The INTERGEN-INA Study

Effect of Chair-Exercise Followed by Social Heterochronic Parabiosis-Based Intervention in Community-Dwelling Elderly People with Physio-Cognitive Decline Syndrome: a Randomized-Controlled Trial

RESEARCH PROTOCOL

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Institution(s)	- **Faculty of Medicine, Universitas Indonesia, Indonesia** - **School of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia**
Subsidising party	**None**
Study Site(s)	- **School of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia** Jalan Pluit Selatan Raya No.19, Penjaringan, North Jakarta, Jakarta 14440
Funding support	**None (funded personally by the investigator)**
Leading Investigators	**Rensa (Principal Investigator)** Department of Internal Medicine, School of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia Jalan Pluit Raya No.2, Penjaringan, North Jakarta, Jakarta 14440 Email: rensa@atmajaya.ac.id ; phone: +6221 6694366
Project Leader	**Rensa**
Team of Investigators	1. **Rensa (Principal Investigator)** Department of Internal Medicine, School of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia. Jalan Pluit Raya No.2, Penjaringan, North Jakarta, Jakarta 14440 Email: rensa@atmajaya.ac.id; phone: +62 6694366 2. **Siti Setiati** Division of Geriatric Medicine, Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia / Cipto Mangunkusumo Hospital Jl. Diponegoro no.71 Central Jakarta, Jakarta 10430, Indonesia

	Email: s_setiati@yahoo.com; phone: +62 31900275 3. **Tirza Z. Tamin** Departement of Physical Medicine and Rehabilitation, Faculty of Medicine, Universitas Indonesia / Cipto Mangunkusumo Hospital Jl. Diponegoro no.71 Central Jakarta, Jakarta 10430, Indonesia Email: tirzaediva.tamin@gmail.com ; phone: +62 31900275 4. **Purwita Wijaya Laksmi** Division of Geriatric Medicine, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia / Cipto Mangunkusumo Hospital Jl. Diponegoro no.71, Central Jakarta, Jakarta 10430, Indonesia Email: pwlaksmi@yahoo.com; phone: +62 31900275
Independent experts	**Utami Susilowati** Research Coordination Center, Department of Internal Medicine Faculty of Medicine Universitas Indonesia / Cipto Mangunkusumo Hospital Jl. Diponegoro no.71 Jakarta Pusat, Jakarta 10430, Indonesia Email: utami.susilowati.ridwan@gmail.com ; phone: +62 8156209540
Study sites	- **School of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia** Jalan Pluit Selatan Raya No.19, Penjaringan, North Jakarta, Jakarta 14440 - **Balita Tunas Bangsa Orphanage** Jalan Bina Marga No.79, Cipayung, East Jakarta, Jakarta 13840 - **Pelayanan Kasih Bakti Mandiri (PKBM) Orphanage** Jalan Abdulrahman No.16, Cibubur, Ciracas, East Jakarta, Jakarta 13720 - **Komunitas Anak Maria Immaculatta (KAMI) Orphanage** Jalan Pondok Mitra Lestari No.2 Blok C.15, Jatiasih, Bekasi, West Java 17424 - **Putra Utama 1 Orphanage**

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

Abbreviation	Definition
ACSM	American College of Sports Medicine
AE	Adverse Event
AMIR	Ayo Minum Air (educational program from Indonesian Hydration Working Group)
ANCOVA	Analysis of Covariance
ASHT	American Society of Hand Therapists
BMI	Body Mass Index
CCI	Charlson Comorbidity Index
CHS	Cardiovascular Health Study
CRF	Case Report Form
GCP	Good Clinical Practice
GDS-15	Geriatric Depression Scale-15
IADL	Instrumental Activities of Daily Living
IHWG	Indonesian Hydration Working Group
ITT	Suspected Unexpected Serious Adverse Reaction
mBDNF	Mature Brain-Derived Neurotrophic Factor
MNA	Mini Nutritional Assessment
MoCA-Ina	Montreal Cognitive Assessment – Indonesian Version
PASE	Physical Activity Scale for the Elderly
PCDS	Physio-Cognitive Decline Syndrome
PEROSI	Perhimpunan Osteoporosis Indonesia (Indonesian Osteoporosis Association)
PP	Per-Protocol
SAE	Serious Adverse Event
SD	Standard Deviation

SF-12	Short Form-12 (health-related quality of life questionnaire)
SHP	Social Heterochronic Parabiosis
SPSS	Statistical Package for the Social Sciences
ToT	Training of Trainers
VAS	Visual Analog Scale
WHO	World Health Organization

SUMMARY

Rationale: Indonesia is an ageing population with increasing life expectancy, but many elderly people experience functional decline leading to physio-cognitive decline syndrome (PCDS), a reversible condition combining physical (slow gait and reduced grip strength) and cognitive decline (without dementia or disability). PCDS increases the risk of frailty syndrome, disability, and reduced quality of life. Structured physical exercise improves the muscle-brain axis and neuroplasticity markers like mature BDNF. Social isolation worsens PCDS; intergenerational interactions (social heterochronic parabiosis, SHP) may improve cognitive and social domains. However, integrated community-based interventions addressing both physical and psychosocial domains remain limited in Indonesia.Sch

Objective: This study aims to evaluate the effectiveness of a structured chair-based exercise program combined with intergenerational activities compared with usual care in improving physical function, cognitive performance, and frailty status among community-dwelling older adults with physio-cognitive decline syndrome.

Study design: This study is a randomized controlled trial with two parallel arms: (1) chair-based exercise followed by intergenerational activities and (2) usual care. The intervention will be conducted over a defined intervention period with baseline and post-intervention assessments.

Setting: This study will be conducted among community-dwelling elderly individuals in programs managed by the School of Medicine and Health Sciences at Atma Jaya Catholic University of Indonesia and the Archdiocese of Jakarta. The study will include remote tele-exercise and nutritional education, as well as in-person intergenerational sessions at orphanages.

Study population: Community-dwelling elderly aged 60-75 years with PCDS, plus healthy cooperative children aged 5-8 years from orphanages for the intervention arm.

Intervention: Both groups receive nutritional education. Participants in the intervention group will receive a structured chair-based exercise program followed by guided intergenerational activities designed to enhance physical capacity, cognitive stimulation, and social engagement. The control group will receive usual care. Intervention group: 12 weeks structured chair-exercise (PEROSI protocol, progressive frequency 1-3x/week, 60 min/session) followed by 4 weeks SHP (8 sessions, 2x/week, 45 min, paired elderly-child activities using AMIR materials). The control group will receive education only.

Main study parameters/endpoints: The primary outcomes include changes in physical performance and cognitive function. Secondary outcomes include changes in frailty status, quality of life, and psychosocial well-being.

Nature and extent of the burden and risks associated with participation, benefit, and group relatedness: Participation in this study involves minimal to low risk. The primary potential risks are related to the structured chair-based exercise, including mild musculoskeletal discomfort, transient fatigue, muscle soreness, dizziness, or shortness of breath, particularly during the initial sessions. These risks are considered low and are commonly associated with light-to-moderate physical activity in older adults. To minimize these risks, all exercise sessions will be conducted under supervision by trained personnel, with prior health screening and continuous monitoring of participants' physical condition.

Intergenerational activities are non-invasive and pose no physical risk; however, minor psychological discomfort, such as temporary feelings of anxiety or social unease, may occur during initial interactions. These activities will be conducted in a supportive and controlled environment to ensure participants' comfort and emotional safety.

The overall burden to participants includes time commitment for attending intervention sessions and undergoing physical, cognitive, and laboratory assessments. Blood sampling for laboratory analysis may cause mild pain, bruising, or discomfort at the puncture site, with no expected long-term adverse effects.

Potential benefits for participants include improvement in physical function, cognitive performance, frailty status, social engagement, and overall quality of life. The anticipated benefits are considered to outweigh the minimal risks associated with study participation.

1. INTRODUCTION AND RATIONALE

Indonesia is a country with an ageing population, with older adults comprising approximately 12% of the total population and a current life expectancy of 72.39 years. The World Health Organization (WHO) has introduced the concept of healthy aging, which emphasizes the importance of maintaining functional ability and intrinsic capacity in older adults to enable them to remain healthy and independent. Impairment of functional ability can lead to disability, which has a greater impact than multimorbidity, underscoring the need for early intervention.

One important early condition in older adults that requires particular attention is physio-cognitive decline syndrome (PCDS), which is defined as the coexistence of physical functional decline (i.e., reduced gait speed or handgrip strength, in the absence of disability) and cognitive decline (without dementia). PCDS increases the risk of frailty and deterioration in quality of life; however, it remains a potentially reversible condition. Multidomain interventions, such as physical and cognitive exercise, have been shown to improve this condition.

One important biomarker of brain neuroplasticity is mature brain-derived neurotrophic factor (mBDNF), which reflects the muscle–brain axis. Social isolation, loneliness, and depression further exacerbate PCDS. Therefore, social interventions such as social heterochronic parabiosis (SHP)—defined as direct interactions between older adults and younger generations, particularly children or adolescents—may represent a promising strategy to improve cognitive function. Intergenerational activities have been shown to enhance mental health, cognitive function, and physical performance in healthy older adults.

To date, no studies have specifically described the model and/or role of SHP-based interventions in improving physical and cognitive decline among older adults with PCDS. This study utilizes educational materials with the potential to facilitate SHP-based interventions in Indonesia, namely the “Ayo Minum Air” (AMIR) campaign developed by the Indonesian Hydration Working Group (IHWG). These educational materials serve as media to facilitate direct interactions between older adults and children (e.g., illustrated comics, exercise videos, and related materials), which are essential components of SHP-based interventions.

This study aims to examine the effects of structured physical exercise followed by SHP-based interventions on frailty syndrome and changes in serum mBDNF levels among older adults with PCDS, as a novel approach integrating physical and social interventions with biomolecular assessment.

2. OBJECTIVES

Primary Objectives

To evaluate the effects of 12 weeks of structured physical exercise (chair-based PEROSI protocol) followed by 4 weeks of social heterochronic parabiosis (SHP)-based intergenerational

intervention on frailty syndrome and serum mature brain-derived neurotrophic factor (mBDNF) levels in community-dwelling elderly with physio-cognitive decline syndrome (PCDS).

Secondary objectives

- To analyze the effects of the combined intervention over 16 weeks on hand grip strength in elderly with PCDS.
- To analyze the effects of the combined intervention over 16 weeks on gait speed in elderly with PCDS.
- To analyze the effects of the combined intervention over 16 weeks on cognitive function as measured by the MoCA-Ina score in the elderly with PCDS.
- To evaluate the effects of the combined intervention over 16 weeks on health-related quality of life in the elderly with PCDS.
- To assess correlations between changes in serum mBDNF levels and changes in MoCA-Ina score, hand grip strength, and gait speed in the elderly with PCDS.

Hypothesis

Elderly people with physio-cognitive decline syndrome (PCDS) who receive 12 weeks of structured physical exercise followed by 4 weeks of social heterochronic parabiosis (SHP)-based intergenerational intervention on top of nutritional education have significantly better frailty syndrome status and higher serum mature brain-derived neurotrophic factor (mBDNF) levels than those receiving nutritional education alone after 16 weeks of intervention, along with greater improvements in hand grip strength, gait speed, cognitive function (MoCA-Ina score), and health-related quality of life.

3. STUDY DESIGN

This is a single-center, randomized, open-label (unblinded), parallel-group controlled clinical trial evaluating the efficacy of a sequential multimodal intervention (structured physical exercise followed by SHP-based intergenerational activities) compared to nutritional education alone in community-dwelling elderly aged 60–75 years with physio-cognitive decline syndrome (PCDS).

The study duration per participant is 16 weeks, consisting of:

- Baseline assessment (week 0)
- Intervention period: 12 weeks of chair-exercise + 4 weeks of intergenerational activities (intervention arm) or continued education (control arm)
- Intermediate assessment (end of week 12)
- Final assessment (end of week 16)

Participants are randomized in a 1:1 ratio into two arms:

- Intervention arm (n=50): Nutritional education + 12 weeks structured chair-based exercise (PEROSI protocol, progressive frequency from 1 to 3 sessions/week, 60 minutes/session, supervised online) followed sequentially by 4 weeks SHP-based intergenerational activities (8 sessions, 2x/week, 45 minutes/session, paired 1:1 elderly-child using AMIR educational materials at selected orphanages).
- Control arm (n=50): Nutritional education only (2 personalized dietitian tele-conferences at weeks 1 and 11; 5 educational e-flyers at weeks 3, 5, 7, 13, and 15).

Randomization is computer-generated using permuted block randomization (block size 4), stratified if necessary, with allocation concealment managed by an independent third party. Blinding of participants and instructors is not feasible due to the nature of the behavioral interventions; however, outcome assessors for laboratory analyses (mBDNF) are blinded to group allocation where possible.

The trial follows intention-to-treat principles with per-protocol sensitivity analysis. Recruitment targets consecutive eligible elderly from community programs under the School of Medicine and Health Sciences at Atma Jaya Catholic University of Indonesia and the Archdiocese of Jakarta. Child participants (aged 5–8 years, n=50) are recruited from cooperating orphanages exclusively for the intervention arm.

4. STUDY POPULATION

4.1 Population (base)

The base population consists of community-dwelling elderly individuals aged 60–75 years residing in Jakarta, Indonesia, who participate in community programs managed by the School of Medicine and Health Sciences at Atma Jaya Catholic University of Indonesia and the Archdiocese of Jakarta. Additionally, healthy children aged 5–8 years from cooperating orphanages (Panti Asuhan) in the Jakarta area are recruited exclusively for the intergenerational activities in the intervention arm.

4.2 Inclusion criteria

For elderly participants:

- Aged 60–75 years
- Meet diagnostic criteria for physio-cognitive decline syndrome (PCDS): gait speed <1.0 m/s and/or hand grip strength <28 kg (men) or <18 kg (women), and MoCA-Ina score 22–26
- Instrumental Activities of Daily Living (IADL) score >5

- Able to understand and follow instructions adequately
- Willing to participate and provide written informed consent

For child participants (intervention group only):

- Aged 5–8 years
- In good health and cooperative
- Able to understand and follow instructions
- Written permission obtained from orphanage management

4.3 Exclusion criteria

For elderly participants:

- Presence of disability or dementia
- Depression or other mental health disorders
- Total immobility
- Acute illness at screening (e.g., pneumonia, acute arthritis with VAS >6/10, acute stroke, acute myocardial infarction, uncontrolled hypertension ≥180/100 mmHg, acute COPD exacerbation)
- Uncontrolled chronic lung or heart disease
- Hemodynamic instability or hypotension (<90/60 mmHg) at screening
- Recent hospitalization or major surgery within 2 weeks prior to screening
- Illiteracy (unable to read/write)
- Unwilling to participate

For child participants:

- History of chronic illness, behavioral disorders, intellectual disability, or psychiatric conditions
- History of sensory integration therapy, speech therapy, or child psychological therapy
- Unwilling to complete the study

4.4 Screening

Potential elderly participants are identified consecutively through community programs. Screening involves:

- Medical history and informed consent
- MoCA-Ina cognitive assessment
- Hand grip strength (dominant hand, best of 3 trials)
- 6-meter gait speed test (average of 2 trials)
- IADL assessment
- Basic physical examination and vital signs to rule out acute/uncontrolled conditions

Eligible elderly are then randomized. Child participants are selected in collaboration with orphanage management based on age, health status, cooperation, and written permission.

4.5 Sample size calculation

The sample size was calculated to detect clinically meaningful differences between the intervention and control groups in key outcome measures, including handgrip strength, gait speed, cognitive function (MoCA-Ina score), health-related quality of life (SF-12), and serum mature brain-derived neurotrophic factor (mBDNF) levels.

Sample size estimation was performed using the formula for comparison of two independent means, with a two-sided significance level (α) of 5% and a statistical power ($1-\beta$) of 80%. The standard deviation and expected mean differences for each outcome were derived from previously published studies involving older adults, as no prior studies have specifically evaluated SHP-based interventions or their combination with structured physical exercise.

Based on these calculations, the required sample sizes for individual outcome parameters ranged from 9 to 42 participants per group. Considering the largest estimated sample size requirement and allowing for potential dropouts, the minimum required sample size for this randomized controlled trial was determined to be 100 older adult participants, with **50 participants allocated to each group (intervention and control).**

This sample size is considered sufficient to evaluate the primary and secondary outcomes of the study and to ensure adequate statistical power while accounting for potential attrition during the study period.

5. TREATMENT OF SUBJECTS

Subjects will be randomly assigned to one of two groups: structured physical exercise followed by a social heterochronic parabiosis (SHP)–based intervention (intervention group) or usual care only (control group). Randomization will be computer-generated using a block-permuted randomization method with variable block sizes of four. The randomization list will be held by an independent third party (staff of the Department of Internal Medicine, School of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia) who is not involved in the research team. Both the investigators and the participants will be blinded to group allocation.

5.1 Investigational product/treatment

All participants (both arms) receive standardized nutritional education as a base intervention:

- Two personalized nutritional consultations via Zoom tele-conference with a certified dietitian (week 1 and week 11), focusing on balanced nutrition tailored to elderly needs.
- Five educational e-flyers on nutrition, physical activity recommendations for the elderly, and related topics (sent via mobile device at weeks 3, 5, 7, 13, and 15).

Intervention group (n=50 elderly + 50 children): In addition to nutritional education, participants receive a sequential multimodal intervention:

1. **Structured physical exercise (weeks 1–12):**
    - Chair-exercise using the Indonesian Osteoporosis Association (PEROSI) protocol, adapted for tele-exercise.
    - Sessions: 60 minutes duration, consisting of 10 min warm-up (light aerobic + flexibility), 30 min core (moderate aerobic, strength, balance), 5–10 min cool-down (light aerobic + stretching).
    - Frequency progression: 1 session/week (weeks 1–2), 2 sessions/week (weeks 3–6), 3 sessions/week (weeks 7–12).
    - Delivery: Online (tele-exercise) supervised by 1 certified PEROSI instructor and assisted by 1 research team member.
    - Safety: Pre-session physical condition check; exercise termination based on Borg scale and American College of Sport Medicine (ACSM) guidelines for the elderly.
2. **Social Heterochronic Parabiosis (SHP)-based intergenerational intervention (weeks 13–16):**
    - Group-based direct interaction: Each elderly participant paired 1:1 with one child participant (aged 5–8 years).

- Sessions: 8 total (2 sessions/week, 45 minutes each) conducted in-person at selected orphanages.
- Content: Educational and interactive activities using “Ayo Minum Air” (AMIR) materials from Indonesian Hydration Working Group (comic reading, simple gymnastics demonstration, educational games promoting hydration and healthy lifestyle).
- Organization: Elderly divided into 5 groups (10 elderly each); scheduled visits with research team accompaniment; facilities prepared for conducive interaction (seating, materials, spacing).
- Preparation: Training of Trainers (ToT) for elderly participants and research team during weeks 11–12 (3 sessions, 30 min each, outside exercise schedule).

Control Group

Participants in the control group will receive usual care according to existing community health services. They will not participate in the structured exercise or SHP-based intergenerational activities during the study period. However, they will continue to receive standard health education and routine activities available within their respective community settings.

5.2 Use of co-intervention (if applicable)

Co-interventions are minimized and monitored:

- Routine medications and medical care are permitted and recorded.
- Additional structured exercise or intergenerational programs outside the study are not allowed during the 16-week period and will be queried at follow-up visits.
- Both arms receive identical monitoring (phone counseling 2–3 times/month) to encourage adherence and prevent dropout.

5.3 Escape medication (if applicable)

Not applicable. This is a non-pharmacological intervention study; no escape medication is provided. In case of clinical deterioration or acute illness, participants are withdrawn and referred for standard medical care.

6. INVESTIGATIONAL PRODUCT

6.1 Name and description of investigational product

This is a non-pharmacological behavioral intervention study. There is no investigational medicinal product or device. The investigational interventions are:

- Structured physical exercise: Chair-based osteoporosis prevention exercise protocol developed by the Indonesian Osteoporosis Association (PEROSI).
- Social heterochronic parabiosis (SHP)-based intergenerational intervention: Direct interactive activities between elderly participants and children using educational materials from the "Ayo Minum Air" (AMIR) program of the Indonesian Hydration Working Group (IHWG), including illustrated comics, simple gymnastics videos, and hydration-focused educational games.

Both interventions are combined sequentially with standard nutritional education (tele-conferences and e-flyers).

6.2 Summary of findings from non-clinical studies

Not applicable. The interventions are non-pharmacological and based on established exercise physiology, geriatrics, and intergenerational program research.

6.3 Summary of findings from clinical studies

Structured chair-based exercise (similar to PEROSI protocol) has been shown in previous studies to improve muscle strength, balance, gait speed, and reduce fall risk in elderly populations, with short (12 weeks) benefits. Sequential multimodal interventions (physical exercise followed by cognitive/social tasks) have demonstrated superior increases in serum BDNF levels compared to the reverse order. Intergenerational programs have shown positive effects on mental health, cognitive function, and social well-being in healthy elderly and youth, with reciprocal benefits. However, no prior studies have specifically evaluated the combination of structured PEROSI exercise followed by SHP-based intervention using AMIR materials in the elderly with PCDS.

6.4 Summary of known and potential risks and benefits

Known risks: Minimal.

- Physical exercise: Mild fatigue, muscle soreness, low risk of fall or strain (mitigated by progressive intensity, supervision, pre-session checks, and termination criteria using Borg scale and ACSM guidelines).
- Blood sampling: Minor bruising, pain, or dizziness at the venipuncture site.
- Intergenerational activities: Initial psychological discomfort (awkwardness or anxiety) in interacting with unfamiliar children or the elderly.
- Overall: Low risk profile comparable to routine community exercise programs for the elderly.

Potential benefits:

- Improved physical function (grip strength, gait speed), reduced frailty, enhanced cognitive performance (MoCA-Ina), increased serum mBDNF (marker of neuroplasticity and muscle-brain axis), and better health-related quality of life.
- Additional benefits: Reduced social isolation, enhanced intergenerational empathy, free nutritional counseling, and health monitoring for participants.

The benefit-risk ratio is considered highly favorable, as the interventions are non-invasive, reversible, and target a reversible condition (PCDS) with established components of low risk.

6.5 Description and justification of route of administration and dosage

Not applicable (non-medicinal product). Justification for “dosage” (intensity/duration):

- Exercise: 12 weeks progressive frequency (1–3 sessions/week, 60 min) based on evidence for sufficient stimulus to improve strength, balance, and neuroplasticity in frail/pre-frail elderly without overload.
- SHP: 4 weeks, 8 sessions (2/week, 45 min) selected to allow meaningful intergenerational bonding and cognitive-social stimulation while minimizing burden on participants and orphanages.

6.6 Preparation and labelling of Investigational Product

Not applicable.

6.7. Preparation of transporting and delivery of investigational product to Indonesia

Not applicable.

6.8 Drug accountability

Not applicable. Exercise sessions and intergenerational activities are documented for adherence (attendance logs, session completion records). Educational materials (e-flyers, AMIR comics/videos) are tracked for delivery/receipt.

7. METHODS

7.1 Study parameters/endpoints

7.1.1 Main study parameter/endpoint

- Change in frailty syndrome status (assessed using Cardiovascular Health Study criteria: score 0 robust, 1–2 pre-frail, ≥3 frail) from baseline to week 16.
- Change in serum mature brain-derived neurotrophic factor (mBDNF) levels (measured by ELISA) from baseline to week 16.

7.1.2 Secondary study parameters/endpoints

- Change in hand grip strength (in kilogram; dominant hand, best of 3 trials using hand dynamometer) from baseline to week 16.
- Change in gait speed (m/s; average of 2 trials over 6-meter walk test) from baseline to week 16.
- Change in cognitive function (MoCA-Ina total score, range 0–30) from baseline to week 16.
- Change in health-related quality of life (SF-12 questionnaire) from baseline to week 16.
- Correlations between changes in serum mBDNF levels and changes in MoCA-Ina score, hand grip strength, and gait speed.

7.1.3. Other parameters (exploratory)

- Adherence to exercise sessions and intergenerational activities (attendance logs).
- Nutritional status (Mini Nutritional Assessment, MNA).
- Physical activity level (Physical Activity Scale for the Elderly, PASE).
- Depressive symptoms (Geriatric Depression Scale-15, GDS-15).
- Loneliness (De Jong Gierveld Loneliness Scale, Indonesian version).
- Quality of life additional domains (EQ-5D-5L).
- Charlson Comorbidity Index (CCI).
- Adverse events and dropout reasons.

7.2 Randomization, blinding, and treatment allocation

Randomization is performed after screening and baseline assessments using computer-generated permuted block randomization (block size 4). Allocation is managed by an independent third party (staff from the Department of Internal Medicine, School of Medicine and

Health Sciences at Atma Jaya Catholic University of Indonesia), not involved in the study. Sequence is concealed until assignment. Participants are allocated 1:1 to intervention or control arm.

Due to the behavioral nature of the intervention, blinding of participants, instructors, and research team is not possible (open-label design). However, laboratory analysts for mBDNF measurement are blinded to group allocation. Outcome assessors for physical measurements (grip strength, gait speed) are trained for consistency (inter-rater reliability tested with Kappa statistic).

7.3 Study procedures

All procedures are performed by trained research personnel (principal investigator, assistants, certified instructors). Inter-rater reliability for grip strength and gait speed measurements is established prior to study start (Kappa evaluation on 50 elderly people between the principal investigator and assistants). Assessments are conducted at three time points: baseline (week 0), intermediate (end of week 12, post-exercise phase), and final (end of week 16, post-full intervention). Additional monitoring occurs as described.

7.3.1 Anthropometry and Vital Signs

- Height: Measured using a stadiometer (or knee-height estimation if standing is difficult).
- Body weight: Measured with calibrated digital scale (light clothing, no shoes).
- Body Mass Index (BMI): Calculated as weight (kg)/height² (m^2).
- Vital signs: Blood pressure (seated, average of 2 measurements), heart rate, respiratory rate (to rule out acute instability).

7.3.2 Nutritional Status

Mini Nutritional Assessment (MNA): Full version administered via interview (screening + assessment sections; maximum 30 points).

Dietary habits: Brief anamnesis on usual intake; no formal 24-hour recall unless needed for dietitian consultation.

7.3.3 Blood sampling and Laboratory analysis

- Venous blood draw (5–10 mL) from the antecubital vein by a trained phlebotomist.
- Timing: Fasting preferred but not mandatory; performed at baseline, week 12, and week 16.
- Processing: Serum separated by centrifugation, aliquoted, and stored at -80°C until batch analysis.
- Primary biomarker: Mature brain-derived neurotrophic factor (mBDNF) quantified using a commercial ELISA kit specific for the mature form (to avoid pro-BDNF cross-reactivity). Analysis performed in an accredited laboratory with blinding to group allocation.

7.3.4 Physical and functional performances

- **Hand-grip strength:** Measured using a calibrated hand dynamometer from the American Society of Hand Therapists (ASHT) protocol:
  - Seated position, shoulder adducted/neutral rotation, elbow 90° flexion, forearm neutral, wrist 0–30° dorsiflexion, and 0–15° ulnar deviation.
  - Feet flat on floor, dry hands.
  - Three maximal efforts on the dominant hand with 30-second rest; the highest value recorded (kg).
  - Procedure terminated if pain or discomfort is reported.
- **Gait speed:** 6-meter walk test:
  - 10-meter straight pathway marked at 0, 2, 6, 8, and 10 meters (2m acceleration, 6m timed, 2m deceleration).
  - Usual walking pace, no running, assistive device allowed if habitual.
  - Two trials; time recorded from 2m to 8m mark; average speed (m/s) calculated.
- **Frailty status:** Cardiovascular Health Study (CHS) criteria:
  - Unintentional weight loss (>4.5 kg or >5% in past year).
  - Weakness (grip strength lowest quintile by sex/BMI).
  - Exhaustion (self-reported).
  - Slowness (gait speed lowest quintile by sex/height).
  - Low physical activity (weighted score of kcal/week).
  - Scoring: 0 = robust, 1–2 = pre-frail, ≥3 = frail.
- **Instrumental Activities of Daily Living (IADL):** Lawton scale (score >5 required at inclusion; monitored for changes).

7.3.5 Cognitive and psychological assessments

- Montreal Cognitive Assessment Indonesian version (MoCA-Ina): Administered face-to-face by trained assessor; total score 0–30 (education adjustment: +1 if ≤12 years formal education).
- Geriatric Depression Scale-15 (GDS-15): Self-reported or interviewer-assisted.
- De Jong Gierveld Loneliness Scale (Indonesian version): 11-item questionnaire.
- Physical Activity Scale for the Elderly (PASE): Interviewer-administered; converted frequency and duration scores.

7.3.6 Health-related quality of life and comorbidity

- Short Form-12 (SF-12): Physical and mental component summaries.
- EQ-5D-5L: 5 domains (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) plus visual analog scale.
- Charlson Comorbidity Index (CCI): Calculated from medical history and records.

7.3.7 Intervention-specific procedures

- Nutritional education (both groups):
  - Tele-conference consultations (Zoom): Personalized meal planning by dietitian.
  - E-flyers: Digital delivery with confirmation of receipt.
- Structured exercise (intervention group):
  - Pre-session screening: Symptom query, vital signs if needed.

- Session monitoring: Borg Rating of Perceived Exertion scale; termination if excessive dyspnea, pain, dizziness, or hemodynamic changes.

- Intergenerational activities (intervention group):
  - Pre-session preparation: Facility check (seating, materials, spacing).
  - Session structure: Introduction, AMIR-based activities (comic reading, joint gymnastics, games), reflection.
  - Post-session: Brief feedback from the elderly and children.

7.3.8 Monitoring and adherence

Adherence and safety are monitored proactively to maximize retention and minimize risks.

- Adherence monitoring:
  - Exercise sessions (intervention arm): Attendance logged by instructor and research assistant; session completion confirmed (≥85% of planned sessions required for per-protocol analysis).
  - Intergenerational activities: Attendance sheets signed by research team and orphanage staff; activity completion checklists.
  - Nutritional education (both arms): Confirmation of tele-conference attendance and e-flyer receipt/viewing (via read receipts or follow-up query).
  - Overall: Monthly telephone counseling (2–3 calls/month) by research team to encourage compliance, address barriers, and reinforce motivation.
- Safety monitoring:
  - During exercise phase: Weekly (Monday) pre-session symptom and condition checks by team/instructor; Borg Rating of Perceived Exertion scale monitored throughout sessions; immediate termination for excessive symptoms (severe dyspnea, palpitations, dizziness, heavy weakness, pre-syncope).
  - Bi-weekly direct evaluations (weeks 4, 6, 8, 10): Remote or in-person query on complaints, with direct supervision during selected sessions.
  - Intergenerational phase: On-site supervision by research team and orphanage staff; post-session brief feedback on comfort/discomfort.
  - General: Participants provided with contact number for immediate reporting; all potential adverse events (fatigue, muscle pain, emotional discomfort, minor injuries) documented, managed, and reported to Ethics Committee if serious.

7.3.9 Questionnaires

All questionnaires are administered by trained research assistants through structured interviews to ensure consistency, especially for participants with limited literacy or visual impairment. Questionnaires are completed at baseline (week 0), intermediate (week 12), and final (week 16) assessments unless otherwise specified. Validated Indonesian versions are used where available.

- **Short Form-12 (SF-12):** Measures health-related quality of life with 12 items covering physical and mental component summaries (PCS and MCS). Scores are calculated using standard algorithms (range 0–100; higher scores indicate better quality of life). Primary focus on changes in physical and mental health domains.

- **EQ-5D-5L (EuroQol 5 Domains – 5 Levels):** Assesses five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) with 5 response levels each, plus a visual analog scale (EQ-VAS) for overall health state (0–100). Utility scores are derived using Indonesian value sets if available.
- **Geriatric Depression Scale-15 (GDS-15):** Screens for depressive symptoms with 15 yes/no items (score range 0–15; ≥5 suggests depression). Used for monitoring psychological well-being and exclusion criteria confirmation.
- **De Jong Gierveld Loneliness Scale (Indonesian version):** 11-item scale measuring emotional and social loneliness (range 0–11; higher scores indicate greater loneliness). Helps evaluate the impact of social isolation and potential benefits from intergenerational activities.
- **Physical Activity Scale for the Elderly (PASE):** Assesses leisure, household, and occupational physical activity over the past week. Scores are calculated based on frequency, duration, and intensity weights (higher scores indicate greater activity level). Administered to monitor baseline activity and changes.
- **Mini Nutritional Assessment (MNA) – Full version:** 18-item tool including anthropometric measures, global assessment, dietetic assessment, and subjective items (maximum 30 points: ≥24 normal, 17–23.5 at risk, <17 malnourished). Complements nutritional education intervention.
- **Charlson Comorbidity Index (CCI):** Calculated from medical history (19 conditions weighted 1–6 points) to quantify comorbidity burden and adjust for confounding in analyses.

7.4 Study visits

Study visits are scheduled to minimize burden while ensuring complete data collection. Visits occur at community centers, participant homes (if needed), or orphanages.

- Screening/Baseline visit (week 0, 1–2 days):
    - Explanation of study, informed consent (elderly and orphanage for children).
    - Medical history, comorbidity assessment (CCI), medication review.
    - Full physical examination, vital signs, anthropometry.
    - Cognitive (MoCA-Ina), physical (hand-grip strength, gait speed), functional (IADL), frailty (CHS), nutritional (MNA), and psychological assessments.
    - All questionnaires (SF-12, EQ-5D-5L, GDS-15, PASE, loneliness scale).
    - Blood sampling.
    - Randomization (post-eligibility confirmation).
    - Nutritional education initiation (first tele-conference scheduling).

- Intermediate visit (end of week 12, post-exercise phase):
    - Repeat anthropometry, vital signs.
    - Physical performance (hand-grip strength, gait speed), frailty status.
    - Cognitive (MoCA-Ina) and selected questionnaires (SF-12, EQ-5D-5L, GDS-15, loneliness).
    - Blood sampling.
    - Adherence review; ToT preparation for SHP (intervention arm).
- Final visit (end of week 16):
    - Comprehensive repeat of baseline assessments (all physical, cognitive, functional, nutritional, psychological, and questionnaires).
    - Blood sampling.
    - Adherence summary, adverse event review.
    - Compensation distribution (transport reimbursement, snacks provision during study).
- Ongoing visits/activities:
    - Exercise: Weekly tele-sessions (intervention group).
    - Intergenerational: 8 in-person sessions at orphanages (weeks 13–16).
    - Nutritional: 2 tele-conferences + 5 e-flyers (both groups).
    - Monitoring calls.

Home visits arranged if mobility limits attendance.

7.5 Withdrawal of individual subjects

Participants (elderly or children via orphanage representative) may withdraw voluntarily at any time without providing reasons and without impact on routine care or relationship with researchers. Withdrawal is documented but no further study procedures performed unless consented for final assessment.

Investigator-initiated withdrawal occurs for:

- Development of exclusion criteria (e.g., new disability, dementia suspicion, uncontrolled chronic disease).
- Acute illness requiring hospitalization or prohibiting continuation (e.g., pneumonia, acute stroke, uncontrolled hypertension).
- Non-adherence (>3 consecutive missed exercise sessions or <85% overall intervention completion).
- Intolerable adverse events suspected related to intervention.

Withdrawn participants are encouraged to complete safety follow-up and/or final assessments for intention-to-treat analysis. All withdrawals are fully documented (reason, date, partial data

collected) and reported to Ethics Committee if related to safety. No replacement of withdrawn subjects.

7.5.1 Drop out Criteria

Subjects are classified as drop-outs if they do not complete the study protocol through the final assessment (week 16) for any reason. Specific drop-out criteria include:

- Non-adherence to intervention: Failure to attend >3 consecutive structured exercise sessions (intervention arm) or <85% of total planned exercise sessions; failure to attend ≥2 intergenerational activity sessions or <85% overall attendance for SHP phase.
- Development of exclusion criteria during study: New onset of disability, suspected/confirmed dementia, depression (GDS-15 score indicating moderate-severe depression requiring intervention), total immobility, uncontrolled chronic disease, or hemodynamic instability.
- Acute illness or clinical worsening: Occurrence of acute conditions (e.g., pneumonia, acute arthritis with VAS >6/10, acute stroke, acute myocardial infarction, uncontrolled hypertension ≥180/100 mmHg, acute COPD exacerbation) requiring hospitalization or prohibiting continuation.
- Adverse events suspected related to intervention: Intolerable or serious symptoms (e.g., persistent severe fatigue, muscle pain, dizziness, fall during exercise, significant emotional distress during intergenerational activities) leading to investigator decision for withdrawal.
- Voluntary withdrawal: Subject (or orphanage representative for children) requests discontinuation for any personal reason (e.g., lack of time, loss of motivation, transportation difficulties).
- Loss to follow-up: Inability to contact subject despite ≥3 attempts via phone/WhatsApp over 2 weeks, or permanent relocation outside study area.
- Death: Any mortality during study period (reported immediately as serious adverse event).

All drop-outs are documented in detail (date, reason, last completed assessment/procedure) on the case report form and in the trial master file.

7.6 Replacement of individual subjects after drop out

Dropped-out subjects are not replaced. The initial sample size calculation (minimum 100 elderly participants, 50 per group) incorporates an anticipated drop-out rate of up to 15% (based on similar community-based geriatric intervention studies) to ensure sufficient statistical power for primary endpoints. Child participants are paired 1:1 with elderly in the intervention group; if an elderly participant drops out during the SHP phase, the paired child continues if feasible and

willing, or the session is adjusted accordingly without recruitment of new children. No over-recruitment or replacement strategy is employed to maintain the integrity of consecutive recruitment and randomization.

7.7 Follow-up of subjects withdrawn from treatment

Withdrawn subjects are encouraged to complete final assessments for intention-to-treat analysis where possible.

7.8 Premature termination of the study

The study may be terminated early if significant safety concerns arise, futility is evident, or upon recommendation of the Ethics Committee.

8. SAFETY REPORTING

8.1 AEs, SAEs and SUSARs

8.1.1 Adverse events (AEs)

An adverse event (AE) is defined as any untoward medical occurrence, unintended symptom, or clinical worsening in a study participant during the study period (from informed consent to final assessment), whether or not considered related to the study interventions (structured exercise, intergenerational activities, nutritional education, assessments, or blood sampling).

All AEs are recorded by the research team:

- Spontaneously reported by participants (elderly or children via orphanage representative).
- Observed during sessions, monitoring calls, or assessments (e.g., fatigue, muscle soreness, minor bruising from blood draw, emotional discomfort).
- Elicited during routine queries (e.g., weekly pre-exercise checks, bi-weekly evaluations, post-session feedback).

AEs are documented in the case report form (CRF) with details on description, onset date, severity (mild/moderate/severe), duration, relationship to intervention (unlikely/possible/probable), actions taken, and outcome. Mild AEs (e.g., transient muscle soreness, initial awkwardness in interactions) are managed supportively (rest, reassurance, session adjustment).

8.1.2 Serious adverse events (SAEs)

A serious adverse event (SAE) is any AE that:

- Results in death.

- Is life-threatening (immediate risk of death).
- Requires hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Constitutes any other medically important event (e.g., acute illness requiring urgent intervention that significantly impacts study participation or health).

Given the low-risk nature of the interventions, SAEs are expected to be rare and mostly unrelated (e.g., acute unrelated illness in elderly). All SAEs are reported to the principal investigator immediately (within 24 hours of awareness) and to the approving Ethics Committee (Komite Etik Penelitian Kedokteran FKUI-RSCM or equivalent) within 15 days. SAEs resulting in death or life-threatening are reported expedited (initial report within 7 days, complete follow-up within additional 8 days).

8.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Not applicable. As this is a non-medicinal product study with established low-risk behavioral interventions (PEROSI chair-exercise and intergenerational programs), no unexpected serious reactions attributable to an investigational product are anticipated.

8.3 Annual safety report

An annual safety report summarizing all AEs and SAEs (including relatedness assessment and cumulative overview) will be submitted to the Ethics Committee if the study duration exceeds one year or upon request. The report includes participant enrollment status, deviations, and any emerging safety concerns.

8.4 Follow-up of adverse events

All AEs and SAEs are followed until resolution, stabilization, or return to baseline. Follow-up may include:

- Additional phone contacts or visits.
- Medical referral (e.g., to geriatrician or primary care physician).
- Repeat assessments if clinically indicated.
- Documentation of outcome (recovered, ongoing, sequelae).

Participants withdrawn due to AEs/SAEs receive continued safety monitoring

8.5 Data Safety Monitoring Board (DSMB) / Safety Committee

Not applicable. Given the minimal risk profile of the interventions (community-based exercise and social activities in screened healthy/cooperative participants), no independent Data Safety Monitoring Board is established. Safety oversight is provided directly by the principal investigator and supervisor. Any emerging patterns of AEs will prompt ad-hoc review and consultation with the Ethics Committee if needed.

9. STATISTICAL ANALYSIS

All collected data will be initially recorded on research case report forms (CRFs) and subsequently transferred to secure electronic storage for data cleaning, coding, and verification. Descriptive data and analytical results will be presented in narrative text, tables, or figures as appropriate.

Normality of data distribution will be assessed using the Kolmogorov-Smirnov or Shapiro-Wilk test ($p > 0.05$ indicates normal distribution). Normally distributed continuous data will be presented as mean ± standard deviation (SD); non-normally distributed data as median with minimum-maximum range. Categorical data will be presented as frequencies and percentages. Statistical significance will be set at $p < 0.05$. All analyses will be performed using SPSS version 20 software.

Primary analyses will be conducted on the per-protocol (PP) population, excluding drop-out subjects. Between-group comparisons of changes in study outcomes (hand grip strength, gait speed, MoCA-Ina score, serum mBDNF levels, and health-related quality of life) will use unpaired t-tests (parametric) or Mann-Whitney U tests (non-parametric), selected based on normality test results.

Correlations between serum mBDNF levels and MoCA-Ina score, hand grip strength, and gait speed will be evaluated using Pearson correlation (for normally distributed variables) or Spearman correlation (for non-normally distributed variables), according to normality assessment of each variable.

10. ETHICAL CONSIDERATIONS

This study will be conducted in accordance with the principles of the Declaration of Helsinki (2013 revision), Good Clinical Practice (GCP) guidelines, and applicable Indonesian regulations for clinical research involving human subjects. The protocol, informed consent forms (for elderly participants and orphanage representatives for children), and all study-related materials have been submitted for review and approval by the Komite Etik Penelitian Kedokteran Fakultas Kedokteran Universitas Indonesia – Rumah Sakit Cipto Mangunkusumo (KEPK FKUI-RSCM) or the relevant institutional ethics committee. The study will not commence until written approval is

obtained. Any amendments to the protocol will be submitted for ethical review and approval prior to implementation.

10.1 Recruitment and informed consent

Eligible elderly participants will be informed about the study purpose, procedures, potential risks, benefits, voluntary nature, and right to withdraw at any time without consequence through verbal explanation and written information sheets. Informed consent will be obtained in writing by the principal investigator or trained research assistant, with opportunity for questions. If needed, family members or caregivers may accompany the participant during consent, but the decision remains with the participant.

For child participants (intervention arm only), written permission will be obtained from the orphanage management (as legal guardian representative). Child-friendly verbal explanations will be provided to children, and assent will be sought based on their understanding and willingness. Children may refuse or withdraw at any time.

10.2 Vulnerable subjects

This study involves two vulnerable groups:

- Elderly (geriatric) participants: Aged 60–75 years with physio-cognitive decline syndrome (PCDS), screened for adequate comprehension (MoCA-Ina 22–26, IADL >5). Protection measures include clear, repeated explanations (with family/caregiver if desired), assurance of voluntariness, close monitoring for discomfort, and immediate withdrawal option.
- Children (aged 5–8 years from orphanages): Recruited only for low-risk intergenerational activities. Protection includes orphanage guardian consent, child-friendly preparation and explanations, constant on-site supervision by research team and orphanage staff, post-session reflection for emotional well-being, and unrestricted right to refuse or stop participation.

10.3 Benefits and risks assessment, group relatedness

The study targets a reversible condition (PCDS) with established low-risk interventions. Potential benefits include improved physical/cognitive function, reduced frailty, enhanced neuroplasticity (mBDNF), better quality of life, reduced social isolation, and free nutritional counseling/monitoring for elderly; social-emotional development and healthy lifestyle education for children. Control group receives education and assessments, minimizing inequity.

Risks are minimal: mild physical strain or fatigue from exercise, minor venipuncture discomfort, initial social awkwardness. These are mitigated by screening, supervised progressive interventions, safety monitoring, and termination criteria. The benefit-risk ratio is highly favorable for both groups.

10.4 Compensation and incentives

Participation is voluntary. Elderly participants receive transport reimbursement (Rp 100,000 per orphanage visit if using their own transport) or free shuttle service, plus snacks/drinks (≈Rp 50,000 value per intergenerational session). Compensation for assessment visits (three time points) covers time/travel. Children receive stationery/books as an appreciation after sessions. No cash incentives are provided to avoid coercion.

10.5 Confidentiality

Participant identity and data confidentiality are strictly protected. Data are coded with unique study IDs; personal identifiers are stored separately in password-protected files accessible only to authorized research team members. Paper records are kept in locked cabinets. Data will be used solely for research purposes; publications/presentations will use aggregated or anonymized data only. No individual data will be shared with third parties without additional consent or ethical approval.

10.6 Insurance and compensation for injury

Although risks are minimal and no serious intervention-related injury is anticipated, the principal investigator maintains professional liability coverage. In the unlikely event of study-related harm, participants will receive appropriate medical care at no cost, coordinated by the research team.

11. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

11.1 Handling and storage of data and documents

All study data will be handled with strict confidentiality and in compliance with Indonesian regulations on personal data protection.

- Participant identifiers (name, contact details, date of birth) will be linked to a unique study ID in a separate, password-protected master file accessible only to the principal investigator and authorized research team members.
- Case report forms (CRFs) will be completed in paper format initially and stored in locked cabinets at the principal investigator's secure office (School of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia or affiliated site).
- Data will be double-entered into a password-protected electronic database (SPSS or equivalent) for analysis. Electronic files will be stored on encrypted institutional computers or secure cloud storage with access restricted to the research team.
- Informed consent forms will be stored separately from CRFs in a locked cabinet.
- Audio/video recordings (if any, e.g., tele-exercise sessions) will be deleted after quality checks.

- Biological samples (serum aliquots) will be coded with study ID only and stored at -80°C in an accredited laboratory until analysis; remaining samples will be destroyed after study completion.
- All study documents and data will be retained for at least 15 years post-study completion, after which they will be securely destroyed.

11.2 Monitoring and Quality Assurance

Given the minimal-risk nature of this community-based behavioral intervention study, formal external monitoring is not required. Quality assurance and internal monitoring will be conducted by the principal investigator:

- Regular site visits to community centers and orphanages to verify adherence to protocol, facility preparation, and session conduct.
- Review of attendance logs, session checklists, and adverse event records monthly.
- Inter-rater reliability checks for physical measurements maintained through periodic calibration and co-assessments.
- Data entry accuracy verified by random spot-checks (10% of CRFs).
- Any protocol deviations will be documented and reported to the Ethics Committee if substantial.

11.3 Amendments

Substantial amendments (changes potentially affecting participant safety, rights, or scientific integrity) will be submitted in writing to the approving Ethics Committee for review and approval before implementation. Non-substantial amendments (e.g., minor administrative updates, contact details) will be recorded internally and notified annually or at study close-out.

11.4 Annual progress report

If the study duration exceeds one year, an annual progress report (including enrollment status, adverse events summary, deviations, and preliminary safety data) will be submitted to the Ethics Committee within 60 days of the approval anniversary date.

11.5 End of study report

- Temporary halt for safety or logistical reasons will be notified to the Ethics Committee within 15 days, with reasons and resumption plan.
- The end of the study (defined as the last participant's final assessment) will be notified to the Ethics Committee within 8 weeks.
- A final study report summarizing methods, results, adverse events, and conclusions will be submitted within one year of study completion.

11.6 Public disclosure and publication policy

The study will be conducted with commitment to transparent dissemination of results.

- Results will be published in peer-reviewed scientific journals.
- Authorship will follow International Committee of Medical Journal Editors (ICMJE) guidelines, with principal contributors listed.
- No sponsor or external party has veto rights over publication.
- Aggregated results will be shared with participating community programs and orphanages for feedback and potential implementation.
- Individual participant data will not be publicly disclosed.
- The study protocol and summary results may be registered on a public clinical trial registry (e.g., ClinicalTrials.gov or Indonesian equivalent) if required by journal policies.

12. STRUCTURED RISK ANALYSIS

12.1 Potential issues of concern

The study involves minimal-risk non-pharmacological interventions in vulnerable populations (elderly with physio-cognitive decline syndrome and young children from orphanages). Potential concerns include:

- Physical risks to elderly participants: Mild fatigue, muscle soreness, minor strain, or low risk of fall during supervised chair-based exercise; minor bruising or discomfort from venipuncture (three blood draws).
- Psychological/emotional risks: Initial anxiety, awkwardness, or discomfort during intergenerational interactions for both elderly (interacting with unfamiliar children) and children (interacting with elderly with physical/cognitive limitations); potential transient emotional distress if interactions are not harmonious.
- Logistical/operational risks: Transportation issues to/from orphanages; adherence challenges due to elderly mobility or motivation; potential loss to follow-up in community setting; coordination difficulties with multiple orphanages.
- Data and confidentiality risks: Unintentional breach of personal data during digital transfer (e-flyers, tele-conferences) or storage.
- Equity and coercion risks: Perception of undue influence on orphanage children or elderly due to incentives (snacks, transport reimbursement, stationery).

- Unforeseen risks: Acute unrelated illness in elderly triggering withdrawal; seasonal factors (e.g., weather, holidays) affecting session attendance.

12.2 Synthesis

This structured risk analysis concludes that the overall risk level is minimal and acceptable given the study's objectives and population. The interventions (PEROSI chair-exercise and AMIR-based intergenerational activities) are established, low-intensity, community-based practices with proven safety profiles in similar geriatric and intergenerational programs.

All identified risks are effectively mitigated through: rigorous screening/exclusion criteria; progressive/supervised exercise with termination guidelines; professional blood sampling; preparatory training (ToT) and on-site supervision for intergenerational sessions; child-friendly approaches and orphanage oversight; proactive adherence support (phone counseling, transport provision); secure data handling; and voluntary participation with clear withdrawal rights.

Potential benefits (improved physical/cognitive function, reduced frailty and isolation, enhanced neuroplasticity via mBDNF, intergenerational empathy, and healthy lifestyle education) substantially outweigh the minimal risks for both elderly and child participants. The control group receives meaningful nutritional education and monitoring, ensuring ethical equipoise. No serious intervention-related harm is anticipated; any adverse events will be promptly managed and reported. The benefit-risk balance strongly supports proceeding with the study under close internal oversight and Ethics Committee approval.

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