Title: Efficacy of Structured Interval Training for Early Mobilization Following Cardiac Surgery - A Randomized Controlled Trial

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1.0 INTRODUCTION

1.1 Research Background

Cardiac surgery, a medical discipline that has advanced considerably over the last century, has become a crucial element in the management of many cardiovascular disorders The median sternotomy is a common surgical procedure that allows direct access to the heart and its surrounding structures by dividing the sternum, the major bone of the chest. (Lautinghausen, 2003). Cardiac surgery has demonstrated the ability to mitigate the risk of adverse cardiovascular events, improve quality of life (QOL) and decrease the necessity for recurring revascularisation. The total volume of cardiac surgical procedures is anticipated to rise at an annual pace of around 5%, ultimately exceeding 1.3 million by 2026 (Jacob, et al., 2023).

Despite the advancement of technology and the accurate preparation of perioperative procedures for cardiac surgeries, the occurrence of postoperative problems continues to be a problem. These problems have a negative impact on patients' physiological and psychological status, which in turn has a negative impact on patients, their families, and the community as a whole (Mosa, Atrous, Mohamed, & El-Sol, 2022). Open heart surgeries are linked to heightened risks of cardiovascular morbidity, pulmonary complications and extended durations of intensive care unit (ICU) admission and hospitalisation, hence increases the financial burden on healthcare (Afxonidis, et al., 2021). Furthermore, the quality of life (QOL) of post-cardiac surgery patients may decline due to postoperative fatigue and pain, and functional capacity has been used to evaluate postsurgical recovery related to QOL (Jacob et al., 2023).

Post-cardiac surgery, in an attempt to reduce or prevent sternal complications, bed rest and routine sternal precautions is often recommended immediately after surgery. These practices impose limitations on physical activity for a duration of 6 to 12 weeks, contingent upon the institution. Patients are advised to refrain from utilising their upper limbs during routine activities, including bed transfers and object lifting. The justification for these limits is to enhance osteosynthesis and bone repair by minimizing the forces and micromotion between the sternal margins (Katijjahbe et al., 2018). Moreover, caretakers and family members may have contributed to the reinforcement of activity limitations, resulting in the participants being apprehensive, lethargic, and excessively cautious (Katijjahbe et al., 2018). Extended bed rest and limitations on activities might adversely impact patient recovery and general health following cardiac surgery.

Cardiac surgery is an invasive treatment that induces muscle catabolism in the postoperative phase by elevating inflammation markers. Therefore, the prevention of muscle catabolism and physical dysfunction may be achieved by promoting muscle activity through early mobilisation, as muscle activity functions as an anti-inflammatory action (Wilkeman, 2007).

Bed rest is recognised to promote alterations in skeletal muscle atrophy and inflammatory markers (Needham, 2008, Kanijima et al., 2022). Furthermore, bed rest induces a reduction in peak oxygen intake as a function of aerobic capacity, which is linked to a reduction in cardiac output and stroke volume (Hung et al., 1983; Natelson et al., 1982).

The effects of bed rest are counteracted by early mobilisation, which may prevent a decrease in aerobic capacity postoperatively. Early mobilisation and in-and-out-of-bed activity programs are defined as the application of physical activity within the first five postoperative days in critically ill patients. These programs are initiated when a patient has minimal ability to engage in therapy, but a stable haemodynamic status and acceptable oxygen levels (Kanejima et al., 2022; Santos et al., 2018). These programs encompass a progressive ambulation program, an active exercise program, activities of daily living (ADL) training, and breathing exercises, as well as the gradual transition from sitting upright in bed to standing. Early mobilisation has substantial impacts on the duration of hospital and intensive care unit (ICU) stays, as well as the incidence of complications, in relation to major surgeries.

Previous research has shown that early mobilisation accelerates the recovery of functional capacity and walking distance by enhancing heart function, ventilation, and respiratory muscle strength. Additionally, early mobility interventions have been demonstrated to mitigate and prevent discomfort, pleural effusion, hospital-acquired infections, pressure injuries, blood sugar levels, surgical site infections, and delirium. Ultimately, these interventions reduce the duration of hospital stays and improve patient satisfaction. Thus, it crucial to implement a mobility and activity program subsequent to cardiac surgery (Jacob et al., 2023). Ramos Dos Santos et al. discovered that early mobilisation had a substantial impact on the improvement of physical function in three-quarters of the cardiac surgery studies they examined. In a recent meta-analysis of six RCT (N= 391 patients) (Kanijima et al., 2022) demonstrated that early mobilisation led to a 54metres increase in the distance walked during the six-minute walk test (6MWT) for patients following cardiac surgery. It is crucial to note that the recovery process is facilitated by the combination of early mobilisation and respiratory exercise in all six studies. Nevertheless, it is imperative to take into account safety concerns regarding respiratory, cardiovascular, neurological, and other conditions prior to initiating early mobilisation for patients who have undergone cardiac surgery in Malaysia.

Despite the fact that early mobilisation is recommended for patients following cardiac surgery, there is a lack of consensus regarding the most effective forms of mobilisation, their optimal intensities, durations, and the earliest possible time to initiate mobilisation after off-sedation. In the interim, physiotherapy care will be initiated preoperatively through education using the MinT (Move in the Tube) protocol. In this exercise, there is no clearly defined protocol regarding its duration post cardiac surgery. In contrast, the ICEAGE protocol is a structured early mobilisation protocol that has been proved to be effective (Boden et al.,

2018). This protocol includes a specific exercise routine that is optimised for both duration and intensity. The ICEAGE protocol has already been implemented in post-emergency abdominal surgery. To date, no studies have compared a program of usual standard to a structured early mobilization in the cardiac surgery population. Therefore, the research question for this randomised controlled trial was:

1.2 Research Question

Primary

Does a structured early mobilisation improve physical function and mobility in people who have undergone cardiac surgery via median sternotomy?

Secondary

For people who have undergone cardiac surgery via median sternotomy, does structured early mobilization improve pain, reduce postoperative pulmonary complications (PPC), improve health-related quality of life, and reduce the unplanned length of stay in the ICU??

1.3 Objectives

1. The goal is to assess how a structured early mobilization protocol affects physical function and mobility in patients who underwent cardiac surgery via median sternotomy.

2. The objective is to evaluate the effect of a structured early mobilization protocol on health-related quality of life, unplanned length of stay in the ICU, pain and postoperative pulmonary complications (PPC) in patients who underwent cardiac surgery via median sternotomy.

1.4 Hypothesis

H1. Structured Early mobilisation performed in patients who undergo cardiac surgery improves physical function and mobility.

H2. Structured Early mobilisation performed in patients who undergo cardiac surgery reduces pain, improves health-related quality of life, and decreases post-operative duration of ICU and post-operative pulmonary complications (PPC).

1.5 Expected Outcome and Benefit

The results of this study will support a structured, early mobilization program for all patients who have undergone cardiac surgery via median sternotomy.

This project is highly significant for people with cardiovascular disease who require cardiac surgery to reduce their mortality/morbidity and improve their quality of life.

2.0 RESEARCH METHODOLOGY

2.1 Study Type Design

The methods are reported in accordance with the Standard Protocol Items: Recommendations for Interventional Trials guidelines for clinical trials and the Template for Intervention Description and Replication (TIDieR) reporting of interventions. This is a phase II prospective clinical trial, double blinded randomized controlled trial (RCT) with concealed randomization, blinding of patients and assessors and intention to treat analysis. Randomisation of participants by using a computer-generated random number (1-58) sequence, which will allocate each participant to either an intervention group or standard care group.

2.2 Study Period

Stage 1: Finalising proposal and Ethics committee approval – 5 months

Oktober 2024 – February 2025

Stage 2: Data Collection an analysis – 12 months

February 2025 – February 2026

Stage 3: Finalising Dissertation – 6 months February 2026 – Julai 2026

2.3 Study Location

This will be a single centre study conducted in Hospital Canselor Tuanku Muhriz (HCTM) PPUKM, Cheras, Kuala Lumpur, Malaysia

2.4 Study Population

Eligibility criteria

Participants who met the eligibility criteria, gave informed consent, and have completed baseline measurement testing performed by a blinded assessor in an inpatient setting are randomised to participate in this trial. Participants were informed that they will be randomised to receive either standard MinT (Move in the Tube) protocol or structured early mobilisation protocol (ICEAGE) are allocated to one of two groups: (1) the control group (standard care) or (2) the intervention group (structured early mobilisation).

Inclusion Criteria

1. Elective cardiac surgical procedure, involving a median sternotomy.
2. Able to provide informed consent.
3. Adults over the age of 18 years.

Exclusion criteria

1. Insufficient Malay/English comprehension to provide informed consent.
2. Unable to complete simple, written questionnaires, and/or understand simple, verbal instructions.
3. Unable to perform physical assessment/6 min walk test.
4. Unwilling to participate in the study.

2.5 Sampling and Sample Size Calculation

The definitive sample size calculation is based on the study by Hojskov (2016) using improvement of physical function and the 6-minute walking test (6MWT).

Formula:

$$n = \frac{2\sigma^2}{\Delta^2} (z_\alpha + z_\beta)^2$$

n = number of samples for each group
z_α = 1.96 (for α 0.05, 95% Confidence Interval)
2.58 (for α 0.01, 99% Confidence Interval)
z_β = 0.84 (80% power of study); 1.28 (90% power of study)
σ = population standard deviation
Δ = mean difference of the two groups

z (alpha) = 2.58 (alpha error 0.01) z (beta) = 1.28

(90% power of study) standard deviation = 93.2 unit

mean difference = 102 unit

n = 2(93.2)^2/(102)^2x(2.58+1.28)^2

= 24 samples per group (x2 for Control and Intervention group)

In-view of drop-out samples, assume 20%, so the total samples size = 58.

2.6 Study Method

Standard care group

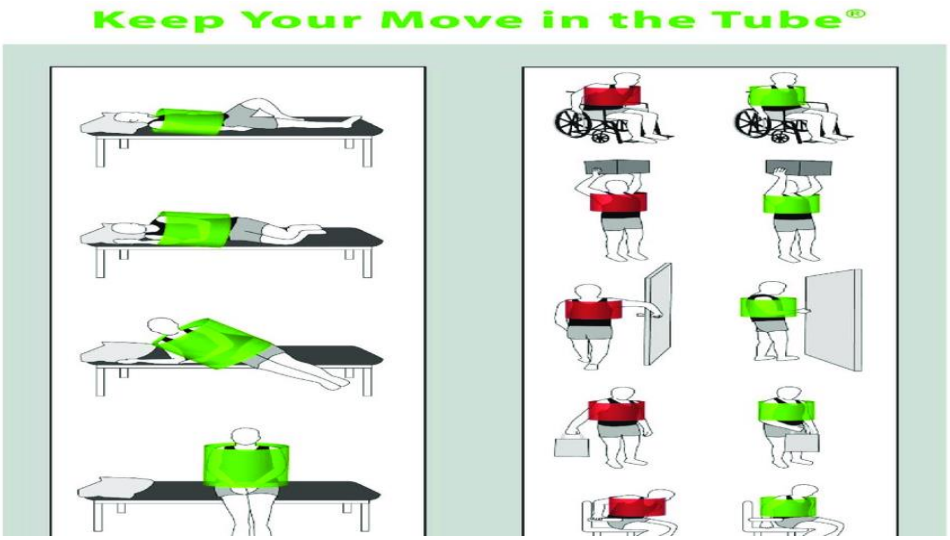
The control group will receive physiotherapy care that is typically delivered in Malaysian hospitals (Md Ali, 2023). This comprises education (talk), early supervised ambulation (walk) once daily from the first postoperative day (if allow), and a single session of coached Deep Breathing and Coughing (DB&C) exercises (breathe).

This includes:

Preoperative physiotherapy care will be initiated through education, including movement in the tube (MinT) protocol, see (Table 1) and early mobilisation. Reiterated postoperatively after achieving stability, a routine assessment and screening of patients for the risk of postoperative pulmonary complications (PPC) will be conducted.

Following extubation, active upper limb, foot, and ankle exercise, as well as progressive mobilisation (e.g., walking) will commence. The patient will be instructed by the physiotherapist to continue with move in the tube (MinT) and a progressive mobilisation program prior to discharge (Nur Ayub et al., 2023) The main difference from the intervention group is that there is no designated protocol for the duration of the exercise.

Table 1



Intervention

Preoperative physiotherapy care will be initiated through education, similar to standard care with an added structured ambulation protocol based on Boden et al. (2018). Refer (Table 2) and will be provided as soon as practical after surgery by a physiotherapist. Patients will receive one supervised ambulation session per day until a threshold score is met or discharge from hospital, whichever occurs first.

At every session, the participant will be progressed sequentially through the protocol stages. The daily aim for the participant is to achieve stage 6 or greater, aiming to achieve a walking time of at least 10 min, but no more than 15 min, at an intensity of at least three on the Borg 10-point visual analogue scale (VAS) (Table 3) of perceived exertion and where breathing is deeper than at rest. The treating physiotherapist will use a stopwatch to ensure the treatment session does not exceed 15 minutes and can provide a walking aid if clinically indicated. If necessary, ambulation sessions can comprise of equal work/rest intervals. Shorter but not longer rest times are allowable. The final achieved ambulation stage corresponds to total time walked, including the marching on the spot time and not including rest periods.

Successful ambulation is defined as continuously marching on the spot beside the bed or walking away from the bedside for more than 1 minute. Time from surgery to time of first successful ambulation will be recorded. If participants are unavailable or unable to achieve ambulation for more than 1 minute, the assisted ambulation session will be attempted once again on the same day. The reasons for participants being unable to ambulate or not achieving a minimum of 10 minutes will be recorded. If a participant is unable to participate in upright ambulation, then no other non-ambulatory exercises will be provided that day.

All treating therapists will be provided with protocol badge cards and trained by the site investigator. An allied health assistant can deliver the ambulation protocol once this is deemed safe to do so by the treating physiotherapist. The professional qualification of the person assisting each ambulation session will be documented.

Table 2: Structured ambulation protocol based on Boden et al. (2018)

Stage 1 (safety)	Sit over edge of bed/sit in chair minimum of 2 min
Stage 2 (safety)	March on spot 0–1 min
Stage 3 (ambulation)	March on spot/walk away from bedside 1–3 min
Stage 4 (ambulation)	March on spot/walk away from bedside 3–6 min
Stage 5 (ambulation)	Walk away from bedside 6–10 min
Stage 6 (ambulation)	Walk away from bedside 10–15 min
Stage 7 (ambulation)	Walk away from bedside > 15 min
Provide assisted early ambulation as soon as possible on the first postoperative day. At each session, progress through each stage in sequence. Time achieved in the session is accumulative. Aim to achieve a rating of perceived exertion greater than 3/10. Aim to assist the patient to ambulate for more than 10 minutes (stage 6 or greater). Once the patient is able to ambulate past stage 3, the patient can be assisted to ambulate with a physiotherapy assistant, as long as it is safe to do so as determined by the ward physiotherapist. Interval training is permissible to obtain target walking time. Each interval of rest time must not exceed the preceding work time. Total session time is the accumulative work time. Provide assisted early ambulation once a day until discharged according to the discharge scoring tool.	

Table 3: The Borg 10-point visual analogue scale (VAS)

2. the revised category-ratio scale (0 to 10 scale).

1 - 10 Borg Rating of Perceived Exertion Scale	
0	Rest
1	Really Easy
2	Easy
3	Moderate
4	Sort of Hard
5	Hard
6	
7	Really Hard
8	
9	Really, Really, Hard
10	Maximal: Just like my hardest race

Method Outcome Measures

Patient demographic and perioperative data were collected. These included ventricular function, mILOA functional assessment, type of surgery, cross-clamp time, haemodynamic function, duration of mechanical ventilation, and length of stay. All outcomes are validated in adult cardiac surgery via median sternotomy population.

Primary Outcomes:

1. Physical Function

The 6-Min Walk Test (6MWT). The 6MWT is a standard measure of functional walking capacity and, as such, provides insight into the likely effect of participation on patients' ability to carry out activities of daily living. This test consists of walking up and down a 30 m indoor track as many times as possible within a 6-minute period (Md Ali et al., 2023).

Hand Grip Strength. It will be measured and recorded by using Jamar Hand Grip. Rate of change in handgrip strength (kg) measured using a handheld dynamometer. The best of three readings will be recorded.

Both the 6-minute walk test (6MWT) and hand grip strength will be measured at 3 timepoints: baseline (pre-op), before discharge, and 1 month post-operatively.

2. Mobility

Rate of change of the Modified Iowa Level of Assistance (mILOA) score over four measures taken daily from the first postoperative day until day seven. It is an observational scoring system. It can be scored at day post-surgery, regardless of whether the patient intubated or extubated. Scoring system see Appendices 3.

The mILOA consists of four mobility tasks (supine to sitting on the edge of the bed, sit to stand, walking, and negotiation of one step), which are graded according to the level of assistance

required, use of gait aid, and the distance that can be walked. Data will be extracted from the medical and physiotherapy records to score.

Scoring the Modified IOWA Level of Assistance typically involves observing the individual's performance in various daily activities and assigning scores based on their level of independence.

The general process usually includes the following steps:

1. Identify Activities: Determine the key activities of daily living (ADLs) to assess, such as bathing, dressing, grooming, eating, and mobility.
2. Observation: Watch the individual perform each activity. Take note of how much help they need and the extent of their independence.
3. Assign Levels: Use a scoring system to categorize the level of assistance required. Common categories might include:
    - Independent: No assistance needed.
    - Supervised: Can perform the task but requires supervision for safety.
    - Partial Assistance: Requires help with some aspects of the task.
    - Total Assistance: Cannot perform the task without help.
4. Calculate Overall Score: Sum the scores for each activity to get an overall level of assistance, which helps in planning care and support services.
5. Documentation: Record the findings and rationale for scoring to maintain a clear record of the individual's abilities and needs.

Secondary Outcomes:

1. Pain

The Numerical Rating Scale for Pain requires participants to rate their pain from 0 to 10 (11-point scale) from 0/no pain to 10/worst possible pain. The numerical scale for pain 1–3 was

related to mild; 4–6 to moderate; and 7–10 to severe pain. The numerical rating scale for pain is an established tool for measuring pain, and importantly, its validity, reliability, and sensitivity to change make it easy to administer for measurement of severity of pain. (Md Ali et. al., 2023; Katijjahbe et. al., 2021). It will be measured daily postoperatively until discharge and at 1 month post operatively.

2. Quality of Life

The EQ-5D-5L is a standardised instrument that is employed to assess the quality of life that is associated with health.

It is composed of two fundamental components:

1. **Descriptive System:** This encompasses five health-related dimensions: Mobility, Self-care, Conducting routine tasks, Pain or Discomfort, and Depression or Anxiety. Respondents are permitted to select one of five levels for each dimension, which correspond to their health status. These levels span from "no problems" to "unable to/extreme problems."
2. **Visual Analogue Scale (VAS):** Respondents evaluate their general health on a scale of 0 to 100, with 0 denoting the most severe health condition and 100 the most favourable.

The EQ-5D-5L is frequently employed in clinical studies, health surveys, and economic evaluations to evaluate the impact of diseases and treatments on quality of life. It offers a straightforward yet comprehensive method for obtaining patient-reported outcomes.

Rate of change of the EQ-5D-5L score. Measures to be taken directly from the patient pre-operatively, before discharge and 1 month postoperatively.

3. Intensive Care Unit (ICU) length of stay

This is defined as continuous days spent in the intensive care unit from the day of admission for an acute condition to the day of discharge to the general ward. Any unplanned ICU admission during an acute hospital stay will be recorded.

4. Post Operative Pulmonary Complication (PPC)

PPC will be defined by the Melbourne Group Score. The Melbourne Group Score is reliable, valid, sensitive to interventions, and has high inter-rater reliability (Boden et al., 2018). It has eight clinical criteria: four factors relating to symptoms and four to diagnostic markers. A PPC will be diagnosed when four or more factors are present at any time from midnight to midnight on one postoperative day. The day a PPC is first diagnosed is the day of onset for purposes of time-to-event analysis.

Diagnosis of pneumonia is defined as the presence of new chest x-ray infiltrates along with at least two of the following: temperature > 38 °C, dyspnoea, cough, and purulent sputum; altered respiratory auscultation; and a white cell count > 14,000/mL or leukopenia < 3000/mL on any day within the first 14 postoperative hospital days.

PPC data will be collected until 7th post-op days. From the 8th to the 14th postoperative day, additional PPC assessments are performed only as clinically suspected based on signs or symptoms of respiratory system deterioration reported within the medical record.

2.7 Data Collection

Demographic data and pre-operative, intra-operative, and post-operative variables were collected. Data were collected from the participants and their medical records. All baseline assessments are performed at the same time of day (0800H–1700H) for each participant in the preoperative period at the inpatient ward. The follow-up and post-operative period at day 7

(+/- 1 day) in the inpatient setting across centres to minimise potential bias in recruiting participants in the outpatient setting at 4 weeks (+14 days) and 3 months (±14 days) take place in the research room at the physiotherapy unit. An independent and trained assessor (located off site) blinded to allocation conducts all measurement sessions. All follow-up tests and questionnaires are administered face-to-face by the outcome assessors and carried out prior to discharge, 4 weeks, and 3 months post-operatively to ensure consistency across participants. Post-hospital discharge follow-up is contacted via phone. Participants who are unable to be contacted by phone for a period of 14 consecutive days from the assessment due date are considered lost to follow up for the post-discharge outcomes measurement. As this is a double-blinded study, none of the physiotherapists involved in supervised resistance training at study sites is recruited as the investigator for this study.

Data Management and Quality

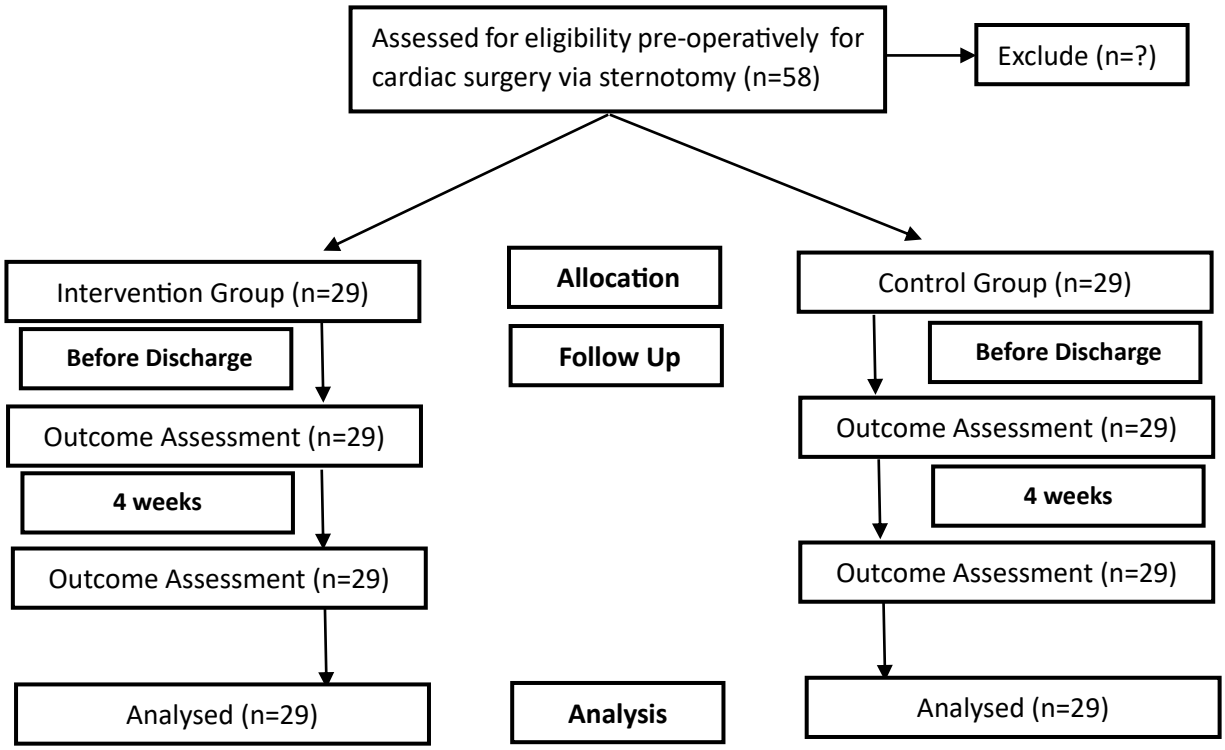
We used the Excel database for through training of those who collect, check, and enter study data; regular data checks for inconsistency between and within measurements and missing data. The Data Safety Monitoring Committee (DSMC), with two independent clinical members, acts in an advisory capacity to the clinical investigators to monitor withdrawals and review ethical conduct and serious adverse events.

2.8 Statistical Analysis Plan

Statistical analyses were performed by the biostatistician. All data will be analysed using the intention to treat principle. Descriptive statistics, including median and interquartile range, number and percentage, and frequency, were used to summarise data (depending on the distribution and type of data). The association between the characteristics of the intervention group and the control group was analysed using the Mann-Whitney U test, the Fisher Exact test, and Pearson chi squared. The secondary outcomes—the changes from baseline to 4 weeks

in the secondary outcome—were analysed using the Mann-Whitney U Test and Friedman Test. The secondary hypothesis was examined by a contrast evaluating change from baseline to the 1-month time point in the intervention group compared to the control group. For all tests conducted, a p value of less than 0.05 (two-tailed) is considered statistically significant.

2.9 Flow Chart



3.0 ETHICAL ISSUE

3.1 Ethics of study

Ethics approval for the study will be obtained from the UKM ethics approval committee. The study will be conducted in compliance with the principles outlines in the Declaration of Helsinki and Malaysia Good Clinical Practice Guideline.

3.2 Informed consent

If a patient meets the above inclusion criteria, they will be invited to participate in the study by the researcher team who will provide them with an information sheet detailing the study aims

and time commitments. Once a potential participant provides informed consent, they will be enrolled to participate in the study. Participant can choose to withdraw at any time.

3.3 Privacy and confidentiality

Subject's names will be kept on a password-protected database and will be linked only with a study identification number for this research. The identification number instead of patient identifiers will be used on subject data sheets. All data will be entered into a computer that is password protected. On completion of study, data in the computer will be copied to hard drive and the data in the computer erased. Hard drive and any hardcopy data will be stored in a locked office of the investigators and maintained for a minimum of three years after the completion of the study. The hard drive and data will be destroyed after that period of storage. Subjects will not be allowed to view their personal study data, as the data will be consolidated into a database.

3.4 Conflict of interest

The investigators declare they have no conflict of interest.

3.5 Publication policy

No personal information will be disclosed and subjects will not be identified when the findings of the survey are published.

3.6 Termination of study

Not applicable

Declaration of interest

We received funding from Research University Grant. However, the sponsors have no contribution to the trial design, data collection, or management, and publications relating to the trial can be submitted without permission or requiring approval.

4.0 GANTT CHART AND MILESTONES

Task	2024			2025			2026		
	Jan-April	May-August	Sept-Dec	Jan-April	May-August	Sept-Dec	Jan-April	May-August	Sept-Dec
Literature Review									
Research Design									
Ethics Approval									
Sample Recruitment									
Data Collection									
Data Analysis									
Report Writing									
Publication Process – full manuscript									

5.0 BUDGET

No financial allocation necessary.

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