**Rawalpindi Medical University**

 **Rawalpindi RMU**

 Observational Research protocol



**Instruction**

**Tool Summary Sheet**

**RMU observational research Protocol Template**

**Purpose:**

The purpose of this document is to provide a standardized instructional template for investigators preparing a protocol for observational research conducted under Rawalpindi Medical University (RMU).

**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:

Observational studies

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

**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 and applicable national regulations. It is intended to ensure ethical integrity, scientific validity, and regulatory compliance in clinical 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

|  |  |  |
| --- | --- | --- |
| Version no | Date  | Revisions made  |
| 01  | 11/06/2025 | Original draft  |
|  |  |  |

< The University Residency Program (Year) and RMU Monogram are applicable **only** for RMU resident trainees enrolled in MS/MD/M Phil or FCPS programs. while non-academic researches, write only principal investigator name on title page

**University Residency Program 2025**

**Rawalpindi Medical University**

<



SYNOPSIS

Insert title

**Principal investigator**

Resident investigator:

# 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 design  | Such as case control, cohort, cross section validation study etc |
| Study objectives  | State key primary and secondary study objectives  |
| Population  | Target population, sample size |
| Study duration  | Time to complete the study  |
| Subject participation duration  | Individual participation duration 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

<Don’t write here. The introduction should be comprehensive. Add appropriate references. The introduction should be of two to three pages >

## 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.
* The introduction should be of two to three pages

##  **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 as are reported in. describe all anticipated risks to the participants with the study interventions. The potential risks described in the protocol should be consistent with the consent document* >

### 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 >

### Study risk /benefit analysis

< This section should provide an assessment of whether the potential benefits of the study outweigh the possible risks. >

### 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 be precise, time bound and measurable in clear concise statement. The objective should start from action phrase such as to determine, to measure etc. The study may have primary, secondary and tertiary objectives and describe these in separate tables

* 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.>

|  |  |  |  |
| --- | --- | --- | --- |
| Study objective  | Rationale /justifications  | Specific instruments/scale  | Time frame  |
| To determine association between physical activity levels and HbAIc in patients with type 2 diabetes  | Physical activity influences glycemic control, HbA1c is a standard marker for long-term glucose control  | International physical activity questionnaire (IPAQ), laboratory measurement of HbA1c levels | Baseline and 6 months follow up |
| To assess the prevalence of depression among caregivers of stroke patients | Caregivers are at risk of psychological distress, understanding prevalence can help need for mental health screening and support programs  | Patient Health questionnaire-9 PHQ-9 | Single assessment at 3rd month post stroke discharge  |

# Study design

<This section should provide description of the study design. The study design should be appropriate for the specific health problem under study and study objectives. The observational research includes descriptive and analytical studies. The study design should be clearly mentioned such as cross sectional, case control cohort studies etc.

For the comparative groups, briefly describe study groups along with the main characteristics of the groups

Briefly state in this section the target population and sample size. duration of the study from initiation to completion, and the expected duration of each participant's involvement in the study, including follow-ups. This information provides a clear understanding of how the study is structured and how participants will be managed throughout its course.>

Schematic diagram

Initial screening of potential patients. Informed consent. Screen eligibility criteria. Document all patients screened. Documents all patient excluded by exclusion criteria wise

Screening visit

Day XX-YY

Eligible patients to proceed to enrollment. Confirm inclusion and exclusion criteria before enrollment. Do Initial assessments, questionnaires such as demographic form, medical history form, relevant baseline clinical workup

Enrollment

Day 0

Visit XX

Day XX-YY

Outline all scheduled visits with separate boxes. Describe schedules tasks for each visit

Complete data collection on all study outcomes including safety outcomes. Study close out procedures. Patient de-briefing etc.

Final visit XX

Day XX-YY

# Study settings

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

Additionally, this section should identify the following:

* The **recruitment center(s)** or **clinical site(s)**
* The **practicing department(s)** responsible for patient care

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

*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

< don’t write here

 In this section describe participants inclusion and exclusion criteria. Patients risks in the study should be mitigated in defining inclusion and exclusion criteria. Same criteria should not be repeated in inclusion and exclusion criteria. >

## Inclusion criteria

 Describe the inclusion criteria here

## Exclusion criteria

Describe the exclusion criteria

## Sampling technique

<The sampling techniques include random and non-random methods. Non-Random methods include convivence sampling, consecutive sampling, snowball sampling. Random sampling methods include such as simple random sampling, stratified random sampling cluster random sampling and systematic sampling.The appropriate sampling technique along with details of sampling procedures should be described. For example, for simple random sampling the investigators should describe the selection of sampling frame and how random sample is drawn from the sampling frame.>

## Recruitment strategies

< 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 should 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 should 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*.

## Strategies to improve adherence

<This section should describe the strategies that will be used by the investigators to improve and monitoring adherence to the study procedures including scheduled visits. Strategies may include regular reminders, patient education, follow-up calls etc. 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.*

## 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 study 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>

## 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 study 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 procedures and evolutions

<This section should describe the study procedures in details. The observational research involves no experimental treatment and these include only routine evaluations and data collection for the research purposes

In this section describe general procedures for data collection such as clinical observations, biospecimens such as body tissues or samples, laboratory results, images, administrations of questionnaires and in context of qualitative designs focus group discussions etc.

For questionnaires used in the study, the questionnaire(s) should be validated and consistent throughout the study. Briefly introduce the questionnaire(s) including its references and how and when in the study the questionnaire will be administered. Such as baseline and follow up visit etc.

If the data collection is from standard or routine procedure, provide the procedure details and who will carry out those procedures. Indicate which data will be collected from this procedure. For example, if data is collected from the fundoscopy, give procedural details of the fundoscopy and type of data obtained from fundoscopy such as hypertensive changes etc.

This section can be arranged in subsections which will improve clarity

For example

* Medical history collection.
* Physical /oral and specific examinations
* Clinical and biological evolutions
* Biological sample collection
* Medical procedures from which data is obtained
* Focus groups include details of such procedures for qualitative designs

# 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***

*The primary outcome for the study is change is sleep quality score from the baseline. The sleep quality will be assessed using the Pittsburg sleep quality index (PSQI) which is a validated questionnaire. The sleep quality score will be taken as mean score and mean changes in sleep quality score will be taken. the study investigators will administer the questionnaire at the study site at baseline, 3rd month and 6-month intervals.*

## Secondary outcomes

***presence of daytime sleepiness***

*This will be assessed using the Epworth Sleepiness Scale, a validated self-administered tool. The measurement scale is ordinal. Data will be collected through participant responses at baseline, 3 months, and 6 months. The scale will be administered by trained investigators at the study site.*

# Assessment of safety

## Harms

< Harms may include patient-related outcomes such as clinical complications, hospitalizations, or mortality, and may also involve markers such as abnormal laboratory values—for example, elevated liver enzymes or changes in ECG findings. The protocol should 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>

## Relationship of the adverse events to the study

<all adverse events (AEs), regardless of their relationship to the study intervention (drug/device/procedure), should be documented in the Case Report Forms (CRFs). The protocol should specify who will determine causality assessment, grading of severity such as principal investigator etc)

**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 such as principal investigator etc. 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 complete 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 sponsors
* Relevant regulatory authorities
* The Institutional Review Board (IRB)/Ethical Review Committee (ERC)

The timelines and reporting formats should 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 >

***Screening Visit***

***Visit Type: Screening
Time Frame: Day -7 to -1 (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 enrollment.*

***Enrollment visit (visit 1, day 0)***

*Objectives & Activities:*

* *Confirm 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.*

***Indeterminate visits.***

*Write in this section all scheduled visits required for the study. lists all visits separately and describe study specific procedures include framework for data collection on study primary and secondary outcomes*

*Visit (visit 2* ***Day 30 ± 5)***

*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.*

***Final visit***

*Describe the final study visit time frame. Describe all tasks /procedures required for the final schedule visit including data collection for any study outcome, data collection on adverse events etc. describe any follow up activities or closing procedures (e.g., resolving missing data, participants feedback, debriefing etc.*

***Final study visit (final visit,*** ***Day 50± 5)***

 ***Data collection on adverse events***

* *Administration of sleep quality questionnaire (final assessment)*
* *administration of quality of life questionnaire (final assessment)*
* *Collection of information on any adverse events since the last visit*
* *Verification and completion of any missing data from previous visits*
* *Review of any changes in participant’s health status*
* *Participant debriefing and opportunity to provide feedback*
* *Closing of the participant’s involvement in the study*

# Statistical considerations

## Sample size estimation

<The following considerations should be made when estimating the sample size for the study. The statistical formula or software used for the calculation should be specified. A two-sided hypothesis test should be used for sample size estimation unless a one-sided test is scientifically justified , ethically correct 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 should essentially be based on the primary outcome measure. Although power for main secondary outcomes should also be considered. The measurement scale for the study variable used for sample size estimation should be clearly stated and correct formula should be used for sample size estimation. The expected effect size should 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 estimation. >

## Statistical analysis

<Study hypothesis

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

## Statistical Analysis plan

 <This section should describe statistical analysis plan. Following points should be considered while writing the 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.
* Select appropriate statistical tests for data analysis
* Mention confidence level and p value for statistical inference
* State clearly statistical tests for different types of data>

## 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 should be adequately trained in data handling procedures, and training logs should be maintained as part of study documentation.

The protocol should describe 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 should 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 should follow a documented amendment process, with justification, authorization by the principal investigator, and with 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 should be verified against source documents to ensure accuracy and completeness. Source documents should 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 should follow Good Clinical Practice (GCP) standards and be outlined in the Manual of Operating Procedures (MOP*)*>*.*

# 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 form 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 including screening procedures using only ERB-approved consent documents. Indicate who is responsible for obtaining consent (PI or designee), where and how it will be conducted (in a private and respectful setting), and that participants must be given enough time to read or be read the consent 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 with the department of medicine. 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

Describe the procedures how confidentiality of the participants will be protected. Describe who will have access to the data such as investigators, study staff, study sponsors, review board representatives etc.

*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.