by G*Power (Perugini et al., 2018) for ANCOVA (fixed effects) is done with following parameters :

- **Effect Size (f):** An effect size of 0.25, which corresponds to a medium effect size based on previous migraine prophylaxis studies. (Perugini et al., 2018; Alam et al., 2024).
- **Significance Level (α):** The significance level will be set at 0.05 (5%), which is standard for clinical trials to minimize the risk of Type I errors.
- **Power (1 - β):** A power of 0.80 (80%) will be aimed for, ensuring that there is an 80% probability of detecting a true effect, if one exists.
- **Number of Groups (k):** The study will include three groups: Propranolol, Flunarizine, and their combination.

Power analysis indicates λ = Noncentrality parameter = 9.875.

So, n per group = $(\lambda) \div (k \times f^2)$

$= 9.875 \div (3 \times 0.0625)$

$= 9.875 \div 0.1875$

$= 52.67 \approx 53$ per group

To account for potential dropout, an attrition rate of 10% will be anticipated. The adjusted sample size will be calculated as follows:

$$n_{adjusted} = \frac{53}{1-0.10} = 58.9 \approx 59\ participants\ per\ group$$

. Thus, the total adjusted sample size will be:

$$n_{total} = 59 \times 3 = 177\ participants$$

. Therefore, the final sample size, accounting for a 10% dropout rate, will be approximately 177 participants (59 participants per group).

5.8. Selection criteria:

5.8.1 Inclusion criteria

1. Participants aged 18 to 55 years.
2. Diagnosis of episodic migraine, defined according to the International Classification of Headache Disorders, 3rd edition (ICHD-3) criteria.
3. Participants experiencing 4 or more migraine attacks per month.
4. Willingness to provide written informed consent to participate in the study.

5.8.2 Exclusion criteria

1. **Comorbidities:**
    - Presence of other primary headache disorders, chronic migraine, hemiplegic migraine, basilar migraine or any secondary headache disorder.
    - Known serious underlying systemic diseases including Cardiac disease (Heart failure, Heart Block, Arrhythmia), Renal dysfunction, Liver dysfunction, Pulmonary disease (Asthma, COPD), Peripheral vascular disease, Extrapyramidal disease (Parkinson disease, Chorea, Dystonia).
    - Pregnancy or breastfeeding.
    - Psychiatric illness (Depression, Psychosis, Obsessive compulsive disorder).
2. **Medications:**
    - Received migraine prophylactic medication within 60 days prior to screening.
    - Use of specific contraindicated medications, including beta-blockers or calcium channel blockers, except as part of the study treatments.
3. **Non-compliance:**
    - Inability or unwillingness to comply with study protocols, including maintaining a headache diary or attending follow-up visits.
4. **History of Allergies:**
    - Known hypersensitivity to propranolol, flunarizine
5. **Substance Use:**
    - Current substance abuse

5.9. List of variables:

Independent Variables:

i. Treatment Group: The primary independent variable will be the treatment type assigned to each participant:
    a) Propranolol
    b) Flunarizine
    c) Combination of propranolol and flunarizine

Dependent Variables:

i. Number of Monthly Migraine Days: The primary outcome measure, representing the reduction in the number of migraine days per month.
ii. Migraine Severity: Measured on Numeric Rating Scale (NRS) for assessing the intensity of migraine attacks.
iii. Migraine Duration: The average duration (in hours) of each migraine attack experienced by the participant during the study period.
iv. MIDAS (Migraine Disability Assessment) Score: A validated scale used to measure the impact of migraine on the participant's daily functioning and quality of life.
v. Responder Rate (≥50% reduction in migraine days): The proportion of participants in each group who experience a 50% or greater reduction in monthly migraine days.
vi. Patient Global Evaluation (PGE): The participant's self-reported overall evaluation of the effectiveness of the treatment, usually assessed on a scale (Score 1-4 where 1= Poor, 2= Good, 3= Very good, 4= Excellent).

Covariates (Other Variables):

i. Age: Participant's age at the time of enrollment, as age may influence migraine frequency and treatment response.
ii. Gender: Participant's gender (male or female), since migraine prevalence and response to treatment may vary by gender.
iii. Body Mass Index (BMI): The participant's BMI at baseline, as weight may influence medication efficacy and migraine frequency.

iv. Comorbid Conditions: Any other pre-existing conditions (e.g., Hypertension, Diabetes) that could affect migraine treatment outcomes or the participant's overall health.

v. Baseline Headache Frequency: The number of headache days experienced per month prior to enrollment, as it could influence the efficacy of the treatment.

vi. Medication Adherence: Self-reported adherence to prescribed medications (propranolol, flunarizine, or combination therapy) verified by pill counting, which could affect treatment outcomes.

vii. Duration of Migraine History: How long the participant has been experiencing migraines, which may impact treatment response.

viii. Adverse Effects of Medication: Any side effects reported by the participants associated with the treatment they are receiving (Propranolol, Flunarizine, or combination therapy), which may include fatigue, dizziness, weight gain, or gastrointestinal disturbances.

5.10 Operational definitions

Migraine without Aura: Diagnostic criteria (ICHD-3):

A. At least five attacks fulfilling criteria B-D.

B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated).

C. Headache must have at least two of the following four characteristics:

   i. Unilateral location.

   ii. Pulsating quality.

   iii. Moderate or severe pain intensity.

   iv. Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs).

D. During the headache, at least one of the following:

   i. Nausea and/or vomiting.

   ii. Photophobia and phonophobia.

E. The condition must not be better accounted for by another ICHD-3 diagnosis.

Migraine with Aura: Diagnostic criteria (ICHD-3):

A. At least two attacks fulfilling criteria B and C.

B. One or more of the following fully reversible aura symptoms:

Visual; Sensory; Speech and/or language; Motor; Brainstem; Retinal.

C. At least three of the following six characteristics:

i. At least one aura symptom spreads gradually over ≥5 minutes.

ii. Two or more aura symptoms occur in succession.

iii. Each individual aura symptom lasts 5-60 minutes.

iv. At least one aura symptom is unilateral.

v. At least one aura symptom is positive.

vi. The aura is accompanied, or followed within 60 minutes, by a headache.

D. The condition must not be better accounted for by another ICHD-3 diagnosis.

Episodic Migraine: Episodic migraine is defined as recurring headaches that last 4-72 hours, are unilateral, pulsatile, of moderate or severe intensity, aggravated by physical activity, and associated with nausea/vomiting and/or photophobia/phonophobia. It occurs fewer than 15 days per month.

Chronic Migraine: Chronic migraine is defined as headaches occurring on at least 15 days per month, with at least eight of these days fulfilling the criteria for migraine.

Individuals with chronic migraine often experience medication overuse, comorbidities (e.g., Depression), and poor compliance with medications.

Hemiplegic migraine:

Migraine with aura including motor weakness.

Diagnostic criteria: ICHD-3

Attacks fulfilling criteria for Migraine with aura and criterion below-

Aura consisting of both of the following:

1) fully reversible motor weakness
2) fully reversible visual, sensory and/or speech/language symptoms.

Basilar Migraine:

Also known as migraine with brainstem aura.

Diagnostic criteria: ICHD-3

A. Attacks fulfilling criteria for Migraine with aura and criterion B below

B. Aura with both of the following:

1. At least two of the following fully reversible brainstem symptoms:

Dysarthria, Vertigo, Tinnitus, Hypacusis, Diplopia, Ataxia not attributable to sensory deficit, Decreased level of consciousness (GCS ≤13)

2. No motor or retinal symptoms.

Secondary headache:

Secondary headaches are those in which the headache is a symptom of another disorder recognized as a potential underlying cause.

Preventive Treatment of Migraine: Preventive treatment is indicated for individuals experiencing four or more monthly migraine days, with the attack causing substantial disability or functional impairment, a frequent need for acute medications, inadequate relief, or intolerable side effects from acute medications. Any of these conditions are sufficient to justify preventive treatment.

Reduction in Monthly Migraine Days: Monthly Migraine Days refers to the total number of days within a month on which a participant experiences a migraine headache. The reduction will be measured as the difference between the baseline number of monthly migraine days and the number recorded at the end of the study. It is considered more reliable than counting the number of migraine attacks, as a single migraine attack may last for more than one day.

Responder Status: A participant will be classified as a 'Responder' if they achieve a reduction of 50% or more in monthly migraine days at Week 12 compared to their individual baseline value. Participants achieving less than 50% reduction will be classified as 'Non-responder'. Responder status will be assessed only at the end of the study period (Week 12) and recorded in the case record form.

Percentage of Responders: The percentage of patients reporting at least a 50% reduction in their monthly migraine days compared to the baseline. This will be expressed as the percentage of total participants in each treatment arm.

MIDAS Score: The Migraine Disability Assessment scale measures the impact of migraines on daily activities. It consists of questions assessing the degree of disability caused by migraines in terms of days missed from work/school, household duties, and other daily activities. The MIDAS questionnaire will be filled out at baseline and at the end of the treatment period by the participant. It grades disability due to migraine as:

Grade 1: Minimal disability.

Grade 2: Mild disability.

Grade 3: Moderate disability.

Grade 4: Severe disability.

Headache Severity: The intensity of headache pain experienced during a migraine attack will be recorded using Numeric Rating Scale (NRS) by the participants, where participants will rate their pain from 0 (No pain) to 10 (Worst pain imaginable).

Headache Duration: The length of time an episode of migraine attack lasts will be measured from the onset of pain to the resolution of the headache, in hours. It will be recorded by the participants.

Patient Global Evaluation: A self-reported measure of the patient's perception of the effectiveness of the treatment. Participants will rate their overall satisfaction with the treatment regimen using a Likert Scale (Score 1-4 where 1= Poor, 2= Good, 3= Very good, 4= Excellent).

Frequency of Adverse Effects: An adverse effect is defined as a harmful or unpleasant effect of a drug at doses intended for therapeutic use, which may require a

reduction in dose or withdrawal of the drug, and/or forecast hazard from future administration. The frequency of a particular adverse effect will be measured by the number of participants reporting that specific adverse effect during the treatment period, expressed as a percentage of the total participants in each group.

Medication Adherence: Adherence refers to the extent to which a patient follows the prescribed medication regimen, including dose, frequency, and duration. In migraine preventive treatment, adherence will be defined as taking at least 80% of the prescribed doses, which is a common threshold used in clinical trials for migraine treatments. Adherence will be calculated as: [(pills dispensed – pills returned) / pills expected to be taken] × 100.

5.11 Data collection instrument: A structured case record form, Headache diary, MIDAS questionnaire.

5.12 Data collection procedure:

5.12.1. Baseline Assessment

During this phase, participants will undergo a comprehensive evaluation to confirm eligibility by inclusion and exclusion criteria and to establish baseline data for key variables. This will include medical history including the collection of demographic information (age, gender, weight, height, BMI), Examination (General and Systemic) and Baseline laboratory tests (ECG, RBS, SGPT, SGOT, Serum creatinine) will be given. Detailed information will be collected on-

- **Migraine history**: Including the frequency, duration and severity of headaches.
- **MIDAS (Migraine Disability Assessment) score**: To assess the level of disability due to migraine. A bengali version of MIDAS questionnaire adopted from Alam et al., 2018 will be used for this purpose with author's permission. It will be filled out by the participant.
- **Headache severity and duration**: Headache severity will be assessed by a Numeric Rating Scale (NRS) and noting the length of each migraine episode in hours.

This baseline data will serve as a comparison for evaluating changes in treatment outcomes. Then patient will be given proper education, counselling and informed consent will be taken regarding their participation in the study. Consenting eligible candidates will be enrolled into the study.

5.12.2. Allocation

After enrollment, participants will be randomly assigned to one of the three treatment groups: propranolol, flunarizine or the combination of both. Random allocation will be performed using a software-generated block randomization with a block size of six, ensuring equal distribution of participants across the three groups. Allocation concealment will be done using sealed opaque envelope.

5.12.3. Blinding

The study will be open-label, with both investigator and participants be aware of their treatment allocation.

5.12.4. Intervention

After allocation, participants will receive their assigned treatment for a period of 12 weeks. The interventions will be as follows:

- **Propranolol Group (Group 1)**: This group will receive propranolol as the sole prophylactic treatment. Propranolol will be started at a low dose (40 mg daily) and increased to 80 mg daily after 7 days (Alam et al., 2024).
- **Flunarizine Group (Group 2):** Participants in this group will receive flunarizine as the sole prophylactic treatment. The starting dose will be 5 mg daily, which will be increased to 10 mg daily after 7 days (Alam et al., 2024).
- **Combination Group (Group 3):** This group will receive a combination of propranolol and flunarizine. It will be started at propranolol 40 mg plus flunarizine 5 mg daily. After 7 days, the dose of propranolol will be kept at 40 mg and flunarizine will be increased to 10 mg daily (Dixit et al., 2024).

Participants will be advised to maintain a daily headache diary to document the occurrence, intensity, and duration of each migraine attack. Participants will be educated at first visit on how to record headache severity using numeric rating scale so that they can later record severity in the headache diary themselves. Adherence to

the prescribed medication will be monitored through regular visits and self-reporting. Contact number of the participant will be noted to facilitate follow up and also contact number of the investigator will be provided for emergency contact. Acute medications like NSAID (Naproxen) or Triptan (Zolmitriptan if Naproxen fails) at appropriate doses will be allowed for acute pain relief.

5.12.5. Follow-Up

Follow-up assessments will occur at two time points: at 6 weeks and at the end of the study (12 weeks). These visits will allow for the monitoring of treatment efficacy and safety as well as any adverse effects experienced by the participants. Pulse, Blood pressure, weight, BMI will be recorded during each visits. During the follow-up visits, the following procedures will be conducted:

- **Headache diary review**: The participants will submit their headache diaries for analysis, recording the number of migraine days, attack severity, and any associated symptoms.
- **Evaluation of adverse effects**: Any side effects or adverse events will be recorded and participants will be assessed for the impact of these side effects on their overall health.
- **Treatment adherence**: Treatment adherence will be checked by self report and pill counting at each follow-up visits.
- **Assessment of migraine disability (MIDAS)**: The MIDAS score will be re-evaluated at the end of the study by the researcher to assess the change in disability due to migraine.
- **Headache severity and duration**: These parameters will be assessed using the Numeric Rating Scale (NRS) and documentation of the length of each migraine attack in hours.
- **Patient Global Evaluation**: Participants will be asked to rate their overall impression of the effectiveness of treatment (Score 1-4 where 1= Poor, 2= Good, 3= Very good, 4= Excellent).

If necessary, participants who experience intolerable adverse effects will be withdrawn from the study and provided with alternative treatment options. At the end

of the follow-up period, the data collected will be analyzed to assess the efficacy and safety of the three treatments.

5.13. Data analysis:

The data analysis will be performed to evaluate the efficacy and safety of Propranolol, Flunarizine, and their combination in migraine prophylaxis. The statistical analysis will be conducted using SPSS (Statistical Package for the Social Sciences) version 27.0 or later, and a significance level of $p < 0.05$ will be considered statistically significant. The analysis will be based on both per-protocol analysis and intention-to-treat (ITT) approach.

Descriptive statistics will be used to summarize the baseline characteristics of the study population. Continuous variables (e.g., age, BMI, baseline headache frequency, baseline MIDAS score) will be presented as means ± standard deviations (SD) or medians with interquartile ranges (IQR) as appropriate. Categorical variables (e.g., gender, treatment group) will be summarized as frequencies and percentages.

The primary outcome measure is the reduction in monthly migraine days. The change from baseline to the 12-week follow-up will be calculated for each participant, and the mean change will be compared across the three treatment groups (Propranolol, Flunarizine, and Combination) using Analysis of Covariance (ANCOVA). ANCOVA will adjust for baseline values and any potential confounders (such as age, gender, and baseline headache frequency). Pairwise comparisons between treatment groups will be conducted using Bonferroni correction to control for multiple comparisons.

For secondary outcomes (migraine severity, MIDAS score, responder rate, headache duration, and adverse effects), the following statistical tests will be used:

- Headache Severity (NRS score): The change in headache severity from baseline to 12 weeks will be analyzed using repeated measures ANOVA.
- MIDAS Score: The change in MIDAS scores from baseline to 12 weeks will be compared using Wilcoxon signed-rank test or paired t-tests, depending on the distribution of the data.
- Responder Rate: The proportion of participants who achieve at least a 50% reduction in monthly migraine days will be analyzed using the Chi-square test or Fisher's exact test for between-group comparisons.

- Adverse Effects: The frequency of adverse effects will be compared across the three treatment groups using the Chi-square test or Fisher's exact test to evaluate the distribution of side effects.

Subgroup analyses will be conducted to explore the impact of potential modifiers of treatment response, including:

- **Age**: Participants will be stratified into two groups: those under 40 years old and those aged 40 and above.
- **Gender**: Differences in treatment effects between males and females will be assessed.

These subgroup analyses will be exploratory and will use appropriate statistical methods (e.g., ANCOVA or logistic regression) to determine if baseline characteristics modify the effectiveness of the treatment.

The safety profile of each treatment will be assessed by examining the frequency of adverse effects experienced by participants in each treatment group. Descriptive statistics will be used to report the incidence of adverse events. The frequency of each adverse effect will be compared between the three groups using the Chi-square test or Fisher's exact test.

Missing data will be handled using an intention-to-treat (ITT) approach, where participants who do not complete the study will still be included in the analysis. If necessary, multiple imputation will be used to handle missing values under the assumption that the data is missing at random.

Effect sizes (e.g., Cohen's d for t-tests, partial eta squared for ANOVA) will also be calculated to assess the magnitude of treatment effects. A confidence interval (CI) of 95% will be reported for all point estimates to provide a range of values within which the true treatment effect is likely to lie.

Dummy Tables

Table 1: Baseline Sociodemographic Characteristics of Study Participants

Variables	Propranolol Group n=59	Flunarizine Group n=59	Combination Group n=59	p-value
Age, years, mean ± SD				
Age group, n (%)				
18–30 years				
31–40 years				
41–55 years				
Sex, n (%)				
Male				
Female				
Residence, n (%)				
Urban				
Rural				
BMI, kg/m², mean ± SD				
Family history of migraine, n (%)				

Table 2: Baseline Clinical Characteristics of Migraine

Variables	**Propranolol Group n=59**	**Flunarizine Group n=59**	**Combination Group n=59**	**p-value**
Duration of migraine, years, mean ± SD				
Migraine type, n (%)				
Migraine without aura				
Migraine with aura				
Monthly migraine days, mean ± SD				
Headache severity score, mean ± SD				
Headache duration, hours, mean ± SD				
Baseline MIDAS score, mean ± SD				
MIDAS grade, n (%)				
Grade I				
Grade II				
Grade III				
Grade IV				

Table 3: Comparison of Monthly Migraine Days at Baseline, 6 Weeks, and 12 Weeks

Time Point	Propranolol Group n=59 Mean ± SD	Flunarizine Group n=59 Mean ± SD	Combination Group n=59 Mean ± SD	p-value
Baseline				
6 weeks				
12 weeks				
Change from baseline to 6 weeks				
Change from baseline to 12 weeks				

Repeated measures ANOVA / mixed model; one-way ANOVA or Kruskal–Wallis for between-group change comparison.

Table 4: Within-group Change in Monthly Migraine Days

Group	Baseline Mean ± SD	6 Weeks Mean ± SD	12 Weeks Mean ± SD	Mean Change at 12 Weeks	p-value
Propranolol					
Flunarizine					
Combination					

Paired t-test / repeated measures ANOVA.

Table 5: Comparison of ≥50% Responder Rate at 12 Weeks

Response Status	Propranolol Group n=59	Flunarizine Group n=59	Combination Group n=59	p-value
≥50% responder, n (%)				
Non-responder, n (%)				

Definition: ≥50% responder = patient with at least 50% reduction in monthly migraine days from baseline. Chi-square test / Fisher's exact test.

Table 6: Comparison of Headache Severity Score

Time Point	Propranolol Group n=59 Mean ± SD	Flunarizine Group n=59 Mean ± SD	Combination Group n=59 Mean ± SD	p-value
Baseline				
6 weeks				
12 weeks				
Change from baseline to 12 weeks				

Visual Analogue Scale or Numeric Rating Scale.

Table 7: Comparison of Headache Duration

Time Point	Propranolol Group n=59 Mean ± SD	Flunarizine Group n=59 Mean ± SD	Combination Group n=59 Mean ± SD	p-value

Baseline duration, hours				
6-week duration, hours				
12-week duration, hours				
Change from baseline to 12 weeks				

Table 8: Comparison of MIDAS Scores Between Treatment Groups

Time Point	**Propranolol Group n=59 Mean ± SD**	**Flunarizine Group n=59 Mean ± SD**	**Combination Group n=59 Mean ± SD**	**p-value**
Baseline MIDAS score				
6-week MIDAS score				
12-week MIDAS score				
Change from baseline to 12 weeks				

Table 9: Comparison of MIDAS Disability Grades at 12 Weeks

MIDAS Grade	**Propranolol Group n=59**	**Flunarizine Group n=59**	**Combination Group n=59**	**p-value**

Grade I: Little or no disability				
Grade II: Mild disability				
Grade III: Moderate disability				
Grade IV: Severe disability				

Table 10: Adverse Events During Trial Period

Adverse Events	**Propranolol Group n=59**	**Flunarizine Group n=59**	**Combination Group n=59**	**p-value**
Any adverse event, n (%)				
Fatigue, n (%)				
Dizziness, n (%)				
Sleep disturbance, n (%)				
Weight gain, n (%)				
Bradycardia, n (%)				
Hypotension, n (%)				
Nausea, n (%)				

Depression/mood change, n (%)				
Others, n (%)				

Table 11: Treatment Discontinuation and Compliance

Variables	**Propranolol Group n=59**	**Flunarizine Group n=59**	**Combination Group n=59**	**p-value**
Completed 12-week follow-up, n (%)				
Lost to follow-up, n (%)				
Discontinued due to adverse event, n (%)				
Discontinued due to poor response, n (%)				
Good compliance, n (%)				
Poor compliance, n (%)				

Table 12: Overall Summary of Treatment Efficacy at 12 Weeks

Outcome Variable	Propranolol Group	Flunarizine Group	Combination Group	p-value
Reduction in monthly migraine days, mean ± SD				
≥50% responder rate, n (%)				

Reduction in headache severity, mean ± SD				
Reduction in headache duration, mean ± SD				
Reduction in MIDAS score, mean ± SD				
Any adverse event, n (%)				

6. Utilization of the study findings:

The results of this study will be utilized to inform clinical decision-making in the management of migraine prophylaxis in Bangladesh and similar resource-limited settings. The findings will provide evidence on the comparative efficacy and safety of Propranolol, Flunarizine, and their combination, helping to guide the selection of appropriate migraine treatments in clinical practice. Additionally, the results will contribute to the broader scientific understanding of migraine management, specifically in populations with limited access to healthcare resources.

The study's outcomes will be disseminated through peer-reviewed publications in scientific journals, presenting the findings to the global medical and research communities. The results will also be presented at relevant academic conferences and shared with healthcare providers in Bangladesh, where the data could potentially influence local treatment guidelines and practices. Recommendations based on the study's findings may be included in clinical guidelines for migraine management, particularly in settings where access to expensive medications is limited.

Furthermore, the results will be useful for policymakers and public health officials in Bangladesh and other developing countries, as they may provide guidance for resource allocation and healthcare planning related to migraine management. The study may also pave the way for future research investigating more personalized treatment strategies for migraine prevention in diverse populations.

7. Ethical Implication: Ethical approval will be obtained from the Ethical Review Committee of Chittagong Medical College prior to initiation.

Informed consent will be obtained from all participants prior to enrollment. Detailed information about the study's objectives, procedures, potential risks, benefits, and the voluntary nature of participation will be provided in a written format. Participants will be given ample opportunity to ask questions and will be informed that they may withdraw from the study at any time without consequence.

Confidentiality will be maintained at all stages of the study. All participant data will be anonymized using a unique identifier, and personal identifying information will be stored securely. Data will be analyzed and reported in aggregate form to protect participant anonymity. Only authorized personnel will have access to the study data.

A Data Safety and Monitoring Committee (DSMC) will be formed to ensure participant safety and the ethical conduct of the trial. The committee will include members who are not directly involved in patient recruitment or treatment allocation. The DSMC will periodically review safety data, adverse events, serious adverse events, protocol deviations, dropout patterns, and overall trial progress. If any participant experiences intolerable side effects or other health concerns, appropriate medical intervention will be provided, and the participant will be withdrawn from the study if necessary. Any serious adverse events will be reported to the DSMC and ethics committee in accordance with ethical guidelines.

Finally, the ethical principle of beneficence will be upheld by ensuring that the potential benefits of participation outweigh any risks. The study will aim to improve the management of migraines, leading to better patient outcomes and a more efficient healthcare system, particularly in underserved regions.

8. Time schedule

Objectives	Major activities	Duration	
		Start	End
Study initiation	1. Protocol preparation 2. Getting ethical approval	01/02/2026	30/04/2026
Capacity development	3. Pretesting data collection instrument	01/05/2026	31/05/2026
Study implementation	4. Data collection 5. Interim analysis	01/06/2026	31/03/2027
Data management	6. Data processing 7. Data analysis	01/04/2027	30/04/2027
Study completion	8. Thesis preparation 9. Submission	01/05/2027	31/05/2027

9. Flow Chart showing sequence of task:

Preparation of the study protocol and development of the case record form, followed by pre-testing and finalization

↓

Obtaining ethical clearance from the Ethical Review Committee of Chittagong Medical College

↓

Screening of patients with migraine attending the outpatient and inpatient Department of Neurology and Medicine at Chittagong Medical College Hospital

↓

Selection of eligible patients based on predefined inclusion and exclusion criteria

↓ *Exclusion as not eligible*

Obtaining written informed consent from eligible participants

↓ *Exclusion if not given consent*

Collection of baseline socio-demographic, clinical, and biochemical data

↓ *Exclusion if exclusion* criteria *found*

Enrollment of consenting eligible candidates into the study

↓ *Exclusion if withdraw consent*

Allocation: Random allocation of participants into any of the three groups (Propranolol, Flunarizine and combination)

↓ *Exclusion if withdraw consent*

Intervention: Administration of the assigned intervention and scheduled follow-up over a 12-week period

↓ *Exclusion if withdraw consent*

Follow-up: Follow-up assessments to evaluate efficacy and safety

↓ *Exclusion if intolerable side effects*

Follow up completed at 3 months

↓

Compilation and organization of collected data into a master data sheet using Microsoft Excel

↓

Statistical analysis of data using the Statistical Package for the Social Sciences (SPSS), version 27.0, with comparison of outcomes among three groups

↓

Interpretation of findings and completion of thesis writing

↓

Completion of the thesis

10. References:

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PART - E

Budget (according to the number of patients)

Total Budget :	**Tk. 2,25,000/ (Two lac Twenty-five thousand taka)**
Detailed Budget:	
Head of expenses	**Amount (in Taka)**
Stationary	**5,000**
Medication cost	**2,00,000**
Compose and printing	**5,000**
Report Writing	**5,000**
Miscellaneous	**10,000**

Appendix-A

Case record form

Protocol Title: "Comparative Efficacy of Propranolol, Flunarizine, and Their Combination in Migraine Prophylaxis: An Open-Label Parallel-arm Randomized Controlled Trial"

Protocol ID: **Patient ID:**

Section 1: Participant sociodemographic information

1. **Age:** _____years
2. **Gender:** ☐ Male ☐ Female
3. **Education:** ☐ No formal ☐ Primary ☐ Secondary ☐ Higher secondary ☐ Graduate and above

Section 2: Medical History and Baseline Assessment

1. **Migraine Diagnosis (ICHD-3 Criteria):**
   ☐ Chronic Migraine ☐ Episodic Migraine ☐ Migraine with Aura ☐ Migraine without Aura
   Comorbidities:
   - ☐ Hypertension ☐ Diabetes ☐ Anxiety
   - Other (specify): _____
2. **Family History of Headache:**
   - ☐ Absent ☐ Present
3. **Duration of total migraine:** _____years
4. **Associated Nausea/ Vomiting:**
   - ☐ Absent ☐ Present
5. **Associated Photo/ Phonophobia**
   - ☐ Absent ☐ Present
6. **Previously taken prophylactic medication** (Yes/ No)
   - ☐ Yes ☐ No
7. **Smoking status**: ☐ Never ☐ Former ☐ Current

Section 3: Randomization and Treatment Allocation

1. **Randomization Group:**
   - ☐ Propranolol Group ☐ Flunarizine Group ☐ Combination Group
2. **Treatment Dose Assigned:**
   - Propranolol: 40mg daily; after 7 days- 80mg daily
   - Flunarizine: 5mg daily; after 7 days- 10mg daily
   - Combination : Propranolol 40mg + Flunarizine 5mg daily; After 7 days, Propranolol 40mg + Flunarizine 10mg daily

Section 4: Baseline and Follow-up Measurements

Parameter	**Baseline (Week 0)**	**Follow-up (Week 6)**	**Follow-up (Week 12)**
Monthly migraine Days			
Headache severity (NRS score)			
Headache duration (in hours)			

MIDAS Score			
Reduction from baseline at 3 months (%)			
Patient Global Evaluation Poor / Good / Very good/ Excellent			
Pulse			
Blood Pressure			
Weight			
RBS			
ECG			
Serum creatinine			
SGOT			
SGPT			
Adherence to medication (%)			

Adverse events

Sl No	**Type (Fatigue, dizziness, weight gain, gastrointestinal disturbance, etc.,)**	**Severity (Mild/ Moderate/ Severe)**	**Action taken (Dose adjustment/ discontinue treatment/ Medical intervention)**

Responder Status at Week 12:

☐ Responder (≥50% reduction in monthly migraine days from baseline)

☐ Non-responder (<50% reduction in monthly migraine days from baseline)

Section 5: Follow-up Status

- Completed 12-week follow-up: ☐ Yes ☐ No
- If no, reason for dropout: _____

Section 6: Investigator Declaration

I confirm that the above information has been recorded accurately and completely according to the study protocol.

- Signature: _____
- Date: ___ / ___ / _____

Headache Diary for .....

Starting Date of Headache	Duration (start/finish)	Intensity Rate 0-10 (No pain 0 to most severe being 10)	Preceding Symptoms (Aura)	Associated Symptoms (e.g. Nausea, Vomiting, Photophobia, Phonophobia)	Provoking factors	Rescue medication (and dosage)	Relief (complete/moderate/ none)

The Migraine Disability Assessment Test

The **MIDAS** (Migraine Disability Assessment) questionnaire was put together to help you measure the impact your headaches have on your life. The information on this questionnaire is also helpful for your primary care provider to determine the level of pain and disability caused by your headaches and to find the best treatment for you.
INSTRUCTIONS

Please answer the following questions about ALL of the headaches you have had over the last 3 months. Select your answer in the box next to each question. Select zero if you did not have the activity in the last 3 months. Please take the completed form to your healthcare professional.

1. On how many days in the last 3 months did you miss work or school because of your headaches? Answer: ..... days

2. How many days in the last 3 months was your productivity at work or school reduced by half or more because of your headaches? (Do not include days you counted in question 1 where you missed work or school.) Answer: ..... days

3. On how many days in the last 3 months did you not do household work (such as housework, home repairs and maintenance, shopping, caring for children and relatives) because of your headaches? Answer: ..... days

4. How many days in the last 3 months was your productivity in household work reduced by half of more because of your headaches? (Do not include days you counted in question 3 where you did not do household work.) Answer: ..... days

5. On how many days in the last 3 months did you miss family, social or leisure activities because of your headaches? Answer: ..... days

Total (Questions1-5)

What your Physician will need to know about your headache:

A. On how many days in the last 3 months did you have a headache? (If a headache lasted more than 1 day, count each day.) Answer: ..... days

B. On a scale of 0 - 10, on average how painful were these headaches? (where 0=no pain at all, and 10= pain as bad as it can be.) Answer:

Scoring: After you have filled out this questionnaire, add the total number of days from questions 1-5 (ignore A and B).

MIDAS Grade	Definition	MIDAS Score
I	Little or No Disability	0-5
II	Mild Disability	6-10
III	Moderate Disability	11-20
IV	Severe Disability	21+

Information Sheet for Participants

Study Title:

Comparative Efficacy of Propranolol, Flunarizine, and Their Combination in Migraine Prophylaxis: An Open-Label Parallel-arm Randomized Controlled Trial

Principal Investigator:

Dr. Mohammad Shaifuddin Shourav, MD (Neurology), Phase-B Resident, Department of Neurology, Chittagong Medical College, Chattogram. Mobile-01832287641

Introduction:

You are invited to participate in a research study that aims to compare the effectiveness and safety of two medications, propranolol and flunarizine, as well as their combination in preventing migraine. The study will take place at Chittagong Medical College Hospital in Bangladesh. Before you decide to participate, it is important that you understand the purpose of the study, the procedures involved, and any potential risks. This information sheet provides details about the study, and you will have an opportunity to ask questions and provide your informed consent before participation.

Purpose of the Study:

The purpose of this study is to compare the efficacy and safety of propranolol, flunarizine, and their combination in reducing the frequency and severity of migraine attacks. Usually doctors start migraine prevention with one medicine alone, like propranolol or flunarizine. In this study, we are testing a combination of the two to see if it works better. This combination is not yet the standard first choice in guidelines, so we are offering it as part of a monitored research trial, with regular checkups and the option to change or stop the medicine if needed. The study will help to determine the most effective treatment for preventing migraines in a local population, particularly in settings with limited access to expensive medications.-

Study Procedures:

If you decide to participate, the following steps will be involved:

1. Screening and Enrollment: You will be asked to undergo a baseline assessment, including a medical history review, headache frequency, and intensity measurement using questionnaires, and a physical examination to confirm your eligibility for the study.
2. Randomization: You will be randomly assigned to one of three treatment groups:

- Propranolol group
- Flunarizine group
- Combination group (Propranolol + Flunarizine)

3. Treatment: You will receive the treatment for 12 weeks. The medication will be determined by your assigned group. It will be given at low dose for 7 days and full dose will be given after that. You will be asked to take the medication daily and keep a headache diary to document any changes in migraine frequency, severity, and duration.
4. Follow-Up: You will attend two follow-up visits (at 6 and 12 weeks). During these visits, you will complete questionnaires on migraine frequency and severity, and any adverse effects of the medication will be monitored. The investigator will assess the impact of the treatment on your condition using several scales, including MIDAS (Migraine Disability Assessment).
5. Safety Monitoring: Your health will be monitored throughout the study, and any adverse effects experienced will be recorded. If any severe adverse effects occur, your participation in the study may be ended, and appropriate treatment will be provided.

Potential Risks:

All medications have the potential to cause side effects. While propranolol and flunarizine are commonly used for migraine prevention, you may experience side effects, including but not limited to:

- Fatigue
- Dizziness
- Weight gain
- Gastrointestinal issues (e.g., nausea, constipation)
- Others, as specified by the researcher

If any adverse effects occur, the study team will address them promptly, and if necessary, you will be withdrawn from the study and treated accordingly**.**

Potential Benefits:

You may experience a reduction in the frequency, severity, and duration of migraine attacks. However, participation in this study may not benefit you directly. The results of the study will contribute to improving the understanding of migraine treatment and help optimize care for future patients in similar settings.

Confidentiality:

Your privacy will be protected throughout the study. All information collected will be kept confidential, and personal identifiers will be replaced with a unique study ID.

Only authorized research staff will have access to your data, and it will be stored securely. The results of the study may be published, but no personal information will be disclosed.

Voluntary Participation:

Your participation in this study is completely voluntary. You may choose not to participate or may withdraw at any time without any negative consequences or loss of care. If you decide to withdraw, all study-related data collected up to that point will be kept confidential and used for analysis**.**

Compensation:

No compensation will be provided for participation in this study. However, any medical treatment related to the study (e.g., treatment of adverse effects) will be provided at no cost to you.

Contact Information:

If you have any questions or concerns about the study, you may contact:

- Dr. Mohammad Shaifuddin Shourav, MD (Neurology), Phase-B Resident, Department of Neurology, Chittagong Medical College, Chattogram. Mobile-01832287641
- Ethics Committee/IRB: [Contact information for the ethics board]

Informed Consent Form

Study Title:

Comparative Efficacy of Propranolol, Flunarizine, and Their Combination in Migraine Prophylaxis: An Open-Label Parallel-arm Randomized Controlled Trial

Principal Investigator:
Dr. Mohammad Shaifuddin Shourav, MD (Neurology), Phase-B Resident, Department of Neurology, Chittagong Medical College, Chattogram. Mobile-01832287641

I, the undersigned, have read the information sheet provided to me regarding this study and have had the opportunity to ask questions. I understand the purpose of the study, the procedures involved, and the potential risks and benefits. I understand that my participation is voluntary, and I may withdraw at any time without penalty or loss of benefits to which I am otherwise entitled.

By signing this consent form, I agree to participate in the study under the conditions described. I understand that all information collected will be kept confidential and that my identity will not be disclosed in any published results. I also understand that I may be withdrawn from the study at any time if I experience any adverse effects or if it is deemed necessary by the investigator.

I agree to follow the study procedures, including the treatment regimen and follow-up visits. I understand that I may be required to take the assigned medication daily for 12 weeks and that my health will be monitored during the study period.

Participant's Full Name (Printed): _____

Participant's Signature: _____

Date: _____

Investigator's Name (Printed): _____

Investigator's Signature: _____

Date: _____

Full name of the witness (Printed): _____

Signature of the witness: _____

Date: _____

Data and Safety Monitoring committee

Title: "**Comparative Efficacy of Propranolol, Flunarizine, and Their Combination in Migraine Prophylaxis: An Open-Label Parallel-arm Randomized Controlled Trial"**

Name of the researcher: This study is being conducted by Dr. Mohammad Shaifuddin Shourav, MD (Neurology), Phase-B Resident, Department of Neurology, Chittagong Medical College, Chattogram.

Place of the study: Department of Neurology, Chittagong Medical College Hospital, Chattogram.

Type of Study: Randomized Controlled Trial

Members of the committee:

• ……. Professor, Department of Neurology Chittagong Medical College Hospital, Chattogram, Bangladesh

• …… Assistant professor, Department of Neurology, Chittagong Medical College Hospital, Chattogram, Bangladesh

• …….. Assistant professor, Department of Medicine, Chittagong Medical College Hospital, Chattogram, Bangladesh

DATA AND SAFETY MONITORING PLAN

Once a protocol is referred to the data and safety monitoring committee (DSMC), the first steps for the principal investigator to develop a Data and Safety Monitoring Plan (DSMP) A DSMP is a written plan that specifies a system for appropriate study oversight to ensure: (1) safety of clinical research subjects, (2) validity and integrity of research data, and (3) appropriate termination study. Once the plan elements listed here are submitted to the DSMC, the DSMC will work with the investigator to finalize the plan and assure that it is implemented.

Enrollment of the study participants by months:

Month	Approached	Eligible	Randomized	Withdrawn	Actual #	Cumulative #
1						
2						
3						
4						

Subject Status:

Patient ID	Date enrolled	Date completed	Status (Active/ completed / Withdrawn)	Reason of withdrawal	Adherence	Intervention duration
1						
2						
3						
4						

Adverse events (AE) Patient ID

Patient ID	AE Onset	AE End	Severity	Related to intervention	Action taken	Outcome	Comment
1							
2							
3							
4							

Appendix

Withdrawal Form

I ..... myself thesis case no..... of Dr. Mohammad Shaifuddin Shourav, Hereby I withdraw myself/ my patient from signed protocol of treatment. I will continue the treatment of myself/my patient according to standard protocol.

Name.....Signature/Thumb Impression:

Name of Witness: .....Signature/Thumb Impression: .....

Date: .....

Name & Signature of researcher.....