F.I.T.AL. (Function – Information – Training) therapy for everyday life to improve instrumental activities of daily living in people with mild cognitive impairment – protocol for a randomised feasibility study

Marina Bruderer-Hofstetter[1,2], Thomas Münzer[3,4], Ansgar Felbecker[5], Karin Niedermann[2]

[1]Department Health Sciences and Health Policy, University of Lucerne, Switzerland

[2]School of Health Professions, Zurich University of Applied Sciences, Switzerland

[3]Geriatrische Klinik, St.Gallen, Switzerland

[4]Department of Geriatrics and Aging Research, University Hospital and University of Zurich, Switzerland

[5]Kantonsspital St.Gallen, Switzerland

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Corresponding author: Marina Bruderer-Hofstetter, Zurich University of Applied Sciences, Katharina-Sulzer-Platz 9, CH-8401 Winterthur.

Contact: marina.bruderer-hofstetter@zhaw.ch

Telephone: +41 58 934 43 03

Abstract

Background: Instrumental activities of daily living (IADL) are key to independently participate in social life for people with mild cognitive impairment (MCI). There is currently no recommended pharmacological treatment available to reduce the impact of cognitive loss on functioning in people with MCI. The primary aim of this protocol is to evaluate the feasibility and acceptability of the F.I.T.AL. individually-tailored, multi-component intervention, aimed at stabilizing or even improve IADL functioning. The secondary aim is to explore the preliminary efficacy of F.I.T.AL.

Methods: A two-arm randomized feasibility trial will be conducted at two memory clinics in Switzerland. Thirty-two people with MCI, aged 60 and over, together with their caregivers, will be recruited and randomly assigned to either the multi-component intervention or to the control intervention. The multi-component intervention F.I.T.AL., developed in a multi-step approach including patient and public involvement, will be conducted for six months. The intervention includes components of cognitive training strategy, physical exercise, and information and support. The control intervention will be comprised of only the information and support portion. Primarily feasibility and acceptability outcomes will be investigated. Feasibility outcomes will include: (1) Recruitment, using the number of eligible individuals; (2) Enrollment, by calculating the proportion of eligible individuals randomised; (3) Retention, assessed by the drop-out rate; and (4) Completeness of outcome measures. Acceptability and adherence outcomes will include: (1) Attendance rates; (2) Adherence to the intervention protocol, in terms of number and duration of completed intervention sessions; and, (3) Intervention intensity. The secondary outcomes will comprise: (1) The German version of the Amsterdam IADL questionnaire; (2) Physical function (i.e. endurance, lower extremity strength, balance, mobility, gait speed, functional mobility, physical

activtity); (3) Cognitive function (i.e. global cognition, memory, executive function, attention); and, (4) Perceived social support.

Discussion: F.I.T.AL. was designed to target IADL functioning in people with MCI, using a multi-step and multi-professional approach that includes patient and public involvement. It is anticipated that F.I.T.AL. will be feasible, acceptable and also have the potential to stabilize or even improve IADL performance.

Keywords: mild cognitive impairment, multi-component intervention, cognitive training, physical exercise, instrumental activities of daily living

Background

Mild cognitive impairment (MCI) describes an intermediate state between healthy cognitive ageing and dementia. MCI is characterized as no dementia, self- or informant reported cognitive decline from a previously achieved level, objective and clinically manifest decline in one or more cognitive domains, and largely preserved functional abilities with minimal use of aids or assistance [1]. The concept of MCI has evolved over a number of years, and has been widely used in clinical and research settings utilizing slightly different criteria [2, 3]. People with MCI may have a pronounced risk of losing autonomy, due to impairments in various domains of cognitive and physical functions [4-6]. Mild problems, e.g., using compensatory startegies or making more errors, in performing Instrumental Activities of Daily Living (IADL) are common in people with MCI [1]. Furthermore, limitations in IADL have been reported in people with MCI [7-9]. However, the debate is ongoing on what level of IADL limitations is consistent with the MCI state [9].

IADL are complex tasks needed to participate independently in society, e.g. managing finances and attending appointments [10, 11]. IADL have been defined as ‘intentional and complex everyday activities for which multiple cognitive processes are necessary, particularly high-level controlled processes’, within the concept of cognitive decline [12]. IADL limitation is an essential aspect of screening for cognitive decline because it is a predictor of the development of major cognitive impairment in the future [10, 11]. The level of IADL functioning is a defining feature in distinguishing MCI from healthy ageing or dementia [13, 14]. IADL limitations in people with MCI are associated with reduced wellbeing [15], higher caregiver burden and supervision time, as well as increased cost to society [16]. Maintanance or even any improvement in IADL functioning is beneficial [17]. Both, people with MCI and their caregivers rated the ability to perform IADL as one of the prioritised treatment outcomes [18]. The nature of IADL limitations in people with MCI is

still unclear. The ability to perform IADLs adequately is related to appropriate physical health [19] and cognitive function [7, 20, 21]. Impaired cognitive function and IADL limitations are interrelated in people with MCI [22]. A newly-developed model on IADL functioning in people with MCI suggests that IADL functioning is not just influenced by cognitive function, but also by physical function, environmental factors and personal factors [23]. Therefore, interventions that encompass a range of these factors may have a beneficial impact on IADL functioning.

It is a public health priority to find strategies to prevent functional impairment due to major cognitive impairment [24]. MCI individuals are at risk of progressive cognitive decline. The application of relevant interventions at this intermediate stage could perhaps assist in decelerating decline progression [25]. No recommended pharmacological treatments are available for people with MCI at the current time [25]. Evidence suggests that non-pharmacological interventions, such as cognitive training or physical exercise, may improve cognitive function in people with MCI [26]. Physical exercise, at a level that meets public health recommendations in terms of intensity and frequency, was found to be effective in improving physical capacity and function [19, 27, 28], as well as cognitive function [29-32] through different pathways [33]. However, the effects of physical exercise on IADL performance has been reported in intervention studies only rarely, and findings are inconsistent [34-36].

Rehearsal-based cognitive training strategies were found to effectively improve cognition in people with MCI, but the intensity, frequency and type of training did not influence the outcomes [37-39]. Cognitive training interventions seem to have primarily had an affect on the immediate tasks trained, with transfer effects only being found to other closely related cognitive domains [40]. A meta-analysis of randomized-controlled trials, investigating cognitive training interventions in both cognitively healthy older adults and

people with MCI, found only weak evidence of transfer effects to not trained domains of cognition and IADL performance [41]. In terms of a “reablement model", individualized and goal-oriented functional cognitive training tasks may improve IADL performance [42]. Functional cognitive tasks are inherently demanding, requiring the activation of a variety of cognitive functions, such as learning, memory, attention and executive function [43]. Cognitive training strategies targeted at everyday activities have been reported to improve IADL performance [15, 44]. Therefore, the repeat practice of challenging tasks, such as everyday activities or learning new activities, in slightly different contexts may have a favourable impact on broad cognitive abilities and facilitate the transfer to IADL performance [45].

Cognitive compensatory strategies, such as a memory notebook, are known to improve IADL functioning in people with MCI [46, 47]. These strategies are particularly valuable if a lost function cannot be entirely regained [42]. In contrast to rehearsal-based cognitive training strategies, external compensatory strategies aim to change how a person remembers, with information being retrieved using external aids [48]. Paper and pencil, as well as digital memory notebooks, may help to support retrospective and prospective memory [48], which have been ascertained to improve IADL performance [49].

A positive effect on IADL performance in people with MCI was found for group-based interventions that provide information on brain health-related lifestyle factors and recommendations on how to integrate these into daily life [50, 51]. Furthermore, benefits to caregivers were found, in the form of improved mood and reduced distress, when they were also included in the intervention [52]. Finally, social engagement is thought to positively affect the psychosocial health of both the MCI-afflicted and their caregivers [53]. Living a socially active life might have an impact on cognitive function [43] and reduce mortality risk

in people with MCI [54]. One review recommends the incorporation of social interaction into physical activity interventions to improve adherence and participation [55].

Multi-component interventions (e.g. lifestyle interventions that combine physical exercise with cognitive training) appear not only to be effective in improving cognition and physical function in the elderly [56-59], but also to be superior to each intervention component being applied individually [60]. Our systematic review also concluded that the intervention components should be implemented sequentially, with at least a part of the intervention being arranged in groups [60]. Combined intervention approaches that are embedded in daily living activities, including challenging cognitive tasks, compensatory strategies, physical exercises and social engagement, seem to be promising [43]. However, the effect of multi-component interventions on IADL performance is unclear and varies between studies [60]. In a two-year lifestyle intervention, the FINGER study found that their intervention group, based on healthy eating, physical exercises, cognitive and social activity, maintained their functional independence [61]. Other multi-component intervention studies have reported no positive effect on IADL performance [34, 35, 62]. The inconsistent findings may be explained by the target of the interventions, since none were specifically targeted at improving IADL functioning [34, 35, 61, 62]. Based on the currently available literature, deriving firm conclusions on the crucial components of a multi-component intervention for people with MCI is challenging, due to the high heterogeneity of the investigated interventions and inconsistent findings regarding IADL performance. In conclusion, there is presently insufficient evidence to support a large, full-scale, randomised controlled trial (RCT) to investigate the effectiveness of an individually-tailored, multi-component intervention on IADL performance in people with MCI. Consequently, a pilot randomised feasibility study is proposed, in accordance with the framework for the development and evaluation of complex interventions of the British Medical Research Council (MRC) [63].

Study aims and research questions

The primary aim of this pilot study is to investigate the feasibility and acceptability of a multi-component intervention to improve IADL performance in people with MCI. It will provide the basis for the conduct of a large-scale RCT to evaluate this type of intervention in the future. The following primary research questions will be addressed in this study:

i) How many eligible people with MCI can be identified, based on a review of medical records and alternate recruitment strategies?

ii) How many people with MCI and caregivers will accept an invitation to participate in this study?

iii) Will people with MCI accept randomisation, either to the multi-component intervention or to the control intervention?

iv) Is adherence sufficiently strong in the multi-component intervention group, taking into account the issues of components, dosage, mode and setting?

v) How many participants will complete the follow-up in this study?

vi) Are the research methods for data collection fit for purpose?

The secondary aim of this study is to estimate the potential efficacy of the multi-component intervention on IADL performance, physical function and cognitive function in people with MCI.

Methods

This study is a two-arm randomised, controlled, feasibility trial of six months duration including people with MCI, comparing an individually-tailored, multi-component intervention to improve IADL performance with a control intervention. The protocol follows the Standard Protocol Items Recommendations for Interventional Trials (SPIRIT) guidance (Supplement 2) [64], complemented with the CONSORT 2010 extension to feasibility and

pilot studies [65]. The intervention is described following the Template for Intervention Description and Replication (TIDieR) checklist (Supplement 3) [66].

Intervention development

A multiple-step approach was used to develop the intervention, according to the guidance of the Medical Research Council (MRC) [63].

Development of IADL model

A deductive approach was used to build a model, using a Delphi approach, on the possible factors that influence IADL functioning in MCI persons [23]. The Delphi study results allow mapping of IADL functioning in people with MCI. The results indicate that IADL functioning in people with MCI may be influenced by several cognitive function and physical function factors, as well as personal and environmental factors. This model was used as the basis for determining the components of the combined intervention implemented. International guidelines [67, 68], together with the current literature in the field, were used to determine the specific design of the intervention, i.e. training type, intensity, frequency and duration of the components. As a result, the first draft of the multi-component intervention was developed.

Development of the intervention design

To increase acceptability and feasibility [69], the potential research users and relevant stakeholders were actively involved in the development of the intervention, using a patient and public involvement approach (PPI) [70, 71]. The PPI's overall goal was to adapt an optimal evidence-based intervention to one suited to clinical practice. The PPI was actioned through a task force meeting, the members of which were recruited as a convenience sample from two memory clinics in Switzerland. They comprised of two people with MCI, two caregivers (unrelated to the people with MCI), six health professionals (i.e., geriatrician,

neurologist, nurse, occupational therapist, physical therapist, and neuropsychologist) who worked on a daily basis with people with MCI in a memory clinic setting, one representative of the Swiss Alzheimer foundation, and one represenatative of the Swiss memory clinics association. The people with MCI and caregivers received reimbursement of their travel expenses and remuneration for their participation in the task force meeting [71]. In contrast to other PPI approaches, a task force is able to decide on important aspects of an intervention [69]. The task force members were empowered through the provision of materials, such as the intervention draft, in lay language. They were also provided, in advance of the meeting, with the relevant issues and questions for discussion. A member of the research team (MB) was available for contact at any time, if questions or uncertainties arose [71]. An experienced researcher (KN) moderated the task force meeting to facilitate the discussion and decision-making. To increase the intervention's practicability, relevant issues for its design were: overall composition and structure of the intervention; setting; duration; frequency; and caregiver inclusion in the intervention. To avoid domination of the meeting by individual task force members, decisions were made using the nominal group technique. Each task force member was asked to respond to the questions posed by the moderator, followed by a group discussion on all ideas and suggestions generated [72]. The task force meeting was audio recorded, transcribed ad verbatim, and finally summarised in a protocol. Based on the decisions made, the intervention was adapted and described in detail using the TIDieR checklist [66]. The task force members were invited to give their feedback and confirm their agreement. A summary of the discussion points and decisions made by the task force can be found in Supplementary Table 1.

Multi-component intervention

F.I.T.AL. (**F**unction – **I**nformation – **T**raining) therapy for everyday life (AL corresponds to the German term "**AL**ltag") is comprised of three main components: (1)

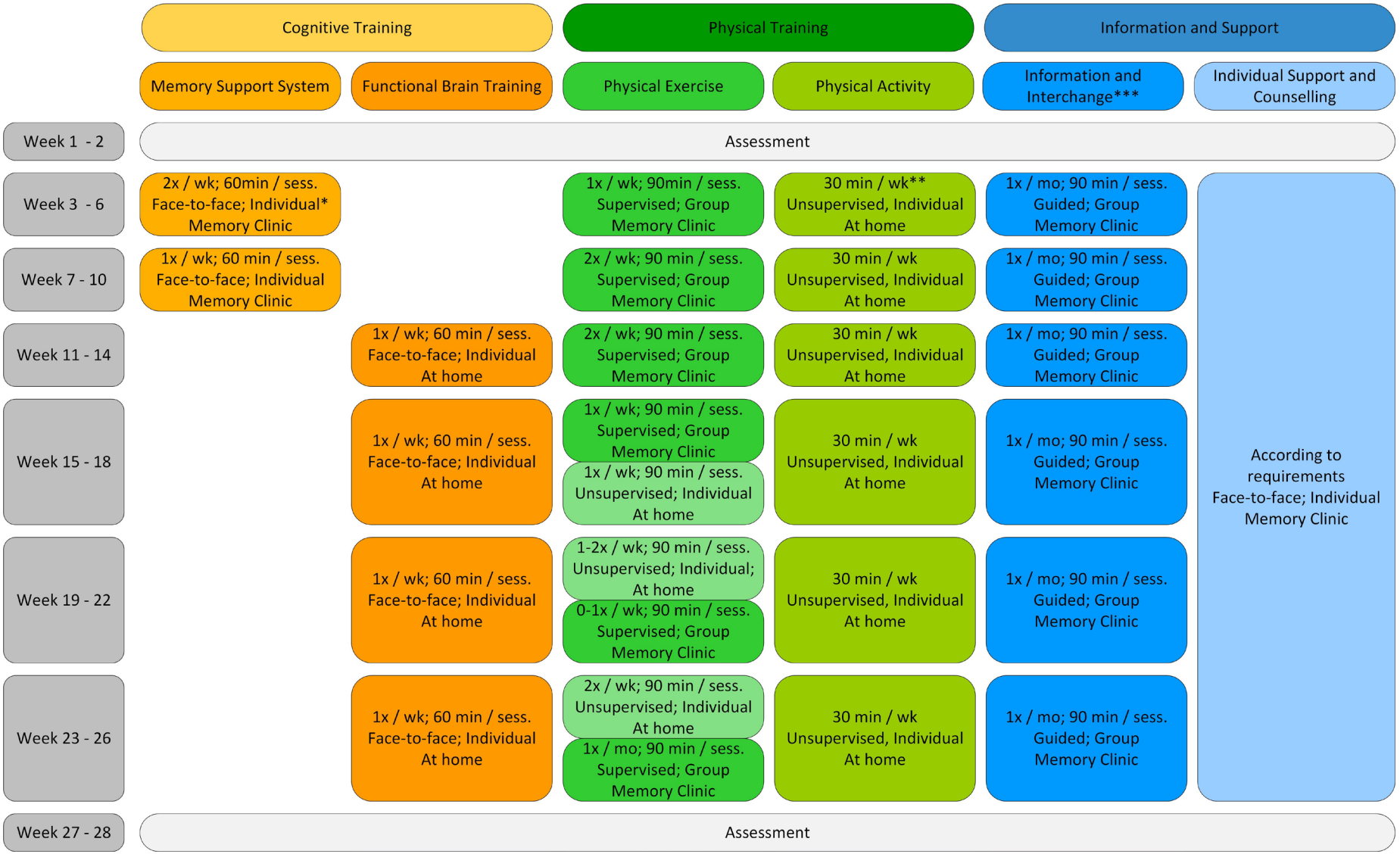
cognitive training; (2) physical training; and, (3) information and support. An overview of the intervention is provided in Figure 1. The intervention is tailored to the participants' physical and cognitive capabilities, which will be assessed with the IADL functioning model for people with MCI [23]. The assessment battery contains seeing and hearing functions, mobility, functional mobility, social network/environment and social support. A personalised training log will be used to document the training sessions.

Cognitive Training

The functional brain training aims to learn new, challenging, meaningful activities to stimulate specific cognitive functions, i.e. attention, executive function and memory. It will be delivered by an experienced occupational therapist (OT) or neuropsychologist and will contains the following two components:

1) Memory support system: The first component is based on the memory support system proposed by Greenaway et al. [47]. The support takes the form of a notebook, similar to an agenda, with a daily calendar, a daily to-do list, and a notes section. It is aimed at learning a strategy to support memory. If a caregiver is available (e.g. spouse, child, close friend), they will be included in the first two sessions, if needed or wanted, so that the caregiver is also informed of the notebook's goal. The notebook will be used in the intervention sessions to plan individual physical activity and personalised physical exercises at home. Booster sessions, embedded in the functional brain training, will be included in the subsequent four months of the intervention.

Figure 1 F.I.T.AL. – Therapy for everyday life: Components, composition and structure, setting, mode, frequency and duration



2) Functional Brain Training: The second component of cognitive training includes learning new, or relearning, challenging, meaningful activities. The activities can either be IADLs with which the participant faces problems, or new activities that the participant would like to learn, e.g. the use of a specific smartphone application, a new technical appliance, or a challenging game (i.e. card games, chess or "Go"). Irrespective of the activity, or activities, learned during the sessions, it is vital that it is meaningful to the participant and that they are motivated to learn it. The sessions will be supervised by an experienced OT. The participant will select the activities himself, together with the OT. To conform with an errorless learning regimen [45], each brain training session will comprise of a goal-setting component (small steps), elaboration on how to reach the goal, and a review of previous goals and homework. The usage of the memory support system will be addressed monthly (e.g. discussions of problems and occasions to use it in daily life).

Physical Training

The physical training component is designed to meet international guidelines for physical activity in elderly adults [68, 73, 74]. The training will be tailored to the individual's physical fitness level, based on an assessment battery [68]. If a participant faces mobility, balance or functional mobility problems, the exercises will be tailored to meet their individual needs. Physical training includes the following two components:

1) Physical Exercise

Physical exercises are a subset of physical activity that aim to improve or maintain one or more domains of physical fitness [75]. Weekly physical exercises include: (1) 60 minutes of aerobic exercise of vigorous intensity; (2) twice-weekly strength training of the main muscle groups using elastic bands or weights (i.e. knee extensors and flexors, abdominal and back muscles, upper back and arm muscles, calf muscles); (3) twice-weekly

balance/coordination exercises; and, (4) flexibility training. Physical exercises will initially be guided and supervised by experienced physical therapists in groups of maximal eight participants in a memory clinic setting. The dosage will be gradually increased (first month to second month). Supervision time will be reduced gradually as time spent on individual training at home is introduced or increased. Written instructions on the exercises, using images and text, will be supplied. The memory support system will be used for the planning, performance and evaluation of the individual training at home. The intensity of the endurance exercises will be based on ratings of perceived exertion (Borg Scale 14 – 17) [76], while that of the strength exercises will be based on the one-repetition maximum (70 – 84% of 1 RM) [68]. The components of physical exercise training are summarized in Table 1.

Table 1 – Physical exercise components and dose

Component	Content	Duration	Intensity	Frequency per week
Warm - up	General movement exercises	5 min	Light	2x
Endurance	Cycling, treadmill walking, Nordic walking, stair climbing	30 min	Vigorous	2x
Strength	Strength training of the main muscle groups; elastic bands or weights	30 min	Vigorous 8 - 15 repetitions 2 - 3 sets	2x
Balance / Coordination	Static and dynamic balance exercises and coordination exercises	15 min	Light to moderate	2x
Flexibility / Cool down	Stretching	10 min	Light	2x

2) Physical Activity

Participants will be encouraged to integrate physical activity training into their daily routines. Overall, physical activity should last at least 30 minutes per week at moderate intensity, based on ratings of perceived exertion (Borg scale 12-13) [76]. Participants are free to choose any form of physical activity that is feasible and enjoyable to them, e.g. climbing

stairs instead of using a lift, walking instead of using public transport/car, or using existing community resources, such as hiking groups. The memory support system will be used for the planning, performance and evaluation of the physical activities in the daily routine.

Information and support

1) Information and interactive groups

A total of six interactive information sessions in groups will be held monthly, with a maximum of eight participants per group. The first, as well as one specific session on nutrition, will be offered to patients and caregivers collectively to facilitate getting to know each other, socializing and enjoyment. The other four sessions will be offered to participants and their caregivers individually, to allow for unhampered interchange. A team of expert clinicians and health professionals (i.e. neurologist, geriatrician, neuropsychologist, occupational therapist, physical therapist and nutritionist) will guide the group sessions and lead the specific health-related themes concerning ageing and cognitive decline:

- Session 1: Brain-ageing and mild cognitive impairment
- Session 2: Physical activity and brain health, recreation and brain health
- Session 3: Cognitive training/activities and brain health
- Session 4: Nutrition and brain health
- Session 5: The importance of being socially active
- Session 6: Comorbidities, medication and healthy sleep.

Each group activity will include an information portion, a questions and answers session, and an expert-led discussion to facilitate interchange amongst the group members. A short, printed summary of the information will be handed out, including suggestions on implementation in daily life,.

2) Individual support and counselling

Individual support and counselling, with no time restriction, will be provided to the participants throughout the intervention by an experienced, trained health professional. If, based on the assessment battery, reasonable suspicion of a sensory impairment is found, individual support may include counselling on the usage of an aid, or referral to a specialist. Another area of individual support could be based on a lack of social support, or a lack of information on the physical activity options available in the community.

Control intervention

Participants randomised to the control group will receive an intervention of usual care plus the content of the component *Information and Support* from the multi-component intervention. To prevent intervention contamination, the *information and support* sessions of the control group will be provided separately to the multi-component intervention sessions. Usual care will be monitored using personalised logs and will include monitoring and management of comorbidities. Participants in the control group will not be prevented from being active on their own (e.g. joining support groups or hiking groups).

Study procedures

Study sample, eligibility criteria and screening

People with MCI will be invited to participate in the study if they fullfill the following critieria: (1) Clinical diagnosis of MCI, according to diagnostic guidelines of the National Institute on Aging-Alzheimer's Association (NIA-AA) [1, 77]; (2) Community-dwelling; and, (3) Age of 60 years or over. People with MCI are able to participate either with or without a caregiver (e.g. spouse, child, close friend).

Individuals are excluded from participation in the presence of: (1) Moderate to severe cognitive decline (Montreal Cognitive Assessment (MOCA) < 24); (2) Cognitive decline due to causes other than Alzheimer's disease or vascular dementia (e.g. delirium, head trauma,

chronic neurological diseases, stroke); (3) Clinical diagnosis of depression; (4) Clinical diagnosis of substance misuse; (5) A current medical condition for which exercise is contraindicated (e.g. instable coronary heart disease); and, (6) Participation in another study.

Screening and Consent

Potentially eligible and interested participants will be invited to participate in a screening meeting at the study site. At this meeting a member of the research team, appropriate and delegated, will obtain written informed consent. Participants may withdraw their informed consent at any time without the need for explanation.

Figure 2 Study flow diagram

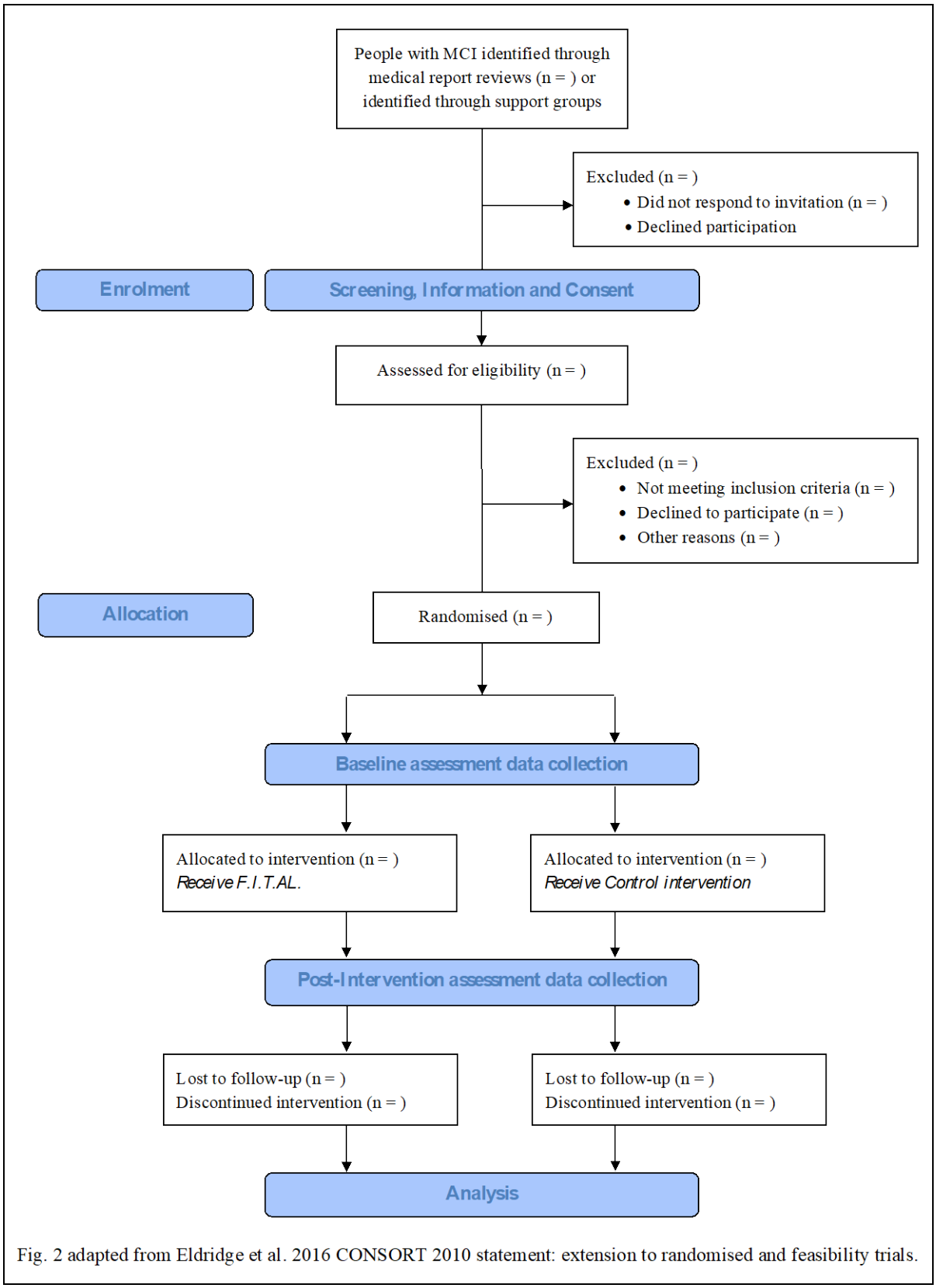


Fig. 2 adapted from Eldridge et al. 2016 CONSORT 2010 statement: extension to randomised and feasibility trials.

Demographic and clinical characteristics

During the screening visit, demographic data and clinical characteristics will also be collected. Demographic data will include the age, sex, weight, height, living situation, marital status, children (number), level of education, medication, and comorbidities (number and type). Clinical characteristics will include:

- Global cognition, assessed using the Montreal Cognitive Assessment (MOCA) (scores range from 0 to 30, with higher scores indicating better cognitive function) [78]
- Mood, measured using the Depression In old Age Scale (DIA-S) (a screening tool for depression with scores ranging from 0 to 10, with score >4 indicating probable depression) [79]
- Seeing functions, will be assessed utilizing the Snellen decimal chart for distant vision, and the Parinaud chart for near vision
- Hearing functions, will be assessed by the Hearing Handicap Inventory for the Elderly Screening (HHIE-S) tool [80]
- Frailty, using handgrip strength as an indicator and assessed with the JAMAR dynamometer of the dominant hand, following a standardised protocol [81, 82]

At the end of the screening visit, eligible participants will be randomised to either the multi-component intervention or control intervention. The half-day baseline assessment appointment will also be scheduled.

Randomisation and blinding

Participants will be randomly allocated into blocks of four, either to the multi-component intervention or the control intervention, stratified by age and sex. Randomisation will be carried out by an independent statistician using the R statistical software R version 3.6.2 or above [83]. Due to the nature of the interventions, it will not be possible to blind

either the participants or the personnel providing the interventions to the randomisation results. Participants will be informed of their assigned group at the time of the baseline measurement. The study personnel performing the assessments and analysis will be blinded to the group allocations.

Outcome measures

Feasibility, acceptability and adherence outcomes

Feasibility in the study was defined as the feasibility of recruitment, enrollment, retention, and the ability to collect clinical outcome measures**.** Feasibility definitions are:

- Recruitment, the identification of 128 eligible individuals within 2 years, based on medical record reviews by the research team at the study sites and alternate recruitment strategies
- Enrolment, 25% (32/128) of eligible individuals are available for randomisation
- Retention, at least 75% (24/32) of randomised participants complete the intervention and scheduled assessments
- Collection of complete outcome measures at baseline and follow-up, at least 80% of complete data for each outcome measure.

Acceptability of and adherence to the multi-component intervention will be measured by session attendance based on the training logs. Acceptable will be defined as an attendance rate of ≥ 80% of sessions attended. Adherence to the multi-component intervention, i.e. carried out in accordance with the study protocol, defined as 80% of scheduled intervention components performed, will be assessed based on the training logs by: (1) Examination of the estimated intervention intensity based on checklists completed by the health professionals providing the intervention; (2) Number of completed sessions; and, (3) Duration of completed sessions. The number and duration of additional face-to-face, email, or telephone contact with the participants will also be recorded [84].

Clinical outcomes

The potential efficacy of the multi-component intervention on IADL performance, physical function and cognitive function will be estimated through repeat assessment of baseline data at the end of the study. The results will be used to estimate the variability of each outcome measure between baseline and study end. At baseline and study endpoint All secondary outcome measurements will be performed at baseline and study end. The appropriateness of each outcome measure for detecting changes in the study stample will also be explored.

IADL performance will be assessed using the informant-based Amsterdam IADL questionnaire short version, in German (A-IADL-Q-SV) [85]. The questionnaire contains 30 items and the scoring is based on item response theory (IRT) [85, 86]. The IRT latent trait scores are transformed into a total score ranging from 20 to 80, with higher scores representing better IADL performance [86].

Endurance will be measured based on the six-minute walking test using a standardised protocol [87]. The distance in meters will be recorded, with higher scores representing better function.

Lower extremity strength will be assessed using the five-chair-rise test based on a standardised protocol [88]. The time required to complete the task will be recorded and rated on a five-point Likert scale from 0 to 4, with higher scores indicate better function [88].

Balance will be assessed using the Berg Balance Scale (BBS) [89]. The BBS is an objective 14-item scale to assess static and dynamic balance [90]. Scores range from 0 to 56, with higher scores indicating better function.

Mobility will be assessed using the Timed Up and Go test (TUG). The TUG measures different aspects of gait, i.e. mobility, walking ability and fall risk [91]. The time required to complete the task will be recorded, with lower score indicating better function[92].

Gait speed will be assessed using a four-meter walking test [88]. Participants are asked to walk as fast as possible for a distance of four meters. The time to complete the distance will be recorded in seconds and walking speed, in meters per second, calculated. Two trials will be performed, with the better trial being recorded [88].

Functional mobility will be assessed using the Modified Physical Performance Test (MPPT) [93, 94]. The MPPT assesses functional mobility aspects that are relevant for daily activities, such as lifting an object, picking up a coin from the floor, or climbing stairs. The maximum score is 36, with higher scores indicating better function [93, 94].

Memory will be assessed using subtests of the CERAD Plus assessment battery with a higher score in the subtest indicating better function [95]. The subtests will be performed in the following standardized sequence: (1) *Word List Learning*, scores range from 0 to 30 [96]; (2) *Constructional Praxis*, scores range from 0 to 11 [96]; (3) *Word List Recall*, scores range from 0 to 10; (4) *Word List Recognition*, the proportion of correctly recognised words out of the ten words on the word list task will be calculated, scores range from 0 to 100%; and, (5) *Recall of Constructional Praxis*, scores range from 0 to 11.

Attention will be measured by the *Trail Making Tests parts A and B* [97]. The time required to complete the tasks will be measured in seconds; the difference between task B and task A will be calculated, with higher scores indicating worse function [98]. Alertness, selective attention and divided attention will be measured using the computerised Test of Attentional Performance (TAP) [99]. The reaction time in seconds and errors are recorded, with lower scores indicating better funciton [100].

Executive function, subdomain *working memory,* will be assessed using the verbal digit span (forward and backward) tests [101]. The scores for both tests range from 0 to 14, with higher scores indicating better performance. The difference between the verbal digit span forward and backward will be used [102]. Subdomain *problem solving and planning* will be

measured by the Tower of London Test [103]; the scores range from 0 to 46, with higher scores indicating better performance [104]. Subdomain *reasoning* will be measured using the Standard Progressive Matrices test, the number of correct complimented matrices in five minutes will be counted, with higher scores represent better function [105].

Social Network / Social Environment will be assessed using the social relationship and social environment subscales of the WHOQOL BREF [106]. The social environment subscale comprises eight items and the social relationship subscale includes three items. The scoring is based on syntax and is converted to a subscale score ranging from 0 to 100, with higher scores indicating a better health condition.

Social Support will be assessed with the ENRICHED Social Support Instrument (ESSI) [107]. The scale contains five items that are rated on a five-point Likert scale and assesses a person's perception of the social support of their family, friends, and important others. Scores range from 5 to 25, with higher scores an indicator of higher perceived social support. A score of <18 points, or at least two items rated at <3, indicates a lack of social support [108].

Physical activity will be assessed with the Community Healthy Activities Model Program for Seniors (CHAMPS) questionnaire [109]; the self-reported questionnaire assesses the weekly frequency and duration of various physical activities [110].

Participant timeline

All assessments will take place at the memory clinic sites and will be applied in a standardised way by trained research staff. The participant timeline is presented in Table 2.

Table 2 - Schedule of enrollment, interventions, and assessment

	STUDY PERIOD		
	Enrollment	Allocation	Post allocation

Time point		Randomisation	Baseline assessment	Intervention delivery	Post-intervention assessment
week			1-2	3 - 26	27 - 28
Enrollment					
Eligibility screening	X				
Informed consent	X				
Allocation		X			
Intervention					
FIT				X	
Control				X	
Assessments					
Feasibility	X	X	X		X
Acceptability				X	
Adherence				X	
IADL performance			X		X
Endurance			X		X
Lower extremity strength			X		X
Balance			X		X
Mobility			X		X
Gait speed			X		X
Functional mobility			X		X
Memory			X		X
Attention			X		X
Executive function			X		X
Social Network / Environment			X		
Social Support			X		X
Physical activity			X		X
Demographic data			X		
Global cognition			X		X
Depression			X		
Seeing functions			X		
Hearing functions			X		
Hand grip strength			X		

FIT, Function – Information – Training Therapy for everyday life; IADL, Instrumental Activities of Daily Living

Sample size

This study is not designed to address the effectiveness of the multi-component intervention. Consequently, no power calculation was used to determine sample size [111]. Different sample sizes are recommended for feasibility studies [112, 113]. The target sample size in this study is twelve participants per group with a complete follow-up. This is based on the long duration of the intervention and the expectation of drop-outs, due to the advanced age of the participants.

Analysis

Data will be analysed per protocol; no imputation of missing data will be made. Baseline characteristics will be analysed descriptively, using either the mean with standard deviation, the median with interquartile range, frequency, and/or percentages, as appropriate.

Feasibility, acceptability and adherence findings will be analysed with descriptive statistics, with the provision of total numbers on proportions, as appropriate. The following feasibility outcomes will be reported: the number of eligible individuals; the proportion of eligible individuals randomised; the proportion of participants dropping-out between randomisation and final assessment; and, rates of the successful collection of clinical measurements at baseline and endpoint assessment. Acceptability will be reported based on the attendance rate and adherence. In addition, based on the proportion of interventions completed in accordance with the targeted intensity, the number and duration of completed sessions and the number and duration of additional contacts with the participant will be reported.

The secondary outcomes will be analysed per group, reporting both the means and standard deviations and the medians and interquartile ranges, respectively, at baseline and endpoint assessment, as well as the changes over the intervention period. Comparisons between the intervention and control groups, after controlling for baseline differences, will be made at the post-intervention assessment using means or medians. Additionally, 95% confidence intervals will be reported for mean differences and interquartile ranges for median differences [65].

Harms

No serious adverse events are expected to be caused by this study. Any adverse events will be recorded, regardless of whether they are associated with the study intervention. Adverse events (e.g., musculoskeletal pain or discomfort, injuries due to physical exercise)

associated with the study interventions will be reported to the respective Ethics Committee by the principal investigator (MB).

Data monitoring and auditing

No formal Data and Safety Monitoring Board will be established. The principal investigator (MB) will inspect the accumulated data from the training logs monthly and review them with the study team.

Ethics and dissemination

The protocol will be submitted to the respective Ethics Committee (Ethics Committee of Eastern Switzerland, EKOS). The study will be conducted according to protocol, the Declaration of Helsinki, the principles of Good Clinical Practice, and the relevant Swiss regulations. Personal data of participants will be encoded before recording. Study-specific, paper-based case report forms (CRF) will be used to record all relevant data on the participants during the study, one for each enrolled participant. CRFs will be kept up-to-date to reflect the subject's status at each phase of the study. Only authorised study personnel will be able to enter data into the password-protected REDCap software. Each access and change in data will be documented. The Ethics Committee and regulatory authorities have the right to access the original data.

The results and conclusions of this study will be disseminated through publications in peer-reviewed journals and conferences. The findings will also be disseminated to the stakeholders and memory clinic personnel.

Discussion

Non-pharmacological lifestyle interventions are thought to improve IADL functioning in people with MCI and could be crucial in maintaining their autonomy. The optimal multi-component intervention to improve IADL performance in people with MCI has yet to be

determined. This paper describes the protocol of a randomised feasibility study, designed to estimate the feasibility and acceptability of a novel, specifically-tailored, multi-component intervention to improve IADL performance in people with MCI.

The study is the first essential step in investigating the potential benefits of improving IADL functioning in people with MCI by means of an evidence-based multi-component intervention (i.e. F.I.T.AL. – therapy for everyday life). The multi-component intervention includes personalised cognitive training strategies, physical exercises, and group-based information and support sessions. Since a multi-step approach was applied in developing the F.I.T.AL. and included patient and public involvement, it is anticipated that the F.I.T.AL. will be feasible and acceptable both to MCI persons and their caregivers. The feasibility and acceptability findings from this proposed study will form the basis for the development of an adequately-powered, full-scale, randomised controlled trial to examine the efficacy of the F.I.T.AL. The long intervention period that could potentially lead to compliance bias, might act as a limitation of the study. This is why careful analysis of patterns of (non-) adherence to the intervention will be crucial.

The clinical outcomes for the people with MCI receiving F.I.T.AL. probably show a constant (or higher) level of IADL performance compared to the participants receiving only the control intervention. Based on the findings of previous multi-component interventions, it is thought that IADL functioning must be targeted directly, because improvements in physical function and cognitive function do not necessarily translate into a better ability to perform IADLs. Consequently, the F.I.T.AL. was designed to specifically target IADL functioning. The results of this randomised feasibility study may provide initial evidence for an individually-tailored, multi-component intervention to improve the functional status of people with MCI. This could have great importance for people with MCI, their caregivers, society and public health costs.

The design of the control intervention might be seen as a limitation of this study, since this group receives much less intervention time. However, considering the early stage of development of this complex intervention [63], the proposed control intervention (of usual care plus the information and support component of F.I.T.AL.) is considered to be the best option. Due to the long intervention duration, a waitlist control study was not considered to be appropriate. Also, sham-interventions for three times a week for half a year (for the cognitive training strategies and physical exercise) were considered to be unethical. Depending on the results of this study, a subsequent randomised controlled trial might use a comparative effectiveness design, rather than comparing the F.I.T.AL. with a control intervention.

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Supplements

Supplementary Table 1 Comparison of evidence-based recommendations and task force decisions

Intervention design			
Evidence-based recommendation		Decision task force	
Duration:	- Six months	Duration:	- Six months
Frequency:	- Training three times per week	Frequency:	- Training three times per week (1x cognitive training, 2x physical exercise) - Variation in structure (e.g. stepwise introduction)
	- Information and counselling every two weeks		- Information and exchange 1x per month - Counselling only individually, if needed/requested
Setting:	- Physical exercise, group-based - Weekly 30 mins. of additional autonomous physical activity at home - Cognitive training, individual - All training sessions in memory clinic settings - All trainings supervised	Setting:	- Physical exercise, mix of individual and group-based - Weekly 30 mins. of additional autonomous physical activity at home - Cognitive training, individual - Location variation, memory clinic setting and at home - Control variation, supervision and independent
	- Information and counselling in groups		- Information in groups
Inclusion of caregivers in the intervention			
Evidence-based recommendation		Decision task force	
	- Inclusion in information and counselling groups		- Information and exchange groups, separate for participants and caregivers - Specific, joyful group sessions together
	- Inclusion in first part of the cognitive training		- Inclusion only in the first two sessions, with aim of informing caregivers on content and goal
Wording intervention			
Researchers recommendation		Decision task force	
	- Combined training therapy		- Name misleading and incomprehensible - Use FIT as acronym for Function / Information / Training - FIT has a positive connotation

Supplement 2 – Completed SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	✓ Title page
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	✓ Title page
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	✓ Footer
Funding	4	Sources and types of financial, material, and other support	✓□T□□□□□□□□□
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	✓ Title page
	5b	Name and contact information for the trial sponsor	✓ Title page
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	✓ pages 5 - 7
	6b	Explanation for choice of comparators	✓ page2 16&17, 28

Objectives	7	Specific objectives or hypotheses	✓ page 8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	✓ pages 8 - 9

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	✓ page 9
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	✓ page 9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	✓ pages 10 - 16
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	✓ page 13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	✓ page 20
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	✓ pages 19 & 20
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	✓ pages 20 – 27
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	✓ Tbl. 2, page 24
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	✓ pages 13 & 14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	✓ page 13

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	✓ page 14
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	✓ page 14
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	✓ page 14
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	✓ page 14
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	✓ Fig. 1, page 12; pages 24 - 27
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	✓ page 27
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	✓ pages 26 - 27
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	✓ page 27
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	✓ page 27
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	✓ pages 27 - 28
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	✓ pages 27 - 28
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	✓ page 13
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	✓ page 27
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	N/A
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	✓ page 27
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	✓ page 27
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

N/A, not applicable

Supplement 3 – Completed TIDieR (Template for Intervention Description and Replication) Checklist

Item number	Item	Where located	
		Primary paper (page or appendix number)	Other † (details)
	BRIEF NAME		
1.	Provide the name or a phrase that describes the intervention.	Title page	_____
	WHY		
2.	Describe any rationale, theory, or goal of the elements essential to the intervention.	pages 5 - 7	_____
	WHAT		
3.	Materials: Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (e.g. online appendix, URL).	pages 16 -20	_____
4.	Procedures: Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.	pages 16 - 20	_____
	WHO PROVIDED		
5.	For each category of intervention provider (e.g. psychologist, nursing assistant), describe their expertise, background and any specific training given.	pages 15 - 20	_____
	HOW		
6.	Describe the modes of delivery (e.g. face-to-face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.	page 15	_____
	WHERE		
7.	Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.	pages 16 - 20	_____

	WHEN and HOW MUCH		
8.	Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity or dose.	page 15	_____
	TAILORING		
9.	If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how.	page 14	_____
	MODIFICATIONS		
10.	If the intervention was modified during the course of the study, describe the changes (what, why, when, and how).	N/A	_____
	HOW WELL		
11.	Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them.	page 20	_____
12.	Actual: If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.	N/A	_____

N/A, not applicable