Community-Based Program Integrating Nurse-Led Mind-Body Exercise and Nutrition for Frailty

Protocol Number: INA-1A72A0C

National Clinical Trial (NCT) Identified Number: -

Principal Investigator: Rista Fauziningtyas, S.Kep.Ns., M.Kep., Ph.D.

IDE Sponsor: Universitas Airlangga

Funded by: Indonesia Endowment Fund for Education (LPDP)

Version Number: v.1.0

12 February 2026

Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale

Table of Contents

STATEMENT OF COMPLIANCE

(1) [The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.]

1 PROTOCOL SUMMARY

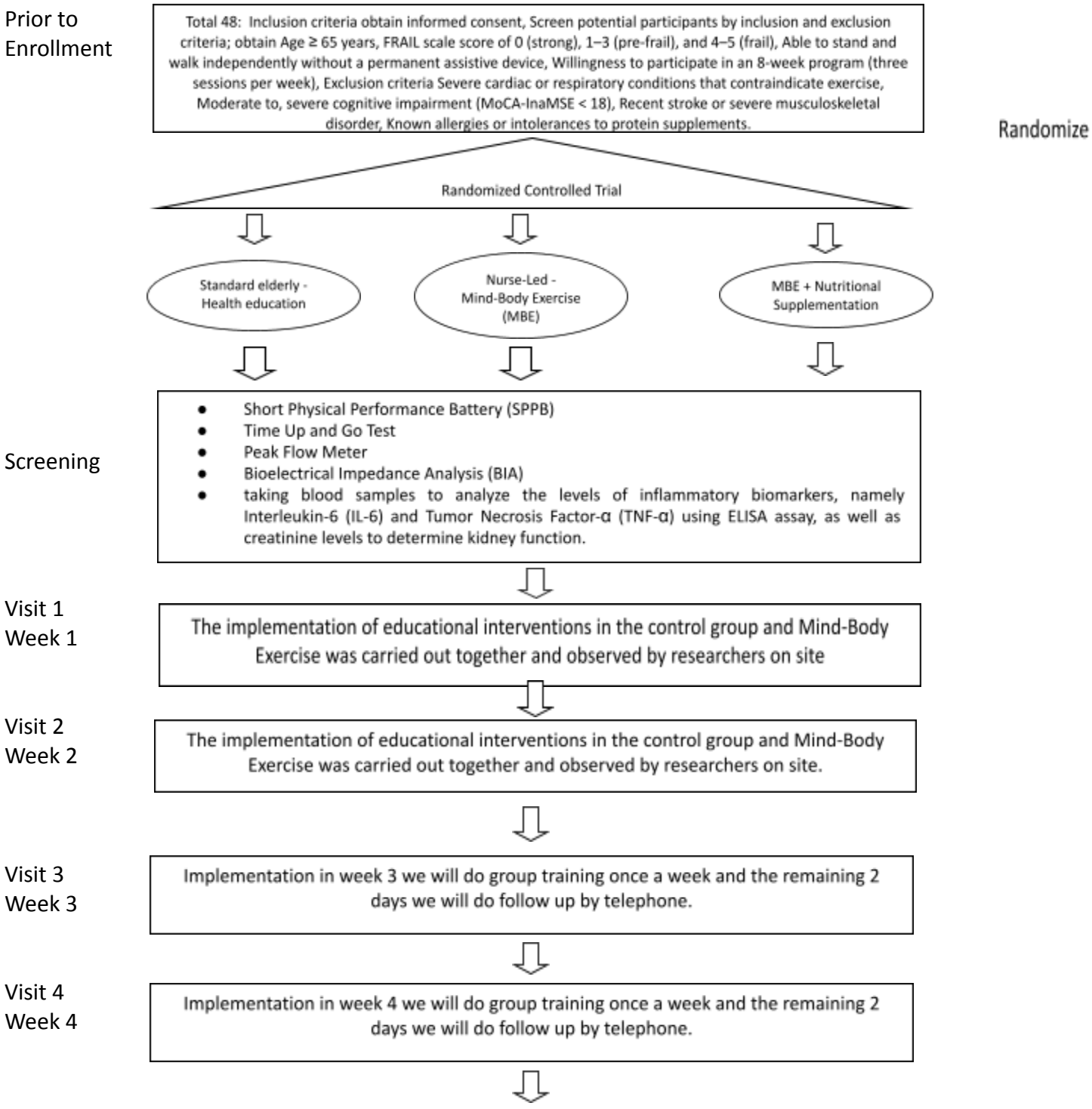
1.1 SYNOPSIS

Title:	*Community-Based Program Integrating Nurse-Led Mind-Body Exercise and Nutrition for Frailty*
Study Description:	*This study is a community-based, three-arm randomized controlled trial evaluating the effectiveness of a nurse-led mind–body exercise program combined with nutritional supplementation, compared with mind–body exercise alone and usual care, in older adults with frailty. The intervention is delivered over the 8 weeks with outcomes assessed at predefined time points. The primary hypothesis is that participants receiving the combined mind–body exercise and nutritional supplementation intervention will demonstrate greater improvements in frailty status compared with those receiving exercise alone or education.*
Objectives:	*The primary objective of this study is to evaluate the effectiveness of a community-based, nurse-led mind–body exercise program combined with nutritional supplementation in improving frailty status among older adults, compared with mind–body exercise alone and education.* *The secondary objectives are to assess the effects of the interventions on physical function, mobility, body composition, pulmonary function, and inflammatory biomarkers, as well as to evaluate the feasibility and safety of implementing a nurse-led, community-based rehabilitation program for frail older adults.*
Endpoints:	*The primary endpoint of this study is the change in frailty status of older adults, measured using the Ina-FRAIL scale, from baseline to the end of the intervention period. Secondary endpoints include changes from baseline to post-intervention in lower extremity physical performance assessed by the*

	Short Physical Performance Battery (SPPB), functional mobility and fall risk assessed by the Timed Up and Go Test (TUGT), pulmonary function assessed by peak expiratory flow (PEF), body composition parameters including muscle mass, fat mass, and body mass index (BMI) assessed by bioelectrical impedance analysis (BIA), and inflammatory biomarkers related to frailty, specifically interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α).
Study Population:	*Older adult age ≥65 years, a Frail Scale score of 1–3 (pre-frail) or 4–5 (frail), ability to stand and walk independently without permanent assistive devices, live within the working area of a Community Health Center in Surabaya City.*
Phase:	N/A
Description of Sites/Facilities Enrolling Participants:	*The study will be conducted at a community-based sites, including primary health care centers, located in Surabaya, Indonesia (outside the United States).*
Description of Study Intervention:	*This study evaluates a nurse-led, community-based intervention consisting of mind-body exercise and nutritional supplementation over an 8-week period. The mind-body exercise program is conducted three times per week and includes low- to moderate-intensity movements tailored for frail older adults. Nutritional supplementation consists of a daily oral protein-based supplement in the form of Ensure Gold Strength Pro. Participants are assigned to one of three groups: mind-body exercise only, mind-body exercise combined with nutritional supplementation, or health education (arm control).*
Study Duration:	*10 months*
Participant Duration:	*2 months*

1.2 SCHEMA

Example #1 Flow diagram *(e.g., randomized controlled trial)*



Visit 5
Week 5

Implementation in week 5 Respondents carry out the intervention independently and we will follow up by telephone.

Visit 6
Week 6

In the 6th week, follow-up was carried out by calling respondents and respondents sending photo or video evidence.

Visit 7
Week 7

In the 7th week, follow-up was carried out by calling respondents and respondents sending photo or video evidence.

Visit 8
Week 8

In the 8th week, follow-up was carried out by calling respondents and respondents sending photo or video evidence.

Final Assessments
SPPB, TUGT, peak flow meter, BIA, Interleukin-6 (IL-6) and Tumor Necrosis Factor-α (TNF-α) using ELISA assay, and creatinin levels

1.3 Schedule of Activities (SoA)

Procedures	Screening Day 0	Enrollment/ Baseline Visit 1, Day 1	Study Visit 2 Day 7 +/-1 day	Study Visit 3 Day 14 +/- 1 day	Study Visit 4 Day 21 +/-1 day	Study Visit 5 Day 28 +/-1 day	Study Visit 6 Day 35 +/-1 day	Study Visit 7 Day 42 +/-1 day	Study Visit 8 Day 49 +/-1 day	Final Study Visit 13 Day 84 +/-1 day
Informed consent	X									
Demographics	X									
Eligibility assessment (inclusion/exclusion criteria)	X									
Medical history & concomitant medication review	X									
Randomization	X									
Assesment (frailty, SPPB, TUGT, PEF, Body composition, Blood sample collection (IL-6, TNF-α))	X									X
Study intervention										
Participant education (control group)		X	X	X	X	X	X	X	X	
Mind–body exercise program		X	X	X	X	X	X	X	X	
Mind–body exercise program and Nutritional supplementation (Ensure Gold® Strength Pro)		X	X	X	X	X	X	X	X	
Follow-up & compliance monitoring (WA/Telp/home visit)				X	X	X	X	X		
End-of-study evaluation										X

2 INTRODUCTION

2.1 Study Rationale

Frailty is a common geriatric syndrome among community-dwelling older adults, characterized by decreased physical reserve, reduced mobility, increased risk of falls, functional decline, hospitalization, and mortality. In Indonesia, the aging population is rapidly increasing, yet frailty is often underrecognized and undertreated in primary and community health care settings. Current standard care for older adults in the community mainly focuses on disease management and does not routinely include structured, nurse-led rehabilitation programs targeting frailty.

Although evidence from international studies suggests that mind–body exercise and nutritional supplementation can improve physical function and reduce frailty, there is limited evidence regarding the effectiveness of integrated, nurse-led interventions in community settings in Indonesia. Additionally, data on the impact of such interventions on inflammatory biomarkers related to frailty in Indonesian older adults remain scarce.

Therefore, this clinical trial is conducted to evaluate whether a community-based rehabilitation program integrating nurse-led mind–body exercise with nutritional supplementation can improve frailty status and physical function outcomes among community-dwelling older adults, and to provide evidence to inform sustainable frailty management strategies in primary health care.

2.2 Background

Frailty is a common geriatric syndrome characterized by reduced physiological reserve, impaired physical function, and increased vulnerability to adverse health outcomes, including falls, disability, hospitalization, and mortality. In community-dwelling older adults, frailty is often underdiagnosed and inadequately managed, particularly in low- and middle-income countries such as Indonesia, where structured community-based rehabilitation programs are limited.

Nonclinical and mechanistic evidence suggests that regular physical activity can improve muscle metabolism and modulate inflammatory processes associated with frailty, including elevated levels of interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α). Adequate protein intake has also been shown to support muscle mass maintenance and counteract sarcopenia-related functional decline in older adults.

Clinical studies conducted in various countries have demonstrated that mind–body exercise interventions improve balance, mobility, muscle strength, and functional performance in older adults. Furthermore, multicomponent interventions combining physical exercise with nutritional supplementation have shown greater benefits in improving frailty status compared with single-modality interventions. Protein-based nutritional supplements have been widely used in older populations and are considered safe when administered orally at recommended doses.

Despite this evidence, there is limited clinical trial data evaluating integrated, nurse-led, community-based interventions targeting frailty in Indonesia. Therefore, this randomized controlled trial aims to evaluate the effectiveness of a nurse-led mind–body exercise program, with and without nutritional supplementation, on frailty status, physical function, body composition, pulmonary function, and inflammatory biomarkers among community-dwelling older adults. The results are expected to provide evidence to support scalable frailty management strategies in primary and community healthcare settings.

2.3 Risk/Benefit Assessment

2.3.1 Known Potential Risks

Based on available clinical evidence, product information, and published literature, the interventions used in this study are considered low risk. No investigational drugs or invasive medical devices are involved.

1. **Physical Risks**

- Mind–body exercise: Potential immediate physical risks include mild muscle soreness, transient fatigue, dizziness, joint discomfort, or imbalance, particularly during the initial adaptation period. These risks are commonly reported in low- to moderate-intensity exercise programs for older adults and are generally self-limiting.
- Nutritional supplementation: The protein-based nutritional supplement (Ensure Gold StrengthPro®) is a commercially available product with an established safety profile. Possible mild gastrointestinal symptoms such as bloating, nausea, or diarrhea may occur, especially in individuals with sensitivity to dairy-based products.
- Blood sampling and physical assessments: Minor risks include temporary pain at the puncture site, bruising, minimal bleeding, or transient dizziness during blood collection.

2. **Psychological Risks**Participants may experience mild anxiety or discomfort related to physical performance testing, health assessments, or receiving information about their health status. These effects are expected to be temporary.
3. **Social, Legal, and Economic Risks**No significant social or legal risks are anticipated. From an economic perspective, participants may incur minimal indirect costs, such as time and transportation expenses related to attending intervention sessions. These potential economic burdens are mitigated by providing consumption or refreshments at each visit, and participation does not involve any direct financial cost or loss of income.
4. **Immediate Risks**Immediate risks include mild musculoskeletal discomfort from exercise, transient gastrointestinal symptoms from supplementation, and minor discomfort related to blood sampling and physical assessments.
5. **Long-Range Risks**

No long-term or cumulative risks are anticipated based on current evidence. The interventions involve short-term, low-intensity activities and standard nutritional supplementation with no known long-term adverse effects when used as directed.

Risk Mitigation and Alternative Procedures

All exercise sessions are supervised by trained nurses, begin with warm-up and end with cool-down periods, and are individually adjusted based on participants' daily physical condition. Participants are monitored before, during, and after sessions, and activities are modified or discontinued if discomfort occurs.

Alternative procedures, such as higher-intensity exercise or pharmacological interventions, were considered but not included due to their higher risk profiles and lower feasibility in community-dwelling frail older adults. The selected interventions were chosen because they are non-invasive, evidence-based, and appropriate for safe implementation in community settings.

2.3.2 Known Potential Benefits

Based on existing clinical evidence and published literature, the interventions used in this study are expected to provide potential health benefits to participants and to contribute to broader public health knowledge. The mind–body exercise program and protein-based nutritional supplementation are non-invasive interventions with established use in older adult populations.

Physical and Psychological Benefits

Clinical studies have demonstrated that regular mind–body exercise can improve muscle strength, balance, mobility, flexibility, and overall physical performance in older adults. Such exercises are also

associated with improvements in breathing control, relaxation, sleep quality, and psychological well-being, including reduced stress and improved mood. Protein-based nutritional supplementation has been shown to support muscle mass maintenance, improve nutritional status, and enhance physical function in older adults, particularly those at risk of frailty.

Immediate Potential Benefits
Participants may experience short-term improvements in physical function, balance, mobility, breathing capacity, and perceived well-being during or shortly after the intervention period. Increased awareness of personal health status and engagement in regular physical activity may also occur as a result of participation.

Long-Range Potential Benefits
Long-term benefits may include sustained improvements in functional independence, reduced progression of frailty, lower risk of falls and disability, and improved quality of life. At the societal level, this study is expected to generate evidence supporting nurse-led, community-based frailty interventions that can be integrated into primary healthcare services. The findings may contribute to the development of scalable, cost-effective strategies for healthy aging and inform health policy and clinical practice in aging populations.

2.3.3 Assessment of Potential Risks and Benefits

The trial uses low-risk, non-invasive therapies to improve frailty in older persons living in the community. Evidence of successful, scalable, nurse-led frailty interventions—which are currently few in community settings—must be produced through exposure to low risks. Exercise-related soreness, nutritional supplements, and routine evaluations are among the mild and temporary dangers. Health screening, customized intervention modification, continued monitoring, and supervision by qualified nurses all help to reduce these hazards.

Improvements in participants' frailty status, physical function, and general well-being are among the expected advantages, along with useful data to guide community-based frailty management. In general, the little dangers connected with involvement are outweighed by the possible advantages for both people and society.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
The effectiveness of a nurse-led, community-based mind-body exercise program with and without nutritional supplementation in improving frailty status among older adults.	Change in frailty status of older adults, measured by the Ina-FRAIL scale, from baseline to the end of the intervention period.	The primary endpoint was chosen because frailty status is the main target of the intervention and represents a clinically meaningful outcome in older adults. The Ina-FRAIL scale is a validated and reliable instrument that

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
		captures multidimensional aspects of frailty and is sensitive to changes following exercise and nutritional interventions, making it appropriate for evaluating the effectiveness of the study interventions.
Secondary		
The effects of the nurse-led mind-body exercise and nutritional supplementation on physical function, mobility, body composition, pulmonary function, and inflammatory biomarkers related to frailty in older adults.	*Secondary endpoints include changes from baseline to post-intervention in lower extremity physical performance assessed by the Short Physical Performance Battery (SPPB), functional mobility and fall risk assessed by the Timed Up and Go Test (TUGT), pulmonary function assessed by peak expiratory flow (PEF), body composition including muscle mass, fat mass, and BMI assessed by bioelectrical impedance analysis (BIA), and inflammatory biomarkers related to frailty that is IL-6 and TNF-α.*	*The secondary endpoints were chosen to provide supportive and complementary information on the effects of the intervention across multiple domains related to frailty, including physical performance, mobility, pulmonary function, body composition, and inflammatory biomarkers, providing a more thorough comprehension of the intervention's wider effects beyond the main result.*
Tertiary/Exploratory		
N/A	*N/A*	*N/A*

4 STUDY DESIGN

4.1 Overall Design

- H1 : Participants who received the combination intervention (mind-body exercises + nutritional supplements) showed a more significant reduction in frailty scores compared to the group that only received health education and mind-body exercises.
- This study will use a randomized controlled trial (RCT) with three parallel groups and an assessor blinding method

- To minimize bias, researchers use assessor blinding. Assessor blinding is a procedure in which the person measuring the research results is unaware of which group the participants are in. The goal is to ensure objective assessments based purely on clinical data.
- The study will comprise three groups : a control group receiving health education, a second group receiving Nurse-Led Mind- Body Exercise (MBE), and a third group receiving MBE + Nutritional Supplementation. The intervention will be implemented over an eight-week period. Health education will be provided once a week, MBE will be administered 3 times a week, and nutritional supplements will be given daily.
- The location of this research is only in one area, namely the Kalijudan Community Health Center area.

4.2 Scientific Rationale for Study Design

The selection of the control group with health education was chosen to provide basic standard of care without providing active physical or nutritional interventions, so that the difference in results was purely due to MBE exercise and supplements. This research is included in the superiority design because it compares 3 groups to find out which is the best. A potential problem that may arise from the control group is that participants may feel bored or disappointed that they are not getting physical exercise or supplements, so they may drop out of the study.

4.3 Justification for Dose

Participants will be provided with milk supplementation for a duration of 8 weeks. The dosage and serving size for each administration will be 230 mL. To prepare, 5 measuring spoons (45 grams) of powdered milk will be added to 198 mL of warm or cold water and stirred until dissolved. The reconstituted milk shall be consumed immediately or stored in a refrigerator and consumed within 24 hours. How to store cans: first, store unopened cans at room temperature, opened cans should be tightly closed and stored in a cool, dry place, and opened cans should be consumed within three weeks. Supplementation is consumed twice a day, around 8 a.m. and 7 p.m., one hour after meals.

4.4 End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study in the form of the final visit and the final physical examination procedures listed in the schedule of activities (SoA).

5 STUDY POPULATION

5.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria :

1. Provision of signed and dated informed consent form
2. Age ≥ 65 years.
3. FRAIL scale score of 0 (robust), 1–3 (pre-frail), and 4–5 (frail).
4. Able to stand and walk independently without permanent assistive devices.
5. Willingness to participate in an 8-week program (three sessions per week).

6. Hasil pemeriksaan ginjal baik (kreatinin lansia pria sekitar 0,9-1,3 mg/dL dan wanita 0,7-1,1 mg/dL BUN)

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Severe heart or respiratory conditions that contraindicate exercise.
2. Moderate to severe cognitive impairment (MoCA-InaMSE <18).
3. Recent stroke or severe musculoskeletal disorder.
4. Known allergy or intolerance to protein supplements.

5.3 Lifestyle Considerations

Alcohol consumption is prohibited during the intervention. Tobacco consumption is not restricted, but will be recorded, and medications will continue to be taken as prescribed.

5.4 Screen Failures

Participants who fail the Trial are considered participants who were successfully enrolled in the clinical trial but were not subsequently randomly assigned to the study intervention or enrolled in the study. Minimal information about participants who fail the Trial is required to ensure transparent reporting of participants who fail the Trial, to meet Consolidated Standards of Reporting Trials (CONSORT) publication requirements, and to respond to inquiries from regulatory authorities. Minimal information includes demographics, details of the Trial failure, eligibility criteria, and serious adverse events (SAEs). Individuals who do not meet the criteria for enrollment in this trial will not be retested.

5.5 Strategies for Recruitment and Retention

- The target respondents are 48 elderly people aged ≥65. Participants come from residents within the Kalijudan Community Health Center (Puskesmas) working area in Surabaya. The source of participants is elderly people aged 65+ in the Kalijudan Community Health Center working area. Researchers will collaborate with community health center nurses to identify participants who meet the research criteria. Community health center nurses will direct community health post (Posyandu) community health worker (kader) to assist researchers in finding elderly people who meet the research criteria. Recruitment of participants will be assisted by community health center nurses and cadres. If agreed, the research coordinator will visit the elderly to explain the research details. Interventions are conducted in groups and individually. Group interventions are conducted during meetings and individual interventions are conducted independently by participants at home. The intervention will be conducted three times per week for 8 weeks, each session lasting 45 minutes. So there is a risk that respondents will forget or get bored. The researcher's strategy to ensure participants do not withdraw is by implementing an observation schedule, In weeks 4-5, direct observation and group exercises will be conducted once a week, and the researchers will check in with participants by phone on the other two days. Then, in week 5, check-ins will be conducted solely by phone via WhatsApp. in week 1-2, we will conduct joint exercises and direct monitoring by researchers; In weeks 3-4, group exercises will be conducted once a week, and the researchers will check in with participants by phone on the

other two days. Then, in week 5, check-ins will be conducted solely by phone via WhatsApp. In weeks 6-7, we will call participants with photo or video evidence by WhatsApp; and week 8, we will conduct joint exercises. Each meeting participant will be given a snack package.

6 STUDY INTERVENTION

6.1 Study Intervention(s) Administration

6.1.1 Study Intervention Description

This study includes three parallel arms: (1) nurse-led mind–body exercise, (2) nurse-led mind–body exercise combined with nutritional supplementation, and (3) a control group receiving usual community care.

1. The mind–body exercise intervention consists of structured, low-impact movements integrated with breathing control and relaxation techniques, delivered by trained nurses in community settings. The program is designed to improve balance, strength, flexibility, and mind–body awareness. Sessions are conducted regularly over the intervention period, with standardized duration and frequency across participants.
2. The nutritional supplementation intervention involves oral nutritional supplements containing protein and essential micronutrients relevant to muscle health and frailty management. The supplement is commercially available and used in accordance with approved labeling, with no modification to formulation, dose, or route of administration. Supplements are administered orally at a standardized dose and frequency throughout the intervention period.
3. The control group receives usual care provided in the community, without structured exercise or nutritional supplementation as part of the study protocol.

No investigational drugs or medical devices under an Investigational Device Exemption (IDE) are used in this study. All interventions are non-invasive, commercially available, and pose minimal risk to participants.

6.1.2 Dosing and Administration

This study does not involve dose escalation or investigational drug dosing. Participants are assigned to one of three study arms with standardized intervention schedules.

For the mind–body exercise intervention, all participants receive the same predefined program delivered by trained nurses. The “dose” is defined by session frequency and duration rather than pharmacological quantity. Exercise sessions are conducted at scheduled times in community settings, with a frequency of three sessions per week and a total duration of 50 minutes per session throughout the intervention period. Each session consists of a 5-minute warm-up, followed by 35 minutes of resistance and balance training, and concludes with a 10-minute cool-down using chair yoga. Participants are instructed to wear comfortable clothing, perform movements within their personal physical limits, and stop the session immediately if any discomfort or adverse symptoms occur.

For the nutritional supplementation intervention, participants receive a protein-based nutritional supplement (Ensure Gold StrengthPro®) in the form of a milk-based oral nutritional supplement for 8 week. Each serving consists of 230 mL of prepared milk, made by adding 5 level scoops (45 grams) of milk powder into a glass, followed by 198 mL of warm or cold water. Participants are instructed to

consume the supplement twice daily, at approximately 08:00 and 19:00, and one hour after meals to improve tolerance. Intake is recommended at a consistent time each day, preferably after meals to reduce gastrointestinal discomfort. No dose escalation or reduction is planned. Missed doses are not replaced; participants resume the regular schedule the following day.

The control group receives health education of elderly without structured exercise or nutritional supplementation as part of the study.

No dose modifications, escalation, or de-escalation criteria are applicable, as the interventions are non-invasive, low risk, and standardized across participants. Safety monitoring is conducted throughout the study, and interventions may be temporarily paused if participants experience discomfort or adverse events, based on clinical judgment.

6.2 Preparation/Handling/Storage/Accountability

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

6.2.1 Acquisition and accountability

The study interventions will be coordinated and overseen by the Principal Investigator (PI) in collaboration with Co-Investigators, including licensed professional nurses and a rehabilitation medicine physician, as well as research assistants. Implementation of the intervention arms will be led by Principal Investigator and Co-Investigator who is a professional nurse, with clinical supervision and guidance provided by a rehabilitation medicine physician to ensure participant safety and adherence to the intervention protocol.

The nutritional supplementation product (protein milk) will be obtained centrally from the manufacturer and managed by the research team. The supplements will be stored, handled, and distributed to participants by trained study personnel according to the prescribed dosing schedule and manufacturer storage recommendations. The mind–body exercise intervention does not involve investigational drugs or devices and will be delivered directly to participants during scheduled sessions in community settings by trained nurses following a standardized protocol.

Participants assigned to the control group will receive health education related to frailty and healthy aging in older adults. This educational intervention will be delivered by the Principal Investigator and a Co-Investigator, with research assistants, using standardized educational materials to ensure consistency across sessions.

To minimize assessment bias, data collection for baseline (pre-intervention) and post-intervention measurements will be conducted by independent assessors who are not involved in delivering the intervention and who have expertise relevant to each outcome measure (e.g., physical performance, body composition, and laboratory assessments). No investigational pharmacy or drug repository is involved in this study.

6.2.2 Formulation, Appearance, Packaging, and Labeling

The nutritional supplement used in this study is Ensure Gold StrengthPro Vanilla 800g (Abbott Laboratories), a commercially available, high-protein powdered milk formulation designed to support muscle strength, immunity, and overall nutritional status in adults. It contains a triple protein blend (whey, casein, and soy), calcium β-hydroxy-β-methylbutyrate (CaHMB), yeast beta-glucan (YBG), 28 essential vitamins and minerals, and omega-3 and omega-6 fatty acids, which together help maintain muscle mass, immune function, and metabolic health.

The product is packaged in sealed metal cans labeled by the manufacturer with product name, flavor, nutritional composition, batch number, and expiration date. Participants receive the 800g vanilla-flavored version, which is mixed with water to prepare a 230 mL serving (as described in the intervention protocol). No modifications to the product's formulation, appearance, packaging, or labeling are made specifically for this study.

The mind–body exercise intervention is non-pharmacological and has no physical formulation, packaging, or labeling. The intervention is supported by a standardized exercise protocol (SOP) and demonstration videos to ensure uniform delivery across sites. These materials are labeled for research use and include structured instructions for warm-up, core exercise movements, and cool-down using chair yoga.

Participants in the control group receive health education on frailty and healthy aging using standardized printed and digital materials, including PowerPoint slides and leaflets developed by the research team. These materials are labeled internally for educational purposes and are not commercial therapeutic products.

6.2.3 Product Storage and Stability

Ensure Gold® StrengthPro is a commercially available powdered nutritional supplement supplied in sealed metal cans by the manufacturer. Unopened cans are stored at room temperature in a dry place, protected from direct sunlight, excessive heat, and humidity, in accordance with the manufacturer's instructions. Once opened, the can must be tightly closed after each use and stored in a cool, dry place; the product should be used within three weeks after opening to maintain stability and nutritional quality. The reconstituted product should be consumed immediately after preparation. If not consumed immediately, it may be stored in a refrigerator and must be consumed within 24 hours. Expired products or unused supplements at the end of the study will be collected and disposed of according to institutional procedures.

The mind–body exercise intervention does not involve a physical product requiring storage. Standardized exercise materials, including standard operating procedures (SOPs) and exercise demonstration videos, are stored in secure digital formats accessible only to authorized study personnel to ensure consistency and data integrity.

Educational materials for the control group (PowerPoint slides and printed leaflets) does not involve a physical product requiring storage. Printed materials are protected from damage, and digital files are stored on password-protected devices. No special stability requirements apply.

6.2.4 Preparation

The nutritional supplementation is prepared by study staff or participants according to standardized instructions. For each serving, 5 level measuring scoops (45 g) of Ensure Gold® StrengthPro powder are placed into a clean glass or container, followed by the addition of 198 mL of warm or cold drinking water to obtain a final volume of 230 mL. The mixture is stirred until fully dissolved. The prepared supplement is intended for immediate consumption. If not consumed immediately, it may be stored in a refrigerator and must be consumed within 24 hours, after which any remaining product is discarded. Participants are instructed to consume the supplement twice daily, approximately at 08:00 and 19:00, one hour after meals. Preparation procedures are explained verbally and in written form, and standardized instructions are included in the study SOP.

No physical product preparation is required. Exercise sessions are delivered using a standardized nurse-led mind–body exercise program, supported by written SOPs and exercise demonstration videos. Sessions are conducted in community settings under the supervision of trained nurses, with guidance from a rehabilitation physician. Participants are instructed to wear comfortable clothing, follow the guided movements, and stop the session if discomfort occurs.

The control intervention requires no product preparation. Educational sessions are delivered by the principal investigator and accompanying staff using PowerPoint presentations and printed leaflets. Study staff prepare the educational materials in advance according to standardized content to ensure consistency across sessions.

6.3 Measures to Minimize Bias: Randomization and Blinding

Participants will be randomly assigned in a 1:1:1 ratio to one of three study groups: (1) nurse-led mind–body exercise combined with nutritional supplementation, (2) nurse-led mind–body exercise alone, or (3) control group receiving health education. Randomization will be performed using a computer-generated random sequence prepared by an independent researcher not involved in participant recruitment, intervention delivery, or outcome assessment. Allocation concealment will be maintained using sequentially numbered codes. Due to the nature of the behavioral and nutritional interventions, blinding of participants and intervention providers is not feasible. To minimize bias, outcome assessors and data analysts will be blinded to group allocation, and data collection for pre- and post-intervention outcomes will be conducted by personnel not involved in intervention delivery. No interim unblinding is planned, and randomization codes will only be accessed if required for participant safety in the event of a serious adverse event, as determined by the principal investigator. Any intentional or inadvertent unblinding will be documented and reported according to the study protocol. The open-label design is considered appropriate, as primary and secondary outcomes are assessed using standardized and objective measurement tools to reduce observer bias.

6.4 Study Intervention Compliance

Adherence to the study protocol will be assessed throughout the intervention period for all study arms. For the mind–body exercise intervention, adherence will be monitored using structured attendance logs and follow-up records. During weeks 1 and 2, adherence assessment will be conducted directly during group exercise sessions held at the community center, where research assistants document attendance, session completion, and participant engagement. During weeks 3 and 4, adherence monitoring will be conducted in a blinded manner, consisting of one home visit per week by trained assessors who are not involved in intervention delivery, while additional follow-up will be performed by the research team via

WhatsApp or telephone communication. In week 5, adherence will be monitored exclusively through follow-up by the researchers via WhatsApp or telephone. During weeks 6 and 7, adherence reporting will be conducted through participant-initiated communication to the research team via WhatsApp or telephone. In week 8, adherence assessment will again be conducted directly during group exercise sessions at the community center.

Adherence to the mind–body exercise intervention will be assessed based on participants' ability to perform exercises including warm-up activities, balance and strength exercises, and cooling-down exercises. Attendance records, follow-up logs, and communication records will be used to calculate adherence rates based on the predefined frequency and duration of the exercise program. These records will document session participation, types of movements performed, any modifications due to physical limitations, and communication between participants and researchers during follow-up.

For the nutritional supplementation intervention, participants will be provided with a supplement intake log to record daily consumption, timing, and any missed doses. Research assistants will review these logs weekly and verify adherence through brief interviews and inspection of returned empty or unused product containers, when applicable. In the control group, adherence to the educational intervention will be assessed through attendance records for education sessions and confirmation of receipt of educational materials.

Documents for adherence assessment include attendance sheets, participant self-report logs, follow-up and communication logs, and researcher verification forms. These documents will serve as mandatory study records and will be used to calculate compliance rates for each intervention component.

6.5 Concomitant Therapy

For this protocol, a prescription medication is defined as a medication that can only be prescribed by a properly authorized/licensed clinician. Data on permitted concomitant therapies will include all prescription medications, over-the-counter (OTC) medications, nutritional supplements (other than the study-provided supplement), and complementary or alternative therapies used by participants during the study period. This information will be collected at baseline/screening and updated at each study visit or follow-up assessment. Concomitant therapies are permitted provided they are stable and do not directly interfere with the study interventions or outcomes. Changes in medication, supplements, or therapies during the study will be documented, including type, dose, frequency, indication, and duration. Allowed concomitant therapies may potentially influence study outcomes (e.g., physical performance, frailty status, body composition, or inflammatory markers) through direct physiological effects or interactions with the nutritional supplementation. To address this, concomitant therapy data will be considered during data analysis, and where appropriate, sensitivity or subgroup analyses will be conducted to help distinguish the independent effects of the study interventions from those of concomitant treatments.

6.5.1 Rescue Medicine

The study will not routinely supply specific rescue medications as part of the protocol. Rescue therapy, if needed, will be obtained locally according to standard clinical practice and under the responsibility of licensed healthcare providers. Rescue treatments may include topical or oral medications for musculoskeletal discomfort, or other standard supportive treatments deemed necessary to ensure

participant safety and comfort. The use of rescue therapy is permitted at any time during the study if participants experience discomfort, pain, or other symptoms that cannot be managed conservatively. However, participants will be advised, where clinically appropriate, to delay the use of rescue medications for at least 24 hours after the study intervention session (mind–body exercise and/or nutritional supplementation) to minimize potential interference with outcome assessments. All use of rescue medications or procedures must be fully documented, including the date and time of administration, name of medication or treatment, dosage, route, duration, and clinical indication, and recorded in the Case Report Form (CRF).

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

Participants may withdraw voluntarily from the study or the PI may discontinue a participant from the study. This section should state which adverse events would result in discontinuation of study intervention or participant discontinuation/withdrawal. In addition, participants may discontinue the study intervention, but remain in the study for follow-up, especially for safety and efficacy study endpoints (if applicable). Consider requiring separate documentation for study intervention discontinuation and participant discontinuation/withdrawal from the study. In addition, a dedicated Case Report Form (CRF) page should capture the date and the specific underlying reason for discontinuation of study intervention or participant discontinuation/withdrawal.

7.1 Discontinuation of Study Intervention

Discontinuation from mind-body exercises and supplements does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) . After enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).
The data to be collected at the time of study intervention discontinuation will include the following:

- Temporary discontinuation is performed for 2-7 days until symptoms improve and pain no longer interferes with daily activities. If the pain resolves or significantly reduces within 7 days, the intervention can be resumed. However, if pain persists after 7 days despite supportive therapy, the investigator will evaluate whether this is a systemic effect and consider permanent discontinuation.
- Before permanently discontinuing the intervention, the researcher will conduct an “early termination visit” procedure which includes: recording the reason for discontinuation in detail on a case report form and a complete physical examination and vital signs.
- Discontinuing the intervention does not result in participant withdrawal from the study. Data analysis will be conducted based on the Intent-to-Treat (ITT) principle. Data from participants who discontinue before the end of the study will remain included in the safety and efficacy analyses to the extent available.
- Any adverse events observed at the time of discontinuation will be monitored until the condition is stable, resolved, or there is another adequate medical explanation. Researchers will continue to follow up by phone and monthly visits until the end of the study.

7.2 Participant Discontinuation/Withdrawal from the Study

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons :

1. Significant study intervention non-compliance.
2. If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
3. Disease progression which requires discontinuation of the study intervention
4. If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
5. Participant unable to receive Mind-Body Exercise and Nutritional Supplementation for 7 days.

The reason for participant discontinuation or withdrawal from the study will be recorded on the Discontinuation Case Report Form (CRF). Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

7.3 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she fails to return for <specify number of visits> scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

1. A participant will be considered lost to follow-up if he or she fails to return for 3 scheduled visits and is unable to be contacted by the study site staff.
2. The following actions must be taken if a participant fails to return to the clinic for a required study visit:
    - The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
    - Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, visiting the participant's house). These contact attempts should be documented in the participant's medical record or study file.
    - Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up

8 STUDY ASSESSMENTS AND PROCEDURES

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

8.1 Efficacy Assessments

All study procedures and evaluations are designed to support the determination of efficacy in accordance with the protocol's primary and secondary objectives. The study includes sequential phases consisting of screening, enrollment/baseline assessment, intervention period, post-intervention follow-up assessment, and end-of-study evaluation.

1. Screening and Eligibility Assessment
   Potential participants will be screened at week 0. Screening procedures include verifying inclusion and exclusion criteria, collecting demographic information, medical history, current medications and supplements, and assessing baseline frailty using a validated frailty instrument. Eligibility decisions will be made based on pre-specified inclusion and exclusion criteria. Participants who do not meet eligibility requirements will not proceed to the baseline assessment.
2. Baseline Assessment (Pre-Intervention)
   Eligible participants who provide informed consent will undergo a baseline evaluation prior to randomization. This includes assessments of physical performance (e.g., Short Physical Performance Battery), functional mobility and fall risk (Timed Up and Go Test), pulmonary function (Peak Flow Meter), body composition (Bioelectrical Impedance Analysis), and collection of biological specimens for inflammatory and metabolic biomarkers (e.g., IL-6 and TNF-α). Baseline questionnaires and standardized instruments will be administered by trained and qualified personnel.
3. Study Intervention and Control ProceduresParticipants will be randomized into one of three study groups:
   a. Mind-body exercise intervention
      Participants in the intervention group received a standardized mind-body exercise program led by trained nurses under the supervision of a rehabilitation physician. Exercise sessions took place three times a week, lasting approximately 45–50 minutes per session, in a community setting. Each session included:
      - Warm-up (≈5 minutes): light stretching and breathing exercises;
      - Core exercise (≈30 minutes): resistance and balance training movements;
      - Cool-down (≈10 minutes): relaxation and flexibility exercises incorporating chair yoga and breathing techniques.

      All participants followed a predetermined exercise protocol, with movements tailored to individual physical capacity. Participants were instructed to stop exercising if discomfort occurred.
   b. Mind-body exercise combined with nutritional supplementation
      Participants assigned to the combined intervention arm receive oral protein nutritional supplementation in the form of a commercially available milk-based supplement (Ensure Gold® StrengthPro). The supplement is provided twice daily for 8 weeks, with one serving prepared as 230 mL per serving according to manufacturer instructions. The supplement is consumed approximately one hour after meals to support protein intake and muscle maintenance during the rehabilitation program
   c. A control group receiving health education
      Participants in the control group receive standard health education for older adults with frailty, delivered by the principal investigator and study team. Education sessions cover topics related to healthy aging, frailty prevention, physical activity, and nutrition, using PowerPoint presentations and printed educational leaflets, without structured exercise or nutritional supplementation.
4. Follow-up and Outcome Assessment (Post-Intervention)

Participants will be monitored throughout the intervention period and assessed at predetermined time points according to the Activity Schedule. Post-intervention follow-up procedures will include reassessment of frailty status, assessment of physical performance (e.g., Short Physical Performance Battery), functional mobility and fall risk (Timed Up and Go Test), pulmonary function (Peak Flow Meter), body composition (Bioelectrical Impedance Analysis), and collection of biological specimens for inflammatory and metabolic biomarkers (e.g., IL-6 and TNF-α), adherence monitoring, and documentation of concomitant therapies and rescue medications.

8.2 Safety and Other Assessments

This study includes a series of procedures and evaluations conducted to ensure participant safety, determine eligibility, support the understanding of the study intervention, and collect study data. All procedures are performed by qualified personnel according to standardized operating procedures, with detailed instructions provided in the Standard Operational Procedures (SOP).

1. Screening and Enrollment Procedures
   Potential participants undergo screening procedures. Screening includes review of demographic data, medical history, frailty status assessment, and confirmation of inclusion and exclusion criteria. Eligibility decisions are made based on predefined criteria, and only meeting participants all requirements are enrolled. Written informed consent is obtained prior to any study-specific procedures. No separate screening protocol is used; screening is integrated into this study protocol.
2. Baseline and Follow-up Safety Assessments
   A targeted physical examination is conducted at baseline, including measurement of height, weight, and functional mobility, as appropriate for older adults with frailty. Vital signs (blood pressure, heart rate, and respiratory rate) are assessed at baseline and during selected follow-up visits to monitor safety.
3. Biological Specimen Collection and Laboratory Evaluations
   Blood samples were collected at baseline and post-intervention for assessment of inflammatory and metabolic biomarkers (e.g., IL-6 and TNF-α) related to frailty. All samples are processed using standardized laboratory methods to ensure consistency across measurements. Laboratory analyzes are conducted in qualified laboratories following applicable regulations; Detailed procedures for sample handling, storage, and analysis are described in the SOP.
4. Intervention Monitoring and Counseling
   Participants receive counseling related to safe participation in mind–body exercise and appropriate consumption of nutritional supplementation. Instructions include physical activity precautions, recognition of discomfort, and dietary guidance related to supplement intake.
5. Adherence and Outcome Assessments
   Adherence to study interventions is monitored through attendance records, follow-up logs, and communication records. Functional performance tests and questionnaires assessing frailty status and related outcomes are administered by trained assessors who are not involved in delivering the intervention, when feasible, to reduce bias.
6. Adverse Event Monitoring
   All adverse events (AEs) and serious adverse events (SAEs) were actively monitored throughout the study period. Participants are instructed to report any discomfort or health changes immediately. Reported AEs/SAEs are documented, evaluated by the study team, and followed until resolution or stabilization.

Overall, these procedures are designed to ensure participant safety, data quality, and reliable assessment of study outcomes, while minimizing participant burden.

8.3 Adverse Events and Serious Adverse Events

8.3.1 Definition of Adverse Events (AE)

An adverse event (AE) is defined as any untoward medical occurrence associated with participation in this study, including during the administration of the mind–body exercise program or nutritional supplementation, whether or not it is considered related to the study intervention, in accordance with the FDA definition (21 CFR 312.32(a)). AEs may include physical, psychological, or functional complaints, abnormal findings, or symptoms that occur or worsen during the study period, regardless of causal relationship to the intervention.

8.3.2 Definition of Serious Adverse Events (SAE)

A serious adverse event (SAE) is defined as any adverse event (AE) or suspected adverse reaction that, in the judgment of the investigator or sponsor, results in one or more of the following outcomes, in accordance with FDA regulations (21 CFR 312.32[a]):

1. Death
2. A life-threatening adverse event
3. Inpatient hospitalization or prolongation of existing hospitalization
4. A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions

In addition, important medical events that may not result in death, be immediately life-threatening, or require hospitalization may also be considered serious if, based on appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. For this study, examples of potential SAEs may include, but are not limited to, serious falls resulting in fracture or hospitalization, severe cardiovascular events occurring during or after exercise sessions, severe allergic reactions to nutritional supplementation, or other unexpected serious medical conditions temporally associated with study participation.

8.3.3 Classification of an Adverse Event

1.1.1.1 Severity of Event

All adverse events (AEs) will be assessed and graded for severity by the study clinician in accordance with a protocol-defined grading system. The grading of AE severity will be based on clinical judgment, considering the intensity of symptoms, the degree of functional limitation, and the need for medical intervention. The grading approach is adapted from commonly used clinical toxicity and safety assessment frameworks and is appropriate for non-pharmacological interventions, including exercise-based and nutritional interventions. For adverse events not specifically included in a protocol-defined grading scale, the following severity categories will be applied:

1. Mild – Events require minimal or no intervention and do not interfere with the participant's usual daily activities.

2. Moderate – Events cause discomfort or functional limitation that interferes to some extent with daily activities and may require simple therapeutic measures.
3. Severe – Events significantly interfere with normal daily activities, may require medical treatment or clinical intervention, and may be potentially life-threatening or result in hospitalization.

It is noted that the term "severe" refers to the intensity of an adverse event and does not necessarily indicate that the event meets the criteria for a serious adverse event (SAE). The distinction between severity and seriousness will be clearly maintained in accordance with regulatory definitions.

1.1.1.2 Relationship to Study INTERVENTION

All adverse events (AEs) will have their relationship to study intervention or study participation assessed by the study clinician based on temporal relationship, clinical judgment, and consideration of alternative etiologies. In accordance with good clinical practice, the study intervention will always be considered a possible cause of an AE unless an alternative explanation is clearly established. If there is any doubt as to whether a clinical observation constitutes an AE, the event will be reported. The assessment of relatedness will take into account the natural history of frailty, age-related comorbidities, intercurrent illness, concomitant medications or supplements, study-related procedures, physical activity–related events, accidents, and other external factors. The degree of certainty regarding the relationship between the AE and the study intervention will be categorized using the following scale:

1. Related – There is a reasonable possibility that the AE is causally related to the study intervention, including a plausible temporal relationship between the intervention and the event, and no more likely alternative explanation.
2. Possibly Related – The AE occurred within a reasonable time after the study intervention, but other contributing factors such as underlying disease, concurrent illness, or concomitant therapy may also have played a role.
3. Unlikely to be Related – The temporal relationship between the AE and the study intervention makes a causal association improbable, and other etiologies provide a more plausible explanation.
4. Not Related – The AE is clearly attributable to causes other than the study intervention, with a documented alternative etiology.

1.1.1.3 Expectedness

Expected adverse reactions are adverse events (AEs) that are known to occur with the study interventions and will be collected in a standardized and systematic manner using a severity grading scale based on functional impact and magnitude of reaction. The determination of expected AEs will be based on reference safety information obtained from approved product labeling for the nutritional supplementation (Ensure Gold®) and published literature and established exercise safety guidelines for mind–body exercise in older adults. Expectedness is assessed based on AEs that have been previously observed with these interventions, rather than on theoretical or anticipated effects.

An adverse event or suspected adverse reaction will be considered unexpected if it is not listed in the approved product labeling, published safety information, or protocol-described risk profile, or if it occurs at a greater specificity, severity, or frequency than previously documented. Unexpected AEs also include events that are known to occur with a class of products or interventions but have not been reported with the specific intervention under investigation. The Principal Investigator (PI) will be responsible for

determining whether an AE is expected or unexpected based on available safety references and clinical judgment. An AE will be classified as unexpected if the nature, severity, or frequency of the event is not consistent with the previously described risk information for the study interventions.

1.1.2 Time Period and Frequency for Event Assessment and Follow-Up

Adverse events (AEs) and serious adverse events (SAEs) will be identified through multiple sources, including scheduled study visits, direct observation during intervention sessions, structured interviews, telephone or WhatsApp follow-up, and spontaneous reports from participants or caregivers. Study personnel will also identify AEs during review of participant records or when participants seek medical care during the study period. All AEs that do not meet the criteria for SAEs will be recorded in the Case Report Form (CRF). Information collected will include a description of the event, date and time of onset, severity grading, assessment of relationship to the study intervention, actions taken, and date of resolution or stabilization. All AEs occurring after informed consent is obtained will be documented regardless of their perceived relationship to the study intervention and will be followed until resolution, stabilization, or study completion.

Baseline medical conditions present at screening will not be reported as AEs unless there is a clinically significant worsening during the study, in which case the change will be recorded as an AE. Changes in severity of an AE over time will be documented to allow assessment of duration at each severity level. Intermittent events will be recorded with separate onset and resolution dates for each episode. Solicited AEs will be actively assessed at each study contact using standardized safety monitoring questions related to common and expected effects of the interventions, including musculoskeletal discomfort, fatigue, dizziness, balance disturbances, and gastrointestinal symptoms related to nutritional supplementation. Unsolicited AEs will be captured through open-ended questioning such as, “Have you noticed any new symptoms or changes in your health since participating in the study?” To avoid double capture, events reported as solicited AEs will not be re-entered as unsolicited events.

Non-serious AEs will be collected from the time of informed consent until 7 days after completion of the intervention, while SAEs will be collected from informed consent through the entire study period and up to 30 days after the last study intervention. All SAEs will be followed until resolution, stabilization, or determination of a chronic condition. AE and SAE assessments will be conducted by qualified study clinicians, including trained nurses and physicians, using protocol-defined assessment tools. Participants experiencing ongoing or unresolved AEs at study completion will be followed until the event is resolved or considered clinically stable.

1.1.3 Adverse Event Reporting

Investigators are responsible for the identification, documentation, assessment, and timely reporting of all adverse events (AEs) and serious adverse events (SAEs) occurring during the study period. All non-serious AEs will be recorded in the Case Report Form (CRF). All SAEs will be reported within 24 hours of the investigator’s awareness of the event. Follow-up information, including outcome and causality assessment, will be submitted as it becomes available until the event is resolved or considered clinically stable. Detailed procedures, including reporting pathways, notification timelines, roles and responsibilities of study personnel.

The PI is responsible for reviewing and signing off on all AE and SAE reports prior to submission. Study staff, including research nurses and research assistants, are responsible for initial documentation and timely notification to the PI. Certain disease-related events (DREs) that are common in the elderly population with frailty, such as transient fatigue, mild musculoskeletal discomfort, or minor balance instability not resulting in injury are anticipated and will not be reported as SAEs unless they meet seriousness criteria. These events will be recorded in the CRF and monitored descriptively throughout the study to assess overall safety trends.

1.1.4 Serious Adverse Event Reporting

Clinical researchers will promptly report any serious adverse events to the sponsor and ethics committee as soon as possible, within 24 hours of receiving the information. Reporting is mandatory regardless of whether the event is related or unrelated to the mind-body workout intervention or the nutritional supplement administered. Researchers will assess whether there is a potential causal link between the intervention (e.g., a physical injury from exercise or an allergic reaction to the supplement) and the event. Each SAE will be closely monitored by the research team until the participant's condition is deemed stable. Sponsors are responsible for reporting any unexpected and life-threatening serious reactions to the regulatory authorities (BPOM or relevant health authorities) as soon as possible, within a maximum of 7 days.

1.1.5 Reporting Events to Participants

All participants will be given a detailed explanation of the potential risks during the informed consent process. If an adverse or serious adverse event occurs during the study, the following actions will be taken:

1. Detection findings through clinical observation during training sessions or through laboratory screening that is part of the nutritional supplementation protocol.
2. Immediate communication, researchers will contact participants (and families if necessary in cases of SAE) directly by telephone or face-to-face to explain the findings within 24 hours.
3. The follow-up plan is for researchers to provide a letter of recommendation for participants to consult independently at a primary health care facility (community health center/clinic). If a life-threatening condition is identified, researchers will immediately refer participants to the emergency room of a partner hospital.
4. The costs of initial diagnosis of incidental findings are fully covered by the researcher. Long-term treatment costs for incidental findings are covered by the participant's personal insurance (BPJS).
5. Risk transparency, researchers will explain whether the incident is directly related to Mind-Body Exercise and the provision of nutritional supplements or is an independent medical condition.
6. If new security findings of general significance emerge, all participants will be re-informed so they can consider continuing their participation.
7. The results of the participants' personal health examinations will be reported to the participants while the overall results of the study will be shared with the participants through a summary report or scientific publication after the study is completed.

1.1.6 Events of Special Interest

N/A

1.1.7 Reporting of Pregnancy

N/A

1.2 Unanticipated Problems

1.2.1 Definition of Unanticipated Problems (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

In this study, unforeseen issues that may arise include:

- The severity of allergies due to nutritional supplement consumption is beyond expectations.
- Participants fall or break bones while performing Mind-Body Exercises.
- Participants experience trauma or extreme anxiety after the exercise.
- Participants have to incur significant medical expenses not covered by the study due to unforeseen events.
- Personal data leaks (e.g., their medical history is leaked), causing participants to feel embarrassed or socially disadvantaged.

1.2.2 Unanticipated Problem Reporting

The principal investigator will ensure that all unforeseen issues are reported to the ethics committee. Clinical research staff or research assistants are responsible for identifying incidents in the field, documenting them, and promptly reporting them to the principal investigator for signature before submission to the regulatory authority.

- Contents of the report
  The report contains the protocol identity (research title, protocol number, principal investigator's name, and ethics approval number), detailed description (detailed explanation of the incident, experience, or outcome that occurred), basic analysis of the unanticipated problems (explanation of why the incident is considered a unanticipated Problems), and corrective actions (description of any protocol changes that have been made or proposed, changes to the informed consent form, or other corrective actions in response to the unanticipated problem).
- Reporting Timeline
  Any unanticipated problem, including a serious adverse event, will be reported to the ethics committee within 24 hours of the researcher's discovery. Unanticipated problems that are not severe adverse events, such as privacy violations or product contamination without any participant illness, will be reported to the ethics committee within 5 days of the researcher's discovery.
- Reporting Process

After an unanticipated problem is detected, research staff must verbally report it to the principal investigator within 12 hours. The principal investigator evaluates the unanticipated problem criteria and signs the unexpected problem report form. The report is then submitted to the ethics committee.

1.2.3 Reporting Unanticipated Problems to Participants

Individual level communication :

- The principal investigator will contact participants directly by telephone or face-to-face within 24 hours, after an unanticipated problem is identified.
- Participants will be given an in-depth explanation of the issue, its potential impact on their health, and the medical steps that have been or will be taken.
- Participants will be given updated information regarding the risks identified and asked again about their willingness to continue or stop the research (re-consenting).

Aggregate level communication
If an unanticipated problem occurs that has the potential to affect the risk profile of the entire participant group, then:

- All participants currently on the course will be promptly informed of the new risks via group meetings or electronic messages (WhatsApp).
- All participants will be asked to review and sign an updated version of the Informed Consent form that includes these new risks.
- Di akhir studi, ringkasan mengenai Masalah Tak Terduga yang signifikan dan bagaimana masalah tersebut dikelola akan disertakan dalam laporan hasil studi agregat yang dibagikan kepada peserta (tanpa membuka identitas individu yang mengalami kejadian tersebut).

2 STATISTICAL CONSIDERATIONS

2.1 Statistical Hypotheses

- Primary Efficacy Endpoint(s):
  Endpoint:
  Change in frailty status from baseline to the end of the 8-week intervention, measured using a validated frailty assessment tool.
  Type of comparison:
  Superiority (between-group comparison)
  Null Hypothesis (H0):
  There is no difference in the change in frailty status from baseline to 8 weeks among older adults receiving (1) nurse-led mind–body exercise combined with nutritional supplementation, (2) nurse-led mind–body exercise alone, and (3) control (health education).
  Alternative Hypothesis (H1):
  Older adults receiving nurse-led mind–body exercise combined with nutritional supplementation will demonstrate a significantly greater improvement in frailty status from baseline to 8 weeks compared with those receiving mind–body exercise alone or control (health education).
- Secondary Efficacy Endpoint(s):
  Endpoints:
  Changes from baseline to 8 weeks in:

a. Lower extremity physical performance (Short Physical Performance Battery)
b. Functional mobility and fall risk (Timed Up and Go Test)
c. Pulmonary function (Peak Expiratory Flow)
d. Body composition (muscle mass, fat mass, and BMI measured by BIA)
e. Inflammatory biomarkers related to frailty (IL-6 and TNF-α)

Type of comparison:
Superiority (between-group comparison)
Null Hypothesis (H0):
There are no differences in secondary outcome measures from baseline to 8 weeks among the three study groups.
Alternative Hypothesis (H1):
Participants in the combined intervention group (mind–body exercise plus nutritional supplementation) will show significantly greater improvements in secondary outcome measures from baseline to 8 weeks compared with the exercise-only and control groups.

2.2 Sample Size Determination

The sample size was determined using Cochran's formula, based on the primary outcome of change in frailty score from baseline to 8 weeks. Using a 95% confidence level (Z = 1.96), an assumed population proportion of 0.5, and an acceptable margin of error, the minimum required sample size was calculated to be 12 participants per group. To account for potential attrition, withdrawal, or incomplete data during the intervention period, the sample size was increased to 16 participants per group. This adjustment was made to ensure an adequate evaluable sample and maintain the robustness of the analysis. The final planned sample size is therefore 48 participants in total across the three study arms. This sample size is considered appropriate for this preliminary randomized controlled trial and will provide data to inform sample size estimation for future larger-scale studies.

2.3 Populations for Analyses

The ITT dataset will include all participants who are randomized into one of the three study groups, regardless of their level of adherence to the assigned intervention, protocol deviations, or withdrawal after randomization. Participants will be analyzed according to their originally assigned groups. This dataset will serve as the primary analysis population for efficacy outcomes to preserve the benefits of randomization.

2.4 Statistical Analyses

2.4.1 General Approach

Descriptive Statistics

- Continuous Data: Data such as frailty scores (Fried Phenotype), handgrip strength, and gait speed will be presented as Mean (Average) and Standard Deviation (SD) if normally distributed. If the data is not normally distributed, it will be presented as Median and Interquartile Range (IQR).
- Data Categories: Demographic characteristics such as gender, education level, and medical history will be presented as frequency (n) and percentage (%).

Hypothesis Testing and Significance

- All statistical tests will be conducted two-tailed.
- The level of statistical significance is set at a p-value <0.05 with a 95% confidence interval.
- To compare the intervention effects between the three groups (Mind-Body & Goldsure combination vs. Mind-Body alone vs. Control), an Analysis of Variance (ANOVA) or Mixed-model ANOVA will be used to examine the interaction between time and group (Pre-test, Post-test 1, Post-test).

Statistical Assumption Check

- Normality Test: Before conducting inferential testing, data distribution will be checked using the Shapiro-Wilk or Kolmogorov-Smirnov test.
- Corrective Procedure: If the assumption of normality is not met, researchers will transform the data or use a relevant non-parametric test (such as the Kruskal-Wallis test instead of ANOVA).
- Homogeneity Test: Levene's test will be performed to ensure equal variances between groups.

Covariates

- Covariates such as age, initial body mass index (BMI), and baseline frailty severity will be considered in multivariate analyses (such as ANCOVA) to control for confounding variables that may influence the intervention efficacy results.

2.4.2 Analysis of the Primary Efficacy Endpoint(s)

The primary endpoint is the change in frailty score from baseline to week 8. Frailty status is measured using a validated frailty assessment instrument as specified in the protocol, and the outcome is calculated as the difference between post-intervention and baseline scores, with greater reductions indicating improvement. The frailty score is treated as a continuous (interval) variable and analyzed as a repeated measure. The primary analysis will be conducted using Linear Mixed-Effects Models or repeated measures ANOVA, with the post-intervention frailty score as the dependent variable, study group (three parallel groups) as the fixed factor, and baseline frailty score as a covariate to improve precision and control for baseline differences. Results will be presented as adjusted means (least-squares means) with standard errors, adjusted mean differences between groups, and 95% confidence intervals, using a two-sided significance level of 0.05. Model assumptions will be assessed through residual diagnostics, and appropriate transformations or nonparametric sensitivity analyses will be applied if needed. The analysis will follow the Intention-to-Treat (ITT) principle, including all randomized participants according to their assigned groups. Missing data will be handled using multiple imputation under the missing-at-random assumption, with sensitivity analyses performed as appropriate. As only one primary endpoint is specified, no adjustment for multiplicity is required; however, post-hoc pairwise comparisons will apply Tukey or Bonferroni correction.

2.4.3 Analysis of the Secondary Endpoint(s)

All secondary endpoints are considered supportive and exploratory and will be analyzed independently of the primary frailty outcome. Physical function will be assessed using the Short Physical Performance Battery (SPPB; total score 0–12), mobility using the Timed Up and Go Test (TUG, seconds), body composition using bioelectrical impedance analysis (fat mass, fat-free mass, skeletal muscle mass, and phase angle), pulmonary function using peak expiratory flow (PEF, L/min), and inflammatory status using serum IL-6 and TNF-α measured by ELISA. All outcomes are treated as continuous variables and measured from baseline to week 8. Analyses will be conducted under the Intention-to-Treat (ITT) principle using Linear Mixed-Effects Models with study group and time as fixed effects and participant as a random effect, adjusting for age, sex, and baseline values of each outcome to achieve a parsimonious

model. Biomarker data (IL-6 and TNF-α) will be log-transformed if distributions are skewed. Results will be presented as adjusted means (LSMEANS) with standard errors and between-group differences with 95% confidence intervals. Model assumptions will be assessed using residual diagnostics and normality tests; nonparametric alternatives or data transformation will be applied if required. Missing data will be handled using likelihood-based estimation inherent to mixed models under the assumption of missing at random, with sensitivity analyses performed for outliers, nonadherence, and loss to follow-up.

2.4.4 Safety Analyses

Safety endpoints will be analyzed descriptively for all participants who receive at least one session of the study intervention or control activity (Safety Analysis Set). Adverse events (AEs) will be summarized using frequencies and percentages by study group and overall, without formal hypothesis testing. Treatment-emergent AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and each AE will be counted once per participant per preferred term. AEs will be presented by System Organ Class (SOC) and preferred term, and further stratified by severity (mild, moderate, severe), relationship to the study intervention (related or not related), and expectedness. For each AE, the following information will be reported: onset date, resolution date, duration, severity grade, seriousness, relationship to the study intervention, expectedness, action taken, and outcome. Serious adverse events (SAEs) and AEs leading to premature discontinuation of the study intervention will be listed separately and summarized in dedicated tables. Changes in safety-related parameters from baseline, if applicable (e.g., vital signs or clinical observations), will be summarized using descriptive statistics and shift tables. All safety analyses and reporting will be consistent with the procedures and definitions described in Section 8.2, Safety and Other Assessments.

2.4.5 Baseline Descriptive Statistics

Baseline characteristics of participants will be summarized by intervention group using descriptive statistics. Continuous variables (e.g., baseline frailty score, physical function measures, laboratory values) will be presented as means and standard deviations or medians and interquartile ranges, as appropriate based on data distribution. Categorical variables (e.g., age, sex, frailty category, comorbidities) will be summarized using frequencies and percentages. Comparability of intervention groups at baseline will be assessed descriptively; formal inferential statistical testing of baseline differences will not be performed, as any observed differences are assumed to be due to random variation. However, clinically relevant imbalances identified at baseline may be considered for inclusion as covariates in adjusted analyses.

2.4.6 Planned Interim Analyses

No formal statistical interim analyses are planned for this study. Given the relatively short intervention period, modest sample size, and the low-risk nature of the study interventions (mind–body exercise and nutritional supplementation), interim analyses for efficacy, futility, or sample size re-estimation are considered not applicable. Safety will be monitored continuously throughout the study by the principal investigator and study clinicians through routine adverse event (AE) and serious adverse event (SAE) reporting, as described in Section 8. Any unexpected pattern of SAEs, a clustering of severe intervention-related AEs, or any event suggesting unacceptable risk to participants may prompt and safety review and temporary suspension of study intervention for the affected participant. Decisions regarding suspension or discontinuation will be based on clinical judgment rather than formal statistical

boundaries and will be reported to the appropriate ethics committee in accordance with institutional procedures.

2.4.7 Sub-Group Analyses

Subgroup analyses of the primary endpoint (change in frailty score) will be conducted to explore whether the effect of the study intervention differs by key demographic characteristics, including age and sex. These subgroup analyses will be performed by including interaction terms between intervention group and the demographic variable (e.g., group × age, group × sex) within the same linear mixed-effects model used for the primary analysis. Results will be presented descriptively and inferentially as adjusted mean changes with 95% confidence intervals. These analyses are exploratory and not powered for definitive subgroup comparisons. Race/ethnicity-based analyses will not be performed, as the study population is expected to be relatively homogeneous with respect to race/ethnicity, and the sample size is insufficient to support meaningful or reliable comparisons across racial/ethnic subgroups.

For secondary endpoints (physical function, mobility, body composition, pulmonary function, and inflammatory biomarkers), similar exploratory subgroup analyses by age and sex will be conducted using the same statistical framework as the main analyses (e.g., linear mixed-effects models or ANOVA, as appropriate). Interaction terms will be used to assess potential effect modification by demographic characteristics. Findings from these analyses will be interpreted cautiously as hypothesis-generating only, given the limited sample size and lack of adjustment for multiple comparisons.

2.4.8 Tabulation of Individual participant Data

Individual participant data will not be listed by measure and time point. Study results will be presented in aggregate form using summary statistics (e.g., means, standard deviations, adjusted means, and confidence intervals) by study group and assessment time point to protect participant confidentiality. Individual-level data may be reviewed internally for data verification and monitoring purposes but will not be included in reports or publications.

2.4.9 Exploratory Analyses.

Exploratory analyses will be conducted to support interpretation of the primary and secondary outcomes and to generate hypotheses for future studies; however, they will not be used as confirmatory evidence of efficacy. All planned exploratory analyses will be prespecified in the protocol and interpreted descriptively without formal adjustment for multiplicity.

3 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

3.1 Regulatory, Ethical, and Study Oversight Considerations

3.1.1 Informed Consent Process

3.1.1.1 Consent/assent and Other Informational Documents Provided to participants

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The following consent materials are submitted with this protocol.

- Informed Consent Form: The main document covering 20 mandatory ethical elements (including confidentiality, right to withdraw, and emergency contact information).
- Subject Information Sheet: Description of mind-body training procedures and dosage guidelines for Goldsure supplements.
- Recruitment Materials: Research brochures and posters to be displayed in community health facilities/senior health posts (Posyandu).
- Oral Explanation Script: A guideline for researchers to explain key points of the study to seniors.
- Medical Data Use Permission Form: Permission to access medical records related to the participant's general health status.

Given that the study population is elderly, the researchers provided the following adaptations to the materials:

- Large Print Materials: All written documents should be in a minimum font size of 14-16 pt (Arial or Times New Roman) to facilitate participants with visual impairments.
- Use of Witnesses: For participants with disabilities in writing or reading, the consent process will be conducted in the presence of an independent witness (family or community leader), and the participant will provide a thumbprint in lieu of a signature.
- Language: Although official documents are in Indonesian, the researchers will provide staff fluent in the regional language (Javanese) to provide oral explanations for participants who are more comfortable communicating in that language.

3.1.1.2 Consent Procedures and Documentation

The informed consent process will begin before individuals agree to participate and will continue throughout the study. A consent form approved by the Ethics Committee (KEPK) will be provided to prospective participants for review. The researcher will verbally explain the study, including the mind-body exercise and nutritional supplementation procedures, and answer any questions that arise. The explanation will be provided in language easily understood by older adults (including Javanese, if necessary). Participants will be given the opportunity to discuss the information with their family or guardian before signing the document. Participants must be informed that participation is voluntary and they can withdraw at any time without prejudice. The researcher will document this process in source documents (including the date), and the form will be signed before participants undergo specific research procedures. Participants' well-being is protected by ensuring that consent to participate will not affect the quality of medical care they receive in the community.

3.1.2 Study Discontinuation and Closure

This study may be paused or terminated early if there is sufficient reasonable cause. Written notification documenting the reasons for the suspension or termination will be provided by the appropriate authorities to the study participants, investigators, funding agencies, and regulatory authorities. If the study is paused or terminated prematurely, the Principal Investigator (PI) will promptly inform the study

participants, the Health Research Ethics Committee (KEPK), and the sponsor, and provide the reasons for the decision. Participants will be contacted to receive information about changes to the visit schedule or other safety measures. Things that may lead to study termination or suspension include, but are not limited to:

1. Safety Risk: The discovery of an unexpected, significant, or unacceptable risk to participants (e.g., severe musculoskeletal injury during exercise or serious metabolic side effects following supplementation).
2. Clear Efficacy: The evidence for the benefit of the intervention is so strong that it would be ethically unfair to immediately deprive the control group of the same benefit.
3. Protocol Non-Compliance: Inadequate adherence to protocol requirements that compromises participant safety or data validity.
4. Data Integrity: Data collected are incomplete or unsuitable for statistical evaluation.
5. Futility: Determination that the primary objective of the study (frailty improvement) is unlikely to be achieved even if the study continues.
6. Institutional Decision: Termination based on the discretion of the Ethics Committee or relevant health authority.

The study may be resumed after concerns regarding safety, protocol compliance, and data quality have been fully resolved and written approval from the KEPK and the Sponsor has been obtained.

3.1.3 Confidentiality and Privacy

The Principal Investigator, research staff, and the host institution strictly maintain the confidentiality and privacy of participants. All clinical data, physical examination results, and biological sample test results (such as albumin/protein levels) will be treated as strictly confidential. The study protocol, documentation, data, and all resulting information will be stored securely. No information regarding the study or participant data will be shared with unauthorized third parties without prior written permission from the investigator or sponsor. Research data will not be directly associated with participants' personal identification (such as full names or addresses). Files will be stored in a coded system. Physical data, including paper, questionnaires, and study medical records, will be stored in a filing cabinet. Data for statistical analysis will be entered into a password-protected electronic database. Only de-identified (anonymous) data will be used for analysis. In accordance with institutional policy, all research records will be retained for a minimum of 5 years after completion of the study, after which the physical data will be destroyed and the digital data will be permanently deleted. Access to the original research data will be granted to the principal investigator and research assistants. Research results will be published in scientific journals or presented in academic forums. In all publications, data will be presented in aggregate form. No individual identifiers, uncensored facial photographs, or family details will be published, making it impossible for readers to identify specific participants. If data must be shared with researchers outside the team (e.g., for meta-analyses), only anonymized data will be submitted.

3.1.4 Future Use of Stored Specimens and Data

All data (questionnaires, physical test results, video recordings/photographs) and biological samples (blood for albumin/protein testing) collected in this study will be used solely for the purpose of this study, namely to evaluate the effectiveness of Mind-Body Exercise and nutritional supplementation on frailty.

No data or samples will be used for any other future secondary research. Once all data analysis for this study is completed and the research results are published, the physical data will be destroyed (shredded) after the institution's mandatory retention period (minimum 5 years) has been met. All remaining blood samples will be immediately destroyed in accordance with laboratory medical waste procedures immediately after the research parameters (albumin/protein) have been analyzed. No samples will be stored long-term (biobanking).

The researcher guarantees that all data collection, processing, and analysis will be conducted entirely within the jurisdiction of the Republic of Indonesia. No biological samples (blood) or raw participant identity data will be sent abroad. Collaboration with foreign researchers is limited to methodology consultation and instrument validation. Data shared with international collaborators (if any) is only aggregate/group statistically processed data, not individual data, so that participant confidentiality and national data sovereignty are fully maintained. Video recordings or photos taken during the Mind-Body Exercise training sessions are only used to verify compliance with the exercise protocol by the research team. These recordings will be permanently deleted immediately after the data verification process is complete and will not be published in any media without strict facial censorship and additional written permission from the participants.

3.1.5 Key Roles and Study Governance

Principal Investigator	**Medical Monitor**
Rista Fauziningtyas, S.Kep., Ns., M.Kep, PhD	Nanda Aulya Ramadhan, dr.
Faculty of Nursing, Airlangga University	General Hospital Universitas Airlangga
Kampus C Mulyorejo, Surabaya, 60115	Jl. Dr. Ir. H. Soekarno, Mulyorejo, Kec. Mulyorejo, Kota SBY, Jawa Timur 60115
081330718027	081388372132
ristafauziningtyas@fkp.unair.ac.id	nanda.aulya.r@fk.unair.ac.id

3.1.6 Safety Oversight

An independent Data and Safety Monitoring Board (DSMB) will not be established for this study. Data safety and integrity oversight will be conducted internally by the core research team using the following procedures:

- The Principal Investigator (PI), along with the Medical Monitor, will be solely responsible for the daily monitoring of participant safety. The Medical Monitor will review any Adverse Events (AD) reported by the nurses or research assistants in the field related to the Mind-Body Exercise intervention and nutritional supplementation.
- Data safety reviews will be conducted periodically at weekly research team meetings. The Principal Investigator will review: Reports of participants' physical complaints after the exercise sessions.
- Records of participants' tolerance to nutritional supplements.
- Participants' adherence to the study protocol.

- Although there is no independent board, the Principal Investigator will conduct a formal evaluation midway through the study (week 12) to assess any unforeseen risks to participants. If the risk is found to be significant, the Principal Investigator has the authority to temporarily suspend the study and is required to report it to the Health Research Ethics Committee (KEPK) of the Faculty of Nursing, Airlangga University within 24 hours to obtain further direction.

3.1.7 Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol.

Internal monitoring for this study will be performed by members of the research team designated by the Principal Investigator (PI) to maintain objectivity and minimize bias.

Monitoring will consist of a combination of on-site visits and centralized data reviews:

- On-site Monitoring: Internal monitors will visit each community site (Puskesmas/Posyandu) at the beginning of the study (Initiation Visit) to ensure all staff have been properly trained.
- Centralized Monitoring: Monthly reviews of the electronic database will be conducted to identify missing data, outliers, or inconsistencies in frailty assessment scores and nutritional intake logs.

The extent of monitoring will include:

- Comprehensive (100%) Verification: All Informed Consent Forms, participant eligibility criteria (inclusion/exclusion), and any reported Adverse Events (AEs) will be verified against source documents.
- Targeted Verification (at least 20%): A random review of 20% of the primary endpoint data (e.g., frailty scores, handgrip strength, gait speed) and nutritional supplement (Goldsure) accountability records will be performed to ensure data integrity.

Monitoring reports summarizing findings and any required corrective actions will be distributed to the Principal Investigator (PI) within 7 days of each visit. Any critical deviations from the protocol will be addressed immediately and documented.

Routine independent audits by external parties will not be conducted; however, the research team will maintain all study records in a state of audit-readiness should the Health Research Ethics Committee (KEPK) or local health authorities choose to conduct an inspection at any time.

3.1.8 Quality Assurance and Quality Control

Each clinical site will implement internal quality management for study implementation, data and biological specimen collection, documentation, and completion. An individual quality management plan will be developed to outline the quality management for each site.

- To maintain data consistency across groups (to prevent bias), the principal investigator will conduct standardized training for all research staff, volunteers, and nurses before the study begins. The training will cover exercise procedures, proper nutritional supplement consumption, and side effect management. Prior to baseline data collection, a calibration exercise will be conducted among research assistants for physical measurements (SPPB score, gait speed, and handgrip strength). This ensures that variations in results are due to the intervention's effects,

not differences in measurement techniques among staff. Each research assistant is required to participate in this activity, and proof of attendance will be recorded in the exercise log as part of the quality record.

- Quality assurance and standard operating procedures (SOPs) refer to written Standard Operating Procedures (SOPs). Researchers will ensure that: The mind-body exercise intervention is carried out according to the module by trained nurses, volunteers, and research assistants; the distribution of nutritional supplements must be recorded to compare the dispensed stock with the participant's intake diary; and blood samples are collected and processed according to standards.
- The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities

3.1.9 Data Handling and Record Keeping

3.1.9.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the Principal Investigator (PI). The PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the reported data.

All source documents must be completed in a neat and legible manner to ensure accurate data interpretation. Hard copies of the study visit worksheets will be provided for use as source document worksheets to record data for each participant enrolled in the study (Combination Group, Exercise-only Group, and Control Group).

Source documents in this study include:

- Physical measurement worksheets (gait speed, handgrip strength, SPPB scores).
- Frailty assessment and nutritional intake questionnaires.
- Daily consumption logs for supplementation.
- Printed laboratory results for clinical data.

Data recorded in the electronic Case Report Forms (eCRF) derived from source documents must be consistent with the data recorded on the original source documents. Clinical data (including Adverse Events (AEs), concomitant medications, and expected adverse reactions) as well as clinical laboratory data will be entered into the data system. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the physical source documents by designated research assistants.

To ensure participant safety, study participation will be formally recorded in the participants' medical records or health books at the local Puskesmas (Public Health Center). This ensures that other healthcare providers accessing the participant's medical records have adequate knowledge that the participant is involved in a clinical trial for physical and nutritional intervention.

Data handling responsibilities consist of:

- Research Staff: Responsible for daily data entry and ensuring the legibility of physical documents.
- Principal Investigator: Performs weekly reviews of the eCRF to ensure timeliness of submission (no later than 48 hours after the visit).
- Storage: All physical source documents will be stored in a secure, locked cabinet, and electronic data will be backed up regularly to prevent data loss.

3.1.9.2 Study Records Retention

Study documents will be retained for a minimum period of 3 years after the research is completed. The retained documents include the original consent form, physical data worksheets, supplement distribution records, and laboratory results. Considering that the sponsor/product provider has no interest or ownership rights over this research data, all control over the integrity and confidentiality of the documents is under the full responsibility of the Principal Investigator (PI). The researcher will ensure the security of the documents by entering a predetermined code or password. After a long period of time has expired, the researcher will extend the data.

3.1.10 Protocol Deviations

A protocol deviation is any form of non-compliance with the approved clinical trial protocol. This non-compliance can originate from participants, investigators, or field staff.

The Principal Investigator (PI) is responsible for continuously monitoring and identifying any deviations. All deviations must be documented in source documents and reported to the Health Research Ethics Committee (KEPK) in accordance with applicable policies.

If a deviation is discovered (such as participant non-attendance at exercise sessions or non-compliance with nutritional intake), the research team will promptly develop and implement corrective actions. Each deviation will be evaluated to determine its impact on data integrity and participant safety.

3.1.11 Publication and Data Sharing Policy

This research will be conducted in accordance with the publication and dissemination policies of scientific information applicable to the Faculty of Nursing, Airlangga University, and international standards.

- This study will be registered on international and national clinical trial registration portals (Clinicaltrial.gov and INA-CRR) before participant recruitment begins. The final results of this clinical trial will also be reported on these portals after the study is completed.
- Every effort will be made to publish the results of this study in a reputable, peer-reviewed international journal. Authorship will be determined based on substantial contributions to study design, data collection, or data analysis, in accordance with the International Committee of Medical Journal Editors (ICMJE) guidelines.
- Data generated from this study may be requested by other researchers for scientific purposes after a minimum of two years from the publication of the primary results. Data requests can be

submitted by contacting the Principal Investigator (PI) and must include a clear analysis protocol and ethical approval from the requesting institution.

3.1.12 Conflict of Interest Policy

The Principal Investigator and all research staff declare that they have no financial or personal conflicts of interest in conducting this research. The independence of this research from industry influence is strictly maintained to ensure scientific integrity.

The product provider had no role in the study design, data collection, statistical analysis, interpretation of results, or the decision to publish the manuscript. All members of the research team have signed a written statement confirming that they have no conflict of interest that could affect the objectivity of the research. All forms of support received for this research (such as institutional grants) have been transparently disclosed and have no strings attached to the research results.

3.2 Additional Considerations

N/A

3.3 Abbreviations

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee

SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

3.4 Protocol Amendment History

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale

4 REFERENCES

[1] *A. A. Pradana, H. L. Chiu, C. J. Lin, and S. C. Lee, "Prevalence of frailty in Indonesia: a systematic review and meta-analysis," BMC Geriatr., vol. 23, no. 1, pp. 1–14, 2023, doi: 10.1186/s12877-023-04468-y.*

[2] *S. Sourdet, B. Vellas, and F. Forette, "Frailty and aging," J. Nutr. Health Aging, vol. 16, no. 4, 2011.*

[3] *R. O'Caoimh et al., "Prevalence of frailty at population level in European ADVANTAGE Joint Action Member States: A systematic review and meta-analysis," Ann. Ist. Super. Sanita, vol. 54, no. 3, pp. 226–238, 2018.*

[4] *T.-L. To, T.-N. Doan, W.-C. Ho, and W.-C. Liao, "Prevalence of Frailty among Community-Dwelling Older Adults in Asian Countries: A Systematic Review and Meta-Analysis," Healthc., vol. 10, no. 5, 2022, doi: 10.3390/healthcare10050895.*

[5] *A. Rizka, A. Indrarespati, N. Dwimartutie, and M. Muhadi, "Frailty among older adults living in nursing homes in indonesia: Prevalence and associated factors," Ann. Geriatr. Med. Res., vol. 25, no. 2, pp. 93 – 97, 2021, doi: 10.4235/agmr.21.0033.*

[6] *M. S. Song and S. Boo, "Effects of a nurse-led multicomponent intervention for frail older adults living alone in a community: a quasi-experimental study," BMC Nurs., vol. 21, no. 1, pp. 1–9, Jan. 2022, doi: 10.1186/s12912-021-00801-1.*

[7] *A. S. Kasa, P. Drury, V. Traynor, S.-C. Lee, and H.-C. (Rita) Chang, "The effectiveness of nurse-led interventions to manage frailty in community-dwelling older people: a systematic review," Syst. Rev., vol. 12, no. 1, 2023, doi: 10.1186/s13643-023-02335-w.*

[8] *G. Kang, H. Ji, and J. Y. Yoon, "The effect of community health nurse-led multi-faceted group-based frailty prevention program for older adults: a multi-site pretest-posttest design," BMC Nurs., vol. 24, no. 1, 2025, doi: 10.1186/s12912-025-03372-7.*

[9] *R. Yu, C. Tong, F. Ho, and J. Woo, "Effects of a Multicomponent Frailty Prevention Program in Prefrail Community-Dwelling Older Persons: A Randomized Controlled Trial," J. Am. Med. Dir. Assoc., vol. 21, no. 2, pp. 294.e1-294.e10, Feb. 2020, doi: 10.1016/j.jamda.2019.08.024.*

[10] *L. F. Tan et al., "Impact of Exercise and Cognitive Stimulation Therapy on Physical Function, Cognition and Muscle Mass in Pre-Frail Older Adults in the Primary Care Setting: A Cluster Randomized Controlled Trial," J. Nutr. Heal. Aging, vol. 27, no. 6, pp. 438–447, 2023, doi: 10.1007/s12603-023-1928-7.*

[11] *S. Setiati et al., "Frailty state among Indonesian elderly: Prevalence, associated factors, and frailty state transition," BMC Geriatr., vol. 19, no. 1, pp. 1–10, 2019, doi: 10.1186/s12877-019-1198-8.*

[12] *K. Kavita, J. S. Thakur, S. Ghai, T. Narang, and R. Kaur, "Nurse - led interventions for prevention and control of noncommunicable diseases in low - and middle - income countries : A systematic review and meta - analysis," Int. J. Noncommunicable Dis., pp. 4–13, 2023, doi: 10.4103/jncd.jncd.*

[13] *M. S. Song and S. Boo, "Effects of a nurse-led multicomponent intervention for frail older adults living alone in a community: a quasi-experimental study," BMC Nurs., vol. 21, no. 1, 2022, doi: 10.1186/s12912-021-00801-1.*

[14] *J. Barrachina-Igual, F. M. Martínez-Arnau, P. Pérez-Ros, C. Flor-Rufino, R. Sanz-Requena, and A. Pablos, "Effectiveness of the PROMUFRA program in pre-frail, community-dwelling older people: A randomized controlled trial," Geriatr. Nurs. (Minneap)., vol. 42, no. 2, pp. 582–591, Mar. 2021, doi: 10.1016/j.gerinurse.2020.10.014.*

[15] *R. Radaelli et al., "Effects of Resistance Training Volume on Physical Function, Lean Body Mass and Lower-Body Muscle Hypertrophy and Strength in Older Adults: A Systematic Review and Network Meta-analysis of 151 Randomised Trials," Sport. Med., vol. 55, no. 1, pp. 167–192, 2025, doi: 10.1007/s40279-024-02123-z.*

[16] *H. Wang, Y. Liang, H. Wu, H. Shi, and R. Hou, "Effect of multicomponent exercise intervention in community dwelling frail elderly: A systematic review and meta-analysis," Arch. Gerontol. Geriatr., vol. 126, 2024, doi: 10.1016/j.archger.2024.105543.*

[17] *I. Rodríguez-Gómez et al., "Relationship between physical performance and frailty syndrome in older adults: The mediating role of physical activ-ity, sedentary time and body composition," Int. J. Environ. Res. Public Health, vol. 18, no. 1, pp. 1–12, Dec. 2021, doi: 10.3390/ijerph18010203.*

[18] *A. Hendry, R. O'Caoimh, M. A. Salem, A. Carriazo, and R. Roller-Wirnsberger, Integrated Care for Frailty. 2024. doi: 10.1007/978-3-031-57361-3_31.*

[19] *J. Pöyhönen et al., "Impact of frailty status on the effect of a multidomain lifestyle intervention on cognition," Age Ageing, vol. 54, no. 2, 2025, doi: 10.1093/ageing/afaf041.*

[20] *G. Maiden, A. Kingsford, A. P. Wang, A. R. Tran-Nam, and J. Nelson, "Reimagining Day Rehabilitation For Frailty and Neurodegenerative Conditions through the integrated Rehabilitation and EnAblement Program (iREAP)," Int. J. Integr. Care, vol. 24, no. 3, 2024, doi: 10.5334/ijic.8066.*

[21] *É. Ní Shé et al., "The systematic approach to improving care for Frail Older Patients (SAFE) study: A protocol for co-designing a frail older person's pathway," HRB Open Researc, vol. 1, no. 9, 2018.*

[22] *M. McDonnell, M. Bell, F. Lawler, A. Duffy, and M. Connolly, "Multidisciplinary Inpatient Community Rehabilitation Programmes for Frail Older People: A Scoping Review," Nurs. Open, vol. 11, no. 11, 2024, doi: 10.1002/nop2.70088.*

[23] *A. A. Kjelsnes and E. Feiring, "Models of integrated care for older people with frailty: a horizon scanning review," BMJ Open, vol. 12, no. 4, 2022, doi: 10.1136/bmjopen-2021-060142.*

[24] *L. Lippi et al., "Closing the Gap between Inpatient and Outpatient Settings: Integrating Pulmonary Rehabilitation and Technological Advances in the Comprehensive Management of Frail Patients," Int. J. Environ. Res. Public Health, vol. 19, no. 15, 2022, doi: 10.3390/ijerph19159150.*

[25] Lembaga Penelitian dan Pengabdian Universitas Airlangga, "Rencana Induk Penelitian (RIP) Universitas Airlangga Tahun 2022-2026," 2021, *Airlangga University Press, Surabaya*.