

 **Rawalpindi Medical University**

 **Rawalpindi RMU**

 Interventional research protocol

 Phase iv post marketing trials



**Instruction**

**Tool Summary Sheet**

**RMU Interventional Protocol Template**

**Purpose:**

The purpose of this document is to provide a standardized instructional template for investigators preparing a protocol for interventional studies (drug, device, or procedural) conducted under Rawalpindi Medical University (RMU). This template is primarily intended for Phase IV post-marketing studies

**Audience/User:**
Principal Investigators (PIs), Resident Researchers, and Study Staff preparing research protocols at RMU or affiliated teaching hospitals.

**Scope:**
This protocol template is intended for:

Interventional studies involving approved drugs, devices, or procedures.

Single-center or multicenter studies where RMU is either the lead or a participating site.

Phase IV studies (post-marketing surveillance or effectiveness studies).

**Guiding Principles of Responsible Research**

This protocol template is developed in alignment with international ethical and regulatory standards, including the Declaration of Helsinki, the International Council for Harmonization (ICH) Good Clinical Practice (GCP) guidelines, SPIRIT and CONSORT guidelines and applicable national regulations. It is intended to ensure ethical integrity, scientific validity, and regulatory compliance in interventional research.

**Best Practice Recommendations**

 Use this template to ensure your protocol includes all required elements.

 Adapt this template as needed to fit the specific requirements of your study, while maintaining the essential structure and content.

 The examples provided in this template serves as a general guideline only and these are some among many possible scenarios; customize it according to your own research context.

 Do not remove headings or subheadings, nor change their order. If certain fields are not applicable to your research, indicate as N/A.

 For multicenter studies, ensure that this version aligns with the sponsor’s protocol and includes RMU-specific details where applicable.

 Maintain consistent formatting throughout the document by using embedded styles (headings, tables, bullets).

* Delete this first introductory pages after protocol is complete.

 Replace all placeholder text (e.g., <Insert Title>, [Insert Date]) with relevant information.

 Complete all tables (e.g., version control, objectives, outcomes) clearly and ensure uniform formatting.

 Submit the finalized protocol, including version history, signatures, and required appendices (e.g., informed consent forms, CRFs), to the ERB

* The instructions are given < > while blue italic text is example. Remove instructions and examples in blue italic and replace with your content

**Formatting and Technical Notes**

* Font and Style: Use a clear, professional font (e.g., Times New Roman or Calibri, size 11–12 pt). Use bold for section headings and standard formatting for content.
* Placeholders: Text enclosed in < > indicates placeholders—replace with appropriate information and remove the brackets.
* Version Control: Use decimal versioning (e.g., Version 0.1, 0.2 for drafts; 1.0 for first final submission). All updates or amendments should follow numeric progression (e.g., 2.0 → 2.1 draft → 3.0 final).
* Consistency: Ensure terminology and structure are consistent across all protocol sections.
* Not Applicable Sections: If a section does not apply to your study, write “N/A” clearly in that section.
* Edits and Comments: Remove all instructional text after use.
* Update table of contents after the document has been finalized

< The University Residency Program (Year) and RMU Monogram are applicable **only** for RMU resident trainees enrolled in MS/MD or FCPS programs.
For all other applicants, please include the **study title**, **principal investigator's name**, and **'Document Submitted By'** section.
The document **must be submitted by one of the investigators listed in the study protocol**. >

**University Residency Program 2025**

**Rawalpindi Medical University**

<



SYNOPSIS

Insert title

**SUBMITTED BY:”**

Submitted By:

Supervised By:

# Protocol version control

|  |  |  |
| --- | --- | --- |
| Version number  | Date  | Summary of changes  |
| 1.0 | 24/5/2025 | First draft submitted  |
|  |  |  |
|  |  |  |

# STATEMENT OF COMPLIANCE

The research protocol identified above has been developed in accordance with all applicable ethical guidelines, including but not limited to the principles of the Declaration of Helsinki, Good Clinical Practice (GCP) International Council for Harmonization (ICH), and all relevant national and institutional regulations.

# Signature page

**Principal Investigator Statement**

I have read and understood the contents of this research protocol titled:

**[Insert Full Protocol Title]**

**Protocol Number/Version:** [Insert Number and Date]

I agree to conduct this study in accordance with the protocol, Good Clinical Practice (GCP), applicable regulatory requirements, and institutional policies. I will ensure the safety, rights, and well-being of study participants are protected at all times.

I accept responsibility for the overall conduct of the study at this site and for ensuring that all study personnel are appropriately trained and supervised.

**Principal Investigator:**
Name: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Signature: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Date: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Institution: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

# List of abbreviations

|  |  |
| --- | --- |
| CRF | Case report form |
| DMC | Data monitoring committee |
| DMSP | Data monitoring and safety plan  |
| EDC | Electronic data capture  |
| GCP  | Good clinical practice  |
| ERB | Ethical review board |
| PI | Principal investigator  |
| SAE | Serious adverse events  |
| SAP | Statistical analysis plan  |
| RMU | Rawalpindi Medical university RWP |
| WHO | World health organization  |

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# Protocol summary

< The information in this section should be consistent with information provided in the body of the protocol. The information required is generic not personal such as organizational address, phone number , email address is required >

|  |  |
| --- | --- |
|  Scientific Title  |  |
| Public Title  |  |
| Primary registryPrimary registry identifier number Date of primary registry  | Describe the primary registry the study is registered. If the study is yet not registered then register the  |
| Source(s) of monetary and material support  |  |
| Primary sponsor  |  |
| Secondary sponsor  |  |
| Contact for public inquiry  | Name Academic qualification/Affiliation Phone numberEmail addressAddress  |
| Contact for scientific inquiry  | Name Academic Qualification/Affiliation Phone number Email addressAddress  |
| Study sites  | Mention all study sites  |
| Study objectives  | State key primary and secondary study objectives  |
| Population  | Target population, sample size |
| Description of interventions  | Brief description of study interventions |
| Study duration  | Time to complete the study  |
| Subject participation duration  | Individual participation in the research  |

# Roles and responsibilities

< The information required is generic and not personal. Institutional phone number, email id and address are required. For Visitor and Multi-center studies where RMU is a site provide the principal investigator at the lead site, principal investigator RMU

Provide list of all study investigators . >.

|  |  |
| --- | --- |
| Principal investigator  | NameAcademic qualification Designation affiliationPhone number Email address Address   |
| Resident trainee  | Name Academic qualification Year training Phone number Email address Address  |

# Introduction

## Background

* Begin with a brief explanation of the health condition or clinical problem under investigation, using clear, concise language suitable for both clinical and academic readers.
* Describe the significance of the problem in terms of patient burden, impact on daily life, disability, or healthcare costs.
* Provide epidemiological data or statistics (e.g., global/regional prevalence, affected age groups, gender distribution, high-risk populations).
* State the problem clearly—what is not working well with current treatment, what issue persists, or what is unknown.
* Give a historical overview of the interventions used to manage this condition, highlighting key milestones and developments in treatment approaches.
* Mention currently accepted or commonly used interventions in clinical practice related to the research problem.
* Review relevant recent literature: summarize findings from prior studies on the interventions you are comparing, focusing on outcomes such as effectiveness, safety, patient satisfaction, etc.
* Identify any gaps, inconsistencies, or limitations in the existing literature (e.g., limited sample size, lack of head-to-head comparison, short follow-up, lack of data in specific populations).
* Justify the need for your study based on this literature gap and clinical relevance—explain how your study will add to current knowledge or improve patient care.
* If applicable, refer to any local or regional data that strengthen the rationale for conducting the study in your specific setting.

##  Study rationale

### In this section describe the rationale of the research

## Study risk assessment

### Potential risk

<*The potential risks are anticipated risks for the study and evidence from the literature review. Give know major or minor risks incidence with the study interventions. The potential risk will help us define what are anticipated or expected. The potential risks stated in this section should be consistent with consent document. This will help to identify unexpected harms or adverse events that may be encountered during conduct of the study*>

### Potential benefits

<Describe the possible benefits that may result from participation in the study. This includes clinical benefits to individual participants, such as improved health outcomes or enhanced disease management resulting from research procedures or interventions. Also mention any anticipated contribution to scientific knowledge that could benefit the broader community in future clinical or public health practices. Do not list financial compensation or monetary incentives as potential benefits; these should be addressed in a separate section. >

### Study risk /benefit analysis

< This section should provide an assessment of whether the potential benefits of the study outweigh the possible risks. In the context of a Phase IV trial, where an approved drug is being compared with another approved drug, or where a change in dose, regimen, or route is being evaluated, clearly outline the expected benefits of the new application. Emphasize how the new intervention, drug, or device may offer advantages over the existing standard of care—such as improved efficacy, reduced side effects, greater patient convenience, or enhanced adherence. The rationale should support that the potential improvements justify conducting the study and may lead to better outcomes than current practices. >

### Study risk level

< Outline in this section, with justification, the risk category into which the study falls, based on the nature of the intervention and the participant population. Clearly explain the rationale for this classification using the **TraCS Institute Clinical and Translational Research Center Protocol Risk Assessment and Monitoring Guidelines**. Additionally, specify the level of monitoring required for the study according to these guidelines, ensuring that the proposed oversight is appropriate for the assessed risk level >

1. ***No Greater than Minimal Risk*** *– “Minimal Risk” means that the probability and magnitude of harm or discomfort anticipated in the research are not greater than those ordinarily encountered in daily life or during the performance of routine physical and psychological examinations or tests and where confidentiality is adequately protected. This category includes protocols that pose “no greater than minimal risk” according to federal regulations.* ***Requires Minimal Intensity Monitoring.***

*Examples of risk level 1:*

* *Study poses no more risk than expected in daily life (blood draw, physical exam, routine psychological testing).*
* *Non-interventional studies (e.g., observational studies of behavior or nutrition). Survey/questionnaire studies of a non-sensitive nature.*

***2 Minor Increase over Minimal Risk*** *– Research involves a minor increase over minimal risk. There is medium to high probability of the occurrence of a low-severity event that is completely reversible (e.g., headache from lumbar puncture) or the likelihood of serious harm occurring is low (e.g., fatal anaphylaxis from allergy skin testing).* ***Requires Low Intensity Monitoring.***

*Examples of risk level 2:*

* *Studies of normal volunteers using well-described research procedures and/or single dose of experimental agent.*
* *Post-marketing study - phase IV drug study or device (as defined by FDA) with minor safety concerns. Interventions or invasive procedures present low risks, reasonably commensurate with those expected in medical or dental practice.*
* *Studies that involve sensitive information or a potential risk of breach of confidentiality*

***3 Moderate Risk*** *- Risks are recognized as being greater than minimal, but are not considered high. There is a medium to high probability of a moderate-severity event occurring as a result of study participation (e.g., reversible worsening of a non-fatal disease such as seasonal allergy while receiving placebo or pneumonia from a bronchoscopy), but there is adequate surveillance and protections to identify adverse events promptly and to minimize their effects.* ***Requires Moderate Intensity Monitoring.***

*Examples of risk level 3:*

* *Subjects treated with placebo for a recognized disease*
* *Substantial risk (>5%) of a Serious Adverse Event originating from the underlying condition of the enrolled subject*
* *Involves subjects with serious viral, autoimmune, and malignant illness in a treatment study of moderate risk Phase I or II, clinical trial with available safety data in humans*
* *Minimal risk studies involving vulnerable populations (e.g. subjects with impaired capacity to give informed consent)*

***4 High Risk -*** *The study risk is greater than a moderate risk study due to the increased probability for generating serious adverse events. There is a high probability of an event that is serious and prolonged or permanent occurring as a result of study participation. In situations where there is the prospect of direct benefit to the subject, study risks are high or there is significant uncertainty about the nature or likelihood of adverse events.* ***Requires High Intensity Monitoring.***

*Examples of risk level 4:*

*Clinical trials of interventions to prevent or treat diseases that lead to death or irreversible morbidity Involves an intervention or invasive procedure with substantial risk or potential for severe toxicity An investigator-initiated IND trial*

*Implantation of a device with an IDE*

*Involves the use of a new chemical or drug for which there is limited or no available safety data in humans A gene transfer study or research involving recombinant DNA molecules*

*An investigator initiated, phase III, clinical trial*

*Industry sponsored, multi-center, randomized, clinical trials (phase 2b, 3, and 4)*

# Study objectives and outcomes

< The study objectives should address both **efficacy** and **safety** parameters. In studies evaluating the efficacy of an intervention—whether a drug or device—it is essential to include specific objectives related to potential harms as well.

Each study should clearly define at least one **primary objective** and may include one or more **secondary objectives**. The outcomes may be **patient-related outcomes** (e.g., morbidity, mortality) or **surrogate markers** (e.g., change in HbA1c levels).

For each objective—whether related to potential benefit or harm—a brief **justification or rationale** must be provided. This includes:

* The **reason** for including it as a study objective
* The **instrument, tool, or questionnaire** used to measure the objective
* The **time point(s)** during the study when the objective will be assessed

Primary and secondary objectives should be presented in **separate tables** for clarity.>

|  |  |  |  |
| --- | --- | --- | --- |
| Study objective  | Rationale /justifications  | Specific instruments/scale  | Time frame  |
| To compare mean systolic blood pressure (SBP) reduction between Drug A and Drug B | SBP is a validated surrogate for cardiovascular risk; commonly used endpoint in hypertension trial | Digital sphygmomanometer, average of 3 seated readings | Baseline and 12 months |
| To assess incidence of dry cough (Drug A) and dizziness (Drug B | Known side effects of ACE inhibitors and ARBs; may affect adherence | Adverse event reporting form, patient diary | Monthly follow-up for 12 months |

# Trial design

<This section should provide a detailed description of the trial design, including whether the study is designed to demonstrate superiority, non-inferiority, or equivalence between interventions. It should specify the type of design being used, such as a parallel-group, crossover, or factorial design, along with the allocation ratio (e.g., 1:1, 2:1). The description should also indicate whether the trial is being conducted at a single center or across multiple centers. A brief overview of the study interventions should be included, outlining the nature and purpose of each treatment or comparison group. Additionally, the section should state the target sample size, method of group allocation randomized or nonrandomized, the total duration of the study from initiation to completion, and the expected duration of each participant's involvement in the trial, including follow-up. This information provides a clear understanding of how the study is structured and how participants will be managed throughout its course.>

*This is a multicenter, randomized, open-label, parallel-group, superiority trial designed to compare the effectiveness and safety of Drug A (an ACE inhibitor) versus Drug B (an angiotensin receptor blocker) in the management of essential hypertension. Participants will be randomly assigned in a 1:1 ratio to receive either Drug A or Drug B. The trial will be conducted across five tertiary care hospitals. Each intervention will be administered according to standard clinical guidelines for a period of 12 months. The total target sample size is 400 participants, with 200 in each treatment arm. The overall duration of the study is expected to be 18 months, including recruitment, treatment, and follow-up. Each participant will be involved in the study for approximately 12 months, including baseline assessment and scheduled follow-up visits at 1, 3, 6, 9, and 12 months to evaluate clinical outcomes and monitor for adverse events. The study aims to determine whether Drug A is superior to Drug B in reducing systolic blood pressure and improving treatment tolerability in a real-world setting.*

**CONSORT 2010 Flow Diagram**

##  Follow-Up

Analysed (n= )
 Excluded from analysis (give reasons) (n= )

##  Analysis

Analysed (n= )
 Excluded from analysis (give reasons) (n= )

Lost to follow-up (give reasons) (n= )

Discontinued intervention (give reasons) (n= )

Lost to follow-up (give reasons) (n= )

Discontinued intervention (give reasons) (n= )

## Enrollment

Allocated to intervention (n= )

 Received allocated intervention (n= )

 Did not receive allocated intervention (give reasons) (n= )

##  Allocation

Allocated to intervention (n= )

 Received allocated intervention (n= )

 Did not receive allocated intervention (give reasons) (n= )

Randomized (n= )

Assessed for eligibility (n= )

Excluded (n= )

  Not meeting inclusion criteria (n= )

  Declined to participate (n= )

  Other reasons (n= )

# Trial settings

<This section should clearly specify the **study site(s)** where the research will be conducted. It must include details about the **settings for patient recruitment**, which may involve but not limited to tertiary care hospitals, community clinics, outpatient departments, or inpatient wards. etc

For **RMU resident trainees**, it is essential to mention the specific **RMU-affiliated hospitals** participating in the trial.

Additionally, this section should identify the following:

* The **recruitment center(s)** or **clinical site(s)**
* The **practicing department(s)** responsible for patient care and trial execution
* The **site(s) where the intervention will be administered**

Any **supporting department(s)** involved, such as **laboratory**, **radiology**, or **pharmacy**, that contribute to diagnostic, monitoring, or supportive functions within the trial >

*The study will be conducted at* ***Benazir Bhutto Hospital, Rawalpindi****, a tertiary care teaching hospital affiliated with Rawalpindi Medical University (RMU). Participants will be recruited from the* ***outpatient department of internal medicine****, where patients with essential hypertension are routinely managed. The* ***Department of Medicine*** *will serve as the primary site for patient recruitment, clinical evaluation, and administration of the study intervention. Laboratory investigations, including serum potassium and renal function tests, will be conducted in the hospital’s* ***central pathology laboratory****. If required, imaging support such as chest X-rays or ECGs will be provided by the* ***radiology department****. This setting provides access to the target patient population and is well-equipped with the necessary clinical and diagnostic infrastructure to support the safe and effective conduct of the trial*

# Participants

< In this section give participants inclusion and exclusion criteria. If possible mention the eligibility criteria for people involved in administration of intervention >

## Inclusion criteria

## Exclusion criteria

## Recruitment

< This section should describe the planned strategies to achieve the target sample size. These strategies may include the use of electronic media, print media, posters, and patient information fliers to raise awareness about the study. Any such recruitment materials must be approved by the relevant ethics committee . If investigators plan to review hospital records or inpatient files to identify potential participants, the process for accessing these records must be outlined, including how privacy and confidentiality will be maintained. The procedure for approaching identified patients, obtaining informed consent, and inviting them to participate in the study should also be described in detail. >

*To achieve the target sample size, eligible patients will be identified during routine outpatient visits to the Department of Medicine at Benazir Bhutto Hospital, Rawalpindi. In addition, hospital records from the internal medicine ward will be reviewed by authorized investigators to screen for patients who meet the inclusion criteria. Permission to access patient files will be obtained from the department head, and confidentiality will be strictly maintained during record screening. Identified patients will be approached during their hospital stay or follow-up visit by a member of the research team. They will be provided with detailed study information and a consent form. Only those who voluntarily agree to participate will be enrolled in the study. If needed, printed fliers describing the study will be displayed in the outpatient area, pending approval from the institutional ethics committee*.

# Study interventions

## Study interventions details

The investigators should describe sufficient details about the intervention which allows replication. All trial related procedures should be described. For drug or device provide the generic name and also commercial products (names) used in the trial should be described. Additionally, information regarding medicine/ device procurement/ storage and dispense should be provided. The following details of intervention should be provided

* Components of the intervention and comparator
* How they will be administered
* When and how long they will be administered
* Any procedure for tailoring the intervention to individual participants
* If the intervention is the therapeutic procedure such as MESH repair technique in surgery then details of the procedure along with necessary photographs required for illustration should be given>

*Participants in the intervention group will receive amlodipine 5 mg once daily, a calcium channel blocker used in the management of hypertension. The active comparator group will receive losartan 50 mg once daily, an angiotensin II receptor blocker (ARB) also approved for the treatment of hypertension. Both medications will be administered orally each morning for a duration of 12 weeks. The first dose of the assigned medication will be administered under medical supervision at the study site, with blood pressure and heart rate monitored for one hour post-administration to assess immediate tolerability. If, at the 4-week follow-up, a participant’s systolic blood pressure remains above 140 mmHg, the dose of amlodipine may be increased to 10 mg daily and the dose of losartan may be increased to 100 mg daily, based on individual response and clinical judgment. Study medications will be procured from authorized pharmaceutical suppliers, stored at controlled room temperature (15–25°C), and dispensed in 4-week supplies at scheduled follow-up visits. Tailoring is permitted based on blood pressure control and tolerability. Adverse effects, such as peripheral edema in the amlodipine group or hyperkalemia in the losartan group, will be monitored regularly. Medication adherence will be assessed through pill counts and participant self-reporting at each visit.*

## Criteria for discontinuation /modification of allocated treatment

<This section describes criteria for discontinuation or modification of the allocated treatment which include both active and comparator group based on but not limited to improvement or worsening of the disease, in response to harms / tolerability or patient request >

*Participants in either treatment group may have their allocated medication discontinued or modified under certain conditions. If a participant develops severe adverse effects such as symptomatic hypotension, significant peripheral edema (in the amlodipine group), or hyperkalemia (in the losartan group), the medication will be either dose-reduced or discontinued based on clinical judgment. Treatment may also be modified if blood pressure readings fall below 100/60 mmHg on two consecutive visits or if the patient reports intolerable side effects despite supportive measures. Participants who show consistently controlled blood pressure for more than 8 weeks without symptoms may have their medication tapered or maintained at the lowest effective dose, as per the investigator’s discretion. Additionally, participants may request to stop or modify treatment at any time, and this will be documented along with the reason. All decisions regarding treatment modification or discontinuation will be recorded in the case report form, and participants will continue to be followed up for study outcomes even if the allocated treatment is stopped.*

## Strategies to improve adherence

<This section should describe the strategies that will be employed to improve and monitoring adherence to both the intervention and the comparator throughout the trial. Strategies may include regular reminders, patient education, follow-up calls, and simplified dosing schedules. Monitoring procedures can include tablet counts, drug diary reviews, electronic monitoring systems, and attendance records for behavioral or training sessions. Additional methods such as usage logs, compliance checklists, or digital tracking tools may also be appropriate. >

*To enhance adherence, participants will receive initial counseling and written instructions. For those on metformin, a once-daily dosing schedule will be followed, supported by weekly SMS reminders. In the lifestyle group, attendance at biweekly dietary and exercise sessions will be recorded, with follow-up for missed sessions. Medication adherence will be monitored through pill counts and patient diaries, while lifestyle adherence will be tracked using activity and diet logs. Random phone check-ins will be conducted to reinforce compliance. All adherence data will be recorded in case report forms.*

## Concomitant care that is allowed or prohibited during the trial

<Use of other medications during the trial period can interfere with the study treatment and potentially mask or exaggerate its effects. Therefore, investigators should specify which concomitant medications are allowed or prohibited during the study. This includes drugs that may interact pharmacologically with the investigational product or influence the condition being studied. All concomitant medications taken by participants at any point during their involvement in the trial must be documented in the case report forms, including dosage, frequency, and indication>

*Medications such as NSAIDs, corticosteroids, or any drugs known to significantly affect blood pressure will be prohibited during the study period, as they may interfere with the evaluation of the trial drug’s efficacy. If a participant develops a newly diagnosed condition that requires the use of any of these prohibited medications, they will be considered for withdrawal from the trial to maintain the integrity of the study outcomes. In such cases, the decision will be made by the principal investigator based on clinical judgment and documented accordingly.*

## Reasons for participation withdrawal /handling

<The reasons which make patient to withdraw from the study should be documented on case report forms. The patients are free to leave the trial at any stage and can withdraw consent. Besides the study investigators can withdraw or discontinue patient(s) from the study. such procedures and criteria for patient withdraw / discontinue from the study should be clearly stated and defined in the protocol>

*Patients are free to withdraw from the trial at any time without providing a reason and without any penalty or loss of benefits. Investigators may also withdraw a patient from the study under certain conditions, such as:*

* *The development of new medical conditions that make continued treatment with the investigational product potentially harmful.*
* *The occurrence of adverse events that require discontinuation of the trial medication for the patient's safety.*
* *Issues related to poor compliance or tolerability of the trial medication, which may compromise the integrity of the study or the well-being of the patient.*

## Premature termination or suspension of the study

The study may be prematurely terminated or suspended under various circumstances, including but not limited to the following

* Poor adherence to the trial protocol
* interim analysis indicates that further continuation of the study is unlikely to provide meaningful results
* Significant risk or harm identified to study participants
* Emergence of new scientific or clinical evidence requiring discontinuation of interventions
* Withdrawal of favorable opinion by the Ethics Review Board (ERB)
* Regulatory authority requires suspension or termination
* Sponsor decides to stop the trial due to feasibility or strategic reasons
* Lack of funding or resources
* Inadequate participant enrollment or high dropout rate

 In case of study termination or suspension:

* All relevant stakeholders will be notified promptly
* Necessary documentation will be completed and submitted to regulatory authorities, ethics committees, and trial registries
* Measures will be taken to ensure participant safety and ethical handling of their data
* Study data up to the point of termination will be managed and analyzed as per protocol and regulatory requirements

# Study outcomes

**<** Describe in this section study outcomes or endpoints. listed in order of importance—beginning with the primary outcomes followed by secondary and tertiary outcomes. Each outcome should be described in detail, including the type of data collected (nominal, ordinal, interval, or ratio), the analysis metric used (such as change from baseline or time to event), the method of data aggregation (such as mean, median, or proportion), and the specific time points within the study when the outcome will be measured. In addition, all procedures and instruments used to measure outcomes should be clearly introduced and described. **>**

## Primary outcome

*Change in Sleep Quality from Baseline to Week 8*

*Sleep quality will be assessed using the Pittsburgh Sleep Quality Index (PSQI), a validated self-reported questionnaire that evaluates various aspects of sleep over the past month. The data collected will be of ordinal type, as the PSQI produces a score based on categorical responses that reflect increasing levels of sleep disturbance. The primary analysis metric will be the change in PSQI score from baseline, allowing evaluation of improvement or worsening in sleep quality over time. Data will be aggregated using the mean and standard deviation to summarize group-level changes. PSQI assessments will be conducted at baseline, Week 4, and Week 8 to monitor changes throughout the intervention period*

## Secondary outcomes

*Fundoscopic Changes from Baseline to Week 12*

*Retinal changes will be detected using fundoscopy, performed by a trained ophthalmologist. The data collected will include nominal variables indicating the presence or absence of abnormal findings, as well as ordinal variables reflecting the severity of changes based on a standardized grading scale. The primary analysis metric will be the change from baseline to assess the development or progression of retinal abnormalities. Data will be aggregated as the proportion of participants exhibiting new or worsening retinal findings. Fundoscopic examinations will be conducted at baseline, Week 6, and Week 12 to monitor changes over the course of the study*.

*Fundoscopy will be performed by a trained ophthalmologist using a slit-lamp biomicroscope with a 90D lens.*

*Pupillary dilation with tropicamide 1% will be done prior to the exam.*

*Retinal findings will be graded based on a standard severity scale (e.g., Early Treatment Diabetic Retinopathy Study [ETDRS] criteria).*

*Images will be reviewed by two independent assessors blinded to the treatment group.*

# Assessment of safety

## Harms

< Harms may include patient-related outcomes such as clinical complications, hospitalizations, or mortality, and may also involve objective markers such as abnormal laboratory values—for example, elevated liver enzymes or changes in ECG findings. The protocol will specify how adverse events will be captured throughout the study duration, including who is responsible for identifying and reporting harms, and whether the assessor will be blinded to study group allocation to minimize bias. Retain below the definitions of adverse events, serious adverse events unanticipated problems in your protocol >

### Adverse Event

An adverse event is defined as any untoward or unfavorable medical occurrence in a study participant, including any abnormal sign (such as abnormal physical examination or laboratory findings), symptom, or disease that is temporally associated with the subject’s participation in the research, regardless of whether it is considered related to the investigational product or procedures. This includes both anticipated and unanticipated medical occurrences that may or may not be related to the study intervention.

### Serious Adverse Event SAEs

A serious adverse event (SAE) is an adverse event that meets one or more of the following criteria: results in death, is life-threatening (i.e., places the subject at immediate risk of death at the time of the event), results in inpatient hospitalization or prolongation of existing hospitalization, leads to a persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect. Additionally, medical events that may not meet the above criteria but require medical or surgical intervention to prevent one of these outcomes may also be considered serious, based on clinical judgment.

### Unanticipated Problems UP

Unanticipated problems are those that are unexpected in nature, severity, or frequency, considering the research procedures outlined in the protocol and informed consent, as well as the characteristics of the study population. These problems are considered related or possibly related to participation in the study, where "possibly related" implies a reasonable possibility that the event was caused by study procedures. Furthermore, they suggest that participants or others may be at greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

*For instance, a participant receiving the investigational product may develop elevated alanine aminotransferase (ALT) levels detected during routine safety laboratory testing at Week 4. Although initially asymptomatic, this laboratory finding is recorded as an adverse event. If the ALT level exceeds three times the upper limit of normal and is accompanied by jaundice, it is classified as a serious adverse event and must be reported immediately to the sponsor and ethics committee.*

*If this liver enzyme elevation and associated symptoms were not anticipated based on prior safety data or preclinical findings, and if the frequency or severity is greater than expected, it may also qualify as an unanticipated problem. This is especially the case if the event is determined to be possibly related to the investigational product and suggests a greater risk to participants than previously recognized. In such instances, the event must be reported as an unanticipated problem to the Institutional Review Board (IRB), following regulatory and ethical guidelines.*

## Relationship of the adverse events to the study

all adverse events (AEs), regardless of their relationship to the study intervention (drug/device/procedure), must be documented in the Case Report Forms (CRFs).

**Causality Assessment:**

The relationship between the adverse event and the study intervention will be assessed using standard criteria to determine if the event is:

* Related (possible or probable)
* Unrelated

1. Related Adverse Event

An AE is considered *related* to the study intervention if:

* There is a reasonable temporal relationship between the administration of the intervention and the onset of the AE.
* The AE is known to occur as a reaction to the study intervention based on existing literature or previous reports.
* Alternative causes (e.g., underlying conditions or concomitant medications) are unlikely

2. Unrelated Adverse Event

* An AE is considered *unrelated* if:
* There is no temporal association between the study intervention and the AE.
* A more likely cause for the event is identified (e.g., pre-existing conditions, intercurrent illness, or other medications).

## Severity of the adverse events

In this section describe the procedures to establish the severity of the adverse events. Which may include clinical decisions, clinical guidelines or toxicity tables. describe who will decide the severity of the adverse events. Following grading system can be employed

The following grading system will be employed:

* **Grade 1 – Mild:** No medical intervention required; no significant impact on daily activities.
* **Grade 2 – Moderate:** Minimal symptoms requiring only local or non-invasive interventions; mild impact on daily function.
* **Grade 3 – Severe:** Marked symptoms requiring medical attention and invasive interventions; significant interference with daily life.
* **Grade 4 – Life-threatening or Disabling:** Events requiring urgent medical intervention and hospitalization.
* **Grade 5 – Fatal:** Death related to the adverse event.

*The severity of adverse events will be determined using a standardized grading system to ensure uniform assessment and documentation. The grading will be based on clinical judgment, relevant clinical guidelines, and established toxicity tables, such as the Common Terminology Criteria for Adverse Events (CTCAE), where applicable.*

*The severity of each adverse event will be assessed by the Principal Investigator (PI) or a designated qualified physician on the research team. When necessary, the determination may involve consultation with clinical specialists or adherence to disease-specific guidelines*.

## Adverse events capture method

<Describe how the adverse events will be captured. Examples include but not limited to patient diaries, clinical examination/ progression notes. Explain Procedures to fill CRF forms about adverse events, how grading will be done. Etc >

*Adverse events (AEs) will be captured using a combination of active and passive surveillance methods throughout the study period. Data sources will include:*

* ***Patient self-reporting*** *through verbal communication or structured patient diaries, where applicable*
* ***Clinical examinations*** *during scheduled follow-up visits*
* ***Review of clinical progression notes*** *and medical records by the study team*

*At each study visit, participants will be specifically asked about any new symptoms or changes in health status. Clinical staff will also review physical findings and laboratory data to identify any AEs.*

*All identified adverse events will be documented in the Adverse Event section of the Case Report Form (CRF). The following details will be recorded:*

* *Description of the event*
* *Date of onset and resolution*
* *Severity (graded using the standard system outlined in Section 1.1)*
* *Assessment of causality (relationship to the study intervention)*
* *Action taken (e.g., discontinuation of study drug, additional treatment)*
* *Outcome of the event*
* *Whether it qualifies as a serious adverse event (SAE)*

*Severity grading will follow a standardized grading system such as the Common Terminology Criteria for Adverse Events (CTCAE) or trial-specific guidelines. Grading will be performed by the Principal Investigator or a designated qualified clinician based on clinical judgment and available clinical data.*

*All AEs and SAEs will be monitored, reviewed, and resolved in accordance with the trial’s Data Monitoring and Safety Plan. Documentation will be complete, timely, and consistent with Good Clinical Practice (GCP) standards.*

## Adverse events reporting procedures

All adverse events (AEs), serious adverse events (SAEs), and unanticipated problems, including serious unanticipated problems, will be promptly documented and reported according to applicable regulatory requirements.

These events must be reported to the following entities:

* The study sponsor
* Relevant regulatory authorities
* The Institutional Review Board (IRB)/Ethical Review Committee (ERC)

The timelines and reporting formats will adhere to national and institutional guidelines. Serious and unexpected adverse events that are related or possibly related to the study intervention must be reported within 24 to 72 hours, as per regulatory requirements.

Detailed procedures for identifying, documenting, evaluating, and reporting adverse events are outlined in the Data Monitoring and Safety Plan (DMSP) of this study. The plan includes specific responsibilities, timelines, and forms to be used during the reporting process.

# Participants timeline

< Describe in this section participant’s duration in research including all schedule visits along with time schedules for each visit which also include pre-randomization screening visits schematic diagram is highly recommended >

***Screening Visit***

***Visit Type: Screening
Time Frame: Week -2 to Day 0 (adjust as per protocol)***

* *Objectives & Activities:*
* *Obtain written informed consent for screening procedures.*
* *Evaluate participants against inclusion and exclusion criteria.*
* *Perform medical history review and review relevant medical records.*
* *Conduct physical examination and record vital signs.*
* *Obtain screening laboratory tests (e.g., CBC, renal function, liver enzymes).*
* *Perform radiological assessments if required (e.g., chest X-ray, ultrasound, ECG).*
* *Assess concomitant medications.*
* *Record total number of participants screened.*
* *Only eligible participants proceed to randomization.*

***Randomization Visit***

***Visit Type: Randomization
Time Frame: Day 0***

*Objectives & Activities:*

* *Confirm continued eligibility per inclusion/exclusion criteria.*
* *Obtain updated medical history and review any new symptoms or diagnoses.*
* *Conduct patient education session about study procedures and interventions.*
* *Collect baseline assessments:*
* *Demographics and anthropometric data (e.g., weight, height, BMI).*
* *Vital signs (e.g., blood pressure, pulse).*
* *Laboratory and radiological tests as required by protocol.*
* *Administer baseline questionnaires or scales.*
* *Assign unique trial ID to participants.*
* *Randomize participants into:*
* *Intervention group (n = )*
* *Active comparator group (n = )*

*3.* ***Follow-Up Visit 1***

***Visit Type: Follow-up Assessment
Time Frame: Week X / Day X (insert specific schedule)***

*Objectives & Activities:*

* *Assess intervention adherence and compliance.*
* *Collect data on primary and secondary outcomes.*
* *Repeat necessary clinical evaluations, lab tests, or imaging as per protocol.*
* *Administer relevant questionnaires or scales.*
* *Monitor for adverse events or side effects.*

*4****. Follow-Up Visit 2***

***Visit Type: Follow-up Assessment
Time Frame: Week X / Day X (insert specific schedule)***

*Objectives & Activities:
(Same as Follow-Up Visit 1)*

*5****. Final Follow-Up Visit***

***Visit Type: Follow-up Assessment
Time Frame: Week X / Day X (insert specific schedule)***

*Objectives & Activities:*

* *Final assessment of intervention compliance.*
* *Final data collection for all outcome measures.*
* *Conduct end-of-study physical examination and clinical review.*
* *Complete all lab/radiological tests and questionnaires.*
* *Discuss post-study follow-up or referral if necessary.*

Figure. Example template of recommended content for the schedule of enrolment, interventions, and assessments.\*

|  |  |
| --- | --- |
|  | **STUDY PERIOD** |
|  | **Enrolment** | **Allocation** | **Post-allocation** | **Close-out** |
| **TIMEPOINT\*\*** | ***-t1*** | **0** | ***t1*** | ***t2*** | ***t3*** | ***t4*** | ***etc.*** | ***tx*** |
| **ENROLMENT:** |  |  |  |  |  |  |  |  |
| **Eligibility screen** | X |  |  |  |  |  |  |  |
| **Informed consent**  | X |  |  |  |  |  |  |  |
| ***[List other procedures]*** | X |  |  |  |  |  |  |  |
| **Allocation** |  | X |  |  |  |  |  |  |
| **INTERVENTIONS:** |  |  |  |  |  |  |  |  |
| ***[Intervention A]*** |  |  |  |  |  |  |  |  |
| ***[Intervention B]*** |  |  | X |  | X |  |  |  |
| ***[List other study groups]*** |  |  |  |  |  |  |  |  |
| **ASSESSMENTS:** |  |  |  |  |  |  |  |  |
| ***[List baseline variables]*** | X | X |  |  |  |  |  |  |
| ***[List outcome variables]*** |  |  |  | X |  | X | etc. | X |
| ***[List other data variables]*** |  |  | X | X | X | X | etc. | X |

# Group allocation and blinding procedures

< Methods of Group Assignment

In experimental research, participants can be allocated to study groups using randomized or non-randomized methods.

Non-Randomized Methods (Quasi-Experimental Studies)

In quasi-experimental studies, group allocation is non-randomized and may rely on but not limited to the following methods :

* Clinical Judgment: Investigators may assign participants to groups based on clinical characteristics or disease severity.
* Patient Preference or Consent: Participants may choose their preferred group based on informed consent.
* Availability of Resources: Allocation may depend on the availability of treatment or facility resources.
* Time-Based Allocation: Participants may be assigned based on time slots (e.g., those enrolled during a certain time period are placed in one group).
* Geographic or Institutional Factors: Grouping may be based on location or the institution where the participant is receiving care.

These methods introduce potential selection bias, and appropriate statistical adjustments or matching techniques should be applied to address these limitations.

**Randomized Methods (Experimental Studies)**

In randomized studies, participants are assigned to groups using objective and unbiased methods to ensure comparability between groups and reduce selection bias. Common methods include:

* Simple Randomization: Using a random number generator, computer algorithm, or lottery method to assign participants.
* Stratified Randomization: Participants are first stratified based on key variables (e.g., age, gender, disease severity), and then randomized within each stratum.
* Covariate Adaptive Randomization: Allocation is adjusted as the trial progresses to balance important covariates across treatment groups.

**Randomization Steps**

**Sequence Generation** The randomization sequence must be generated using a reliable and secure method.

This may involve web-based randomization software, centralized randomization systems, or services provided by an independent third party (e.g., a data coordinating center or statistics unit).

Investigators should have no involvement in the sequence generation to ensure objectivity.

The process should be clearly documented and transparent to avoid any potential manipulation or disclosure of the allocation sequence.

**Allocation Concealment Mechanism**

Procedures must be in place to conceal group assignment until the moment of allocation. Examples include:

Sealed, opaque, sequentially numbered envelopes

Centralized web-based or telephone randomization services

These steps are essential to prevent selection bias and preserve the integrity of the study.

**Implementation**

The responsibility for implementing the randomization process should be delegated to personnel not involved in patient recruitment or treatment.

The person generating the randomization sequence must be independent from those assigning participants to groups.

A designated data manager or trial coordinator should maintain the randomization records securely, with limited access.>

## Group assignment / randomization

### Sequence Generation

*Stratified block randomization will be used to ensure balance in key prognostic variables across study groups. Participants will be stratified based on [e.g., age group (<60 vs ≥60 years) and disease severity (mild vs moderate/severe)], and within each stratum, randomization will occur in variable block sizes (e.g., blocks of 4 or 6) to maintain allocation concealment and balance over time. The randomization sequence will be generated using validated computer software by an independent statistician who is not involved in participant recruitment or clinical management. The sequence will be securely stored and accessible only to designated trial personnel responsible for allocation.*

### Allocation Concealment Mechanism

*Allocation will be concealed using sealed, opaque, and sequentially numbered envelopes prepared for each stratum. Each envelope will contain the pre-assigned group based on the stratified block sequence. Envelopes will be opened sequentially only after confirming participant eligibility and obtaining informed consent.*

### Implementation

*An independent trial coordinator, who has no role in patient recruitment or treatment, will implement the randomization procedure. This individual will ensure that the correct envelope is selected based on the participant’s stratification characteristics and will record the allocation in a secure trial database. The randomization list and envelopes will be stored securely, with restricted access to preserve the integrity of the study.*

## Blinding and masking

< *Blinding, or masking, is a crucial aspect of clinical trial design. Knowledge of the assigned treatment can introduce various types of bias and errors. For example, if participants become aware they are not receiving their desired treatment, they may be more likely to withdraw from the trial, potentially compromising the validity of the results.*

*The trial protocol must clearly specify* ***who will be blinded to the treatment allocation****. This may include:*

Participants

Care providers

Outcome assessors

Data analysts

To maintain effective blinding, the protocol should outline the **specific interventions or strategies** that will be used. These may include the use of:

Identical placebos

Double-dummy procedures

Centralized randomization

Use of third-party blinding for data analysis

Blinding procedures can vary depending on the level of masking and the roles of those involved. Strategies to maintain blinding may also need to be tailored to individual participants or settings.

Importantly, the protocol must also describe **conditions under which unblinding is permissible**, such as in the case of serious adverse events or when knowledge of the treatment is necessary for patient safety. Clear procedures for emergency unblinding should be established to minimize risk to participants while preserving the integrity of the trial as much as possible.>

*This is a double-blind, randomized, placebo-controlled trial in which participants, care providers, outcome assessors, and data analysts will all be blinded to treatment allocation. To maintain blinding, the investigational drug and placebo will be identical in appearance, packaging, labeling, and administration schedule. A double-dummy design will be used in cases where treatments differ in route of administration; for example, participants receiving an oral drug will also receive a placebo injection, while those receiving an injectable treatment will receive a placebo tablet. Randomization will be managed through a centralized system, and treatment codes will be held by an independent party not involved in the trial. Unblinding will only be permitted when necessary for the clinical management of a participant, such as in the event of a serious adverse event requiring knowledge of the treatment for appropriate care. In such cases, the investigator may request emergency unblinding through the trial’s electronic system, and all instances will be documented and reported to the sponsor and ethics committee. Every effort will be made to minimize unblinding in order to preserve the scientific integrity of the trial, and participants who are unblinded may continue in the study if deemed safe and appropriate.*

# Statistical considerations

## Sample size estimation

<The following considerations should be addressed when estimating the sample size for the study. The statistical formula or software used for the calculation must be specified. A two-sided hypothesis test should be used for sample size estimation unless a one-sided test is scientifically justified and clearly explained in the protocol. The acceptable Type I error rate (α), typically set at 5%, and the Type II error rate (β), usually corresponding to a power of 80% or 90%, must be stated explicitly.

The sample size calculation must be based on the primary outcome measure. The outcome variable’s measurement scale—whether it is continuous (e.g., mean difference) or categorical (e.g., proportion)—should be clearly defined. The expected effect size must be stated and, where possible, justified using historical data, pilot studies, or relevant published literature.

Adjustments to the calculated sample size should be made to account for anticipated dropouts, withdrawals, or non-compliance. The estimated attrition rate and the rationale for its use should also be included in the sample size justification. All assumptions made in the calculation must be documented clearly in the protocol or the accompanying statistical analysis plan. >

## Statistical analysis

Study hypothesis

State the null and alternate hypothesis at least for the primary end point of the study

## Analysis plan

 <This section should describe statistical analysis plan

* Mention the software for used for data entry and analysis
* Define the measurement scales (nominal, ordinal interval or ratio ) for study variables
* Define how missing values will be handled in the data
* Define how descriptive statistics will be performed such as mean and standard deviation for continuous data or median interquartile range if data violates normality assumptions
* State statistical procedures/tests for checking assumptions of normality.
* Mention confidence level and p value for statistical inference
* State clearly statistical tests for different types of data
* State effect size for study end points such as efficacy parameters

## Subgroup analysis

<If subgroup analysis is planned state clearly with justification. For any subgroup analysis state power of the study in analysis>

## Interim analysis

<If interim analysis is planned mention its detail>

# Data collection quality and management procedures

## Data collection method

*<*This section outlines procedures of data collection and related procedures to ensure integrity of the collected data. Describe in this section how study data will be collected such as paper case report forms, or electronic data capture methods. If EDC system is used describe the specific EDC system used for the study. The protocol should also specify who will be involved in data collection such as but not limited to participants can report adverse events in their diaries, nurse or care givers. Procedures should be described who will assess the outcomes such as but not limited to participants, nurses and doctors etc. special focus should be made on quality of data. How errors in data collection, missing data duplicated entries will be assessed. Describe trial instruments such as questionnaires lab tests for data collection*>*

## Data management

<This section should detail the study’s procedures for data entry, data coding, validation, and secure storage. Describe how data will be entered (e.g., directly into an electronic data capture system or transcribed from paper forms), and outline strategies to minimize errors, such as double data entry, automated data validation checks, and routine monitoring. All staff involved in data collection and management must be adequately trained in data handling procedures, and training logs should be maintained as part of study documentation.

The protocol should briefly mention specific procedures for handling data queries, ensuring accurate data entry and coding, and maintaining both hard and electronic copies of study data. Detailed procedures will be described in detail in the Manual of Operating Procedures (MOP). This includes how corrections are documented, who is authorized to make changes, and audit trail maintenance.

Measures to ensure data security must be clearly outlined. These should include physical security (e.g., storing paper records in locked cabinets, restricting access to data storage areas) and electronic safeguards (e.g., use of password-protected computers, role-based access control, and data encryption). Access to sensitive data should be limited to authorized personnel only. After all data has been entered and verified, the soft copy should be locked to prevent unauthorized changes. Any modifications required after data locking must follow a documented amendment process, with justification, authorization by the principal investigator, and full audit trail documentation.>

*Study data will be initially recorded on paper case report forms (CRFs) by trained staff. These forms will be reviewed for completeness and accuracy before being manually entered into password-protected departmental computers. To ensure accuracy, a subset of forms will undergo double data entry, and discrepancies will be resolved using source documents. Data queries will be documented and addressed within the defined procedures, including comments added and changes tracked. Once all data is verified and queries are resolved, the dataset will be locked to prevent further editing. If changes are required after data lock, they must be approved by the principal investigator, documented with reasons, and recorded in the change log as per the procedures defined in the study’s Manual of Operating Procedures (MOP). Paper CRFs will be stored securely in locked cabinets in a restricted-access area.*

## Source documentations

<This section outlines the management of source documents during the study. Source documents are original records where participant data is first recorded, including but not limited to medical records, clinical notes, laboratory reports, radiological results, questionnaires, and measurement tools. In cases where data is recorded directly onto the case report form (CRF), the CRF may serve as the source document.

All data entered into CRFs must be verified against source documents to ensure accuracy and completeness. Source documents must be stored securely, either in locked cabinets for paper files or on password-protected departmental computers for electronic records. In this regard institutional policies should be followed. Access should be restricted to authorized study personnel only. Procedures for handling, reviewing, and correcting source documents must follow Good Clinical Practice (GCP) standards and be outlined in the Manual of Operating Procedures (MOP*)*>*.*

## Methods monitoring

< All clinical trials must have a clearly defined plan for data and safety monitoring (DSMP). However, not all studies require a formal Data Monitoring Committee (DMC). The need for a DMC should be justified based on the study’s risk level, complexity, and the vulnerability of the population. If a DMC is planned, describe its composition (independent experts in relevant fields), roles (monitoring safety and efficacy), reporting structure (to sponsor or steering committee), handling of conflicts of interest, and operational details (meeting frequency, format, closed/open sessions).

If a DMC is **not** planned, describe the alternative oversight mechanism, typically involving the Principal Investigator and/or an internal safety officer or monitoring team. Include how adverse events will be reviewed and reported, who will conduct interim analyses if needed, and how findings will be shared with the IRB or Ethics Committee.>

*This trial does not involve a formal Data Monitoring Committee due to the short duration of treatment, minimal risk associated with the intervention, and the well-established safety profile of the study medication. Instead, a robust Data and Safety Monitoring Plan will be implemented. The Principal Investigator will be responsible for continuous safety oversight, including weekly reviews of all adverse events. A designated Safety Officer, who is independent of the study team, will conduct monthly evaluations of cumulative safety data and protocol compliance. All serious adverse events will be reported to the Institutional Review Board (IRB) within 24 hours and summarized in periodic safety reports. Interim analyses, if applicable, will be performed by an independent statistician. The IRB will review study progress and safety outcomes at regular intervals to ensure participant safety and ethical conduct of the trial.*

# Ethics

## Research Ethics approval

All participating sites must obtain ethical approval from the relevant ethical boards. The ethical approval should be sought before any trial participant can be enrolled. Consent documents, study protocol and case report forms and other participants material should be approved from ERB

Protocol amendments

## Consent or assent

### Informed consent process

<Describe the informed consent process clearly. State that participation is voluntary and withdrawal is allowed at any time. State that written informed consent must be obtained before any study procedures is started , using only ERB-approved documents. Indicate who is responsible for obtaining consent (PI or designee), where and how it should be conducted (in a private and respectful setting), and that participants must be given enough time to read or be read the document. Explain that the process should include discussion of risks and procedures, allow for questions, and address language barriers. Allow family members or aides to be present if desired.>

*Participation in the study is completely voluntary, and participants may withdraw consent at any time without penalty. Written informed consent will be obtained prior to any study-related procedures using only ERB-approved documents. The consent process will be conducted by the Principal Investigator or a designated team member in a private and respectful setting. Participants will be given time to read or have the consent form read to them, and they may be accompanied by a family member or aide. All study procedures, risks, and methods will be explained, and participants will be encouraged to ask questions. Language barriers will be addressed through translated documents and interpreter support where necessary.*

## Subject confidentiality

Subjects’ confidentiality will be strictly protected and maintained by the study investigators and authorized staff. Personal identifiers such as name, address, and phone number will not be disclosed to any third party. All collected data will be anonymized or coded to ensure privacy, with identifying information securely separated from the research data. For any future use or storage, the data will be de-identified. Study-related records and data will be securely stored and retained for a minimum of three years after study completion, in accordance with institutional policies and regulatory requirements. Access to the data will be restricted to authorized personnel only.

# Publication policy

The investigators will comply with Rawalpindi Medical university publication and data sharing policies including the authorship for the study investigators

# Glossary and references

The Vancouver referencing style is permitted for this template for references and should be used consistently throughout the document. All sources cited in the text must be numbered consecutively in the order in which they appear and listed in the reference section accordingly. Proper citation ensures academic integrity and allows verification of the referenced material.