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ORIGINAL ARTICLE

The "Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies" (SPRINTT) randomized controlled trial: design and methods

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Abstract The sustainability of health and social care systems is threatened by a growing population of older persons with heterogeneous needs related to multimorbidity, frailty, and increased risk of functional impairment. Since disability is difficult to reverse in old age and is extremely burdensome for individuals and society, novel strategies should be devised to preserve adequate levels of function and independence in late life. The development of mobility disability, an early event in the disablement process, precedes and predicts more severe forms of inability. Its prevention is, therefore, critical to impede the transition to overt disability. For this reason, the Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies (SPRINTT) project is conducting a randomized controlled trial (RCT) to test a multicomponent intervention (MCI) specifically designed to prevent mobility disability in high-risk older persons. SPRINTT is a phase III, multicenter RCT aimed at comparing the efficacy of a MCI, based on long-term structured physical activity, nutritional counseling/dietary intervention, and an information and communication technology intervention, versus a healthy aging lifestyle education program designed to

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prevent mobility disability in 1500 older persons with physical frailty and sarcopenia who will be followed for up to 36 months. The primary outcome of the SPRINTT trial is mobility disability, operationalized as the inability to walk for 400 m within 15 min, without sitting, help of another person, or the use of a walker. Secondary outcomes include changes in muscle mass and strength, persistent mobility disability, falls and injurious falls, disability in activities of daily living, nutritional status, cognition, mood, the use of healthcare resources, cost-effectiveness analysis, quality of life, and mortality rate. SPRINTT results are expected to promote significant advancements in the management of frail older persons at high risk of disability from both clinical and regulatory perspectives. The findings are also projected to pave the way for major investments in the field of disability prevention in old age.

Keywords Disability · Functional impairment · Physical activity · Nutrition · Prevention · Unmet needs

Introduction

The current social and healthcare systems are built upon the traditional paradigm of patients suffering from a single acute illness. As such, they are unsuited to address the care needs of older, multimorbid, and functionally impaired persons, who represent a growing and increasingly demanding share of western populations [1]. Hence, although the prolongation of life remains an important public health goal, the preservation of adequate levels of function and independence into late life is a fundamental requisite for assuring sustainability of social and healthcare systems [2]. To this end, growing efforts have been directed toward the development and testing of novel models of care specifically oriented to the identification and take-in-charge of the complex medical problems of older persons [3].

The lifestyle interventions and independence for elders (LIFE) study has been the most notable initiative in the field [4]. LIFE was a phase III, multicenter, randomized controlled trial (RCT) that compared the effects of a physical activity program with a successful aging educational program in more than 1600 functionally impaired older persons, over an average follow-up of 2.6 years. Physical function impairment was operationalized as a short physical performance battery (SPPB) [5] summary score of 9 or below. The primary outcome of the study was incident mobility disability, defined as new onset inability to complete the 400-m walk test [6]. The physical activity intervention reduced the risk of developing mobility disability by 18% relative to the control group. Results were comparable across strata identified by ethnicity/race, gender, history of cardiovascular disease, history of diabetes, or cognitive status. Remarkably, participants with lower physical function at baseline (i.e., SPPB < 8) were those who mostly benefited from the intervention.

Although the LIFE study has surely become a landmark in the field of physical disability prevention, it did not target a specific condition. Participants were considered eligible to the study if presenting with functional impairment in the absence of mobility disability. Such a selection criterion, while identifying a population at risk of adverse health outcomes, did not allow framing a definite clinical entity. This approach may, therefore, detract regulatory authorities from recognizing functional impairment as a true nosographic entity. In addition, LIFE adopted a monodimensional intervention (i.e., physical activity) to prevent the outcome of interest, whereas the complex framework within which functional impairment develops is more likely to be addressed through multidomain interventions [7].

The "sarcopenia and physical frailty in older people: multi-component treatment strategies" (SPRINTT) project was designed, based upon the successful experience of LIFE, to overcome the existing limitations in the field. The project has been funded by the innovative medicines initiative (IMI), a joint undertaking between the European Union and the European Federation of Pharmaceutical Industries and Associations (EFPIA) [8]. The SPRINTT project has been designed to provide a clear operationalization of the presently vague concept of physical frailty, through the identification of (1) target organ damage; (2) a specific clinical phenotype; and (3) a set of related measurable functional parameters [9]. The operationalization of this novel condition, termed physical frailty & sarcopenia (PF&S), has, in turn, allowed a specific population of older adults with unmet medical needs to be defined.

The ad hoc RCT sponsored by the SPRINTT project will compare the efficacy of a multi-component intervention (MCI), based on long-term structured physical activity, nutritional counseling/dietary intervention, and an information and communication technology (ICT) intervention, versus a healthy aging lifestyle education (HALE) program for preventing mobility disability in community-dwelling older persons with PF&S.

Methods

Overview

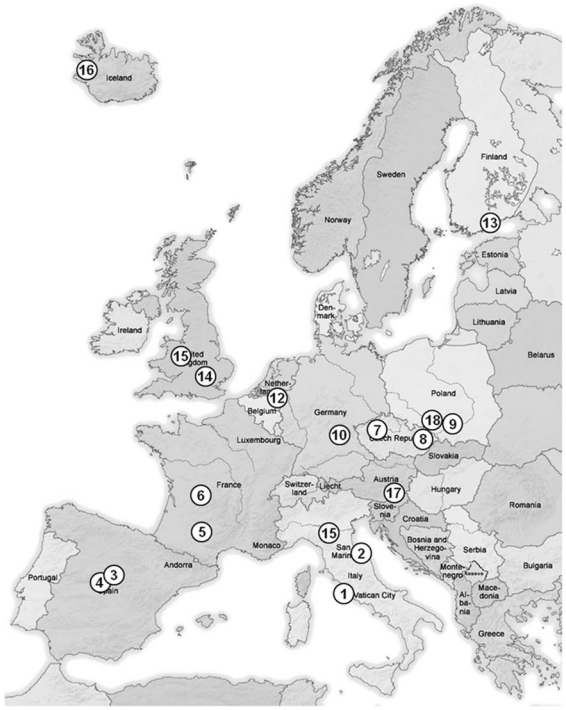
The SPRINTT trial is a phase III, single-blind, multicenter RCT (ClinicalTrials.gov identifier: NCT02582138) designed to compare the efficacy of a MCI program (physical activity, nutritional counseling/dietary intervention, and ICT intervention) versus a HALE program for preventing mobility disability in initially non-disabled older persons

with PF&S. Analogously to the LIFE study [4], the primary outcome of mobility disability has been operationalized as the incident inability to complete the 400-m walk test. Secondary outcomes of SPRINTT are listed in Table 1.

SPRINTT trial operations take place in 15 clinical sites, located in nine European countries, under the coordination of the Department of Geriatrics at the Catholic University of the Sacred Heart (Rome, Italy) (Fig. 1). Each center has been assigned a specific recruitment target, ranging from 54 to 108 participants (Fig. 1). Three additional sites have been engaged and serve as centralized backup centers to support participant recruitment as needed. Trial operations are also be supported by members of EFPIA (Sanofi-Aventis R&D, Novartis, GlaxoSmithKline, and Servier).

Table 1 Secondary outcomes of the SPRINTT clinical trial

Physical performance
Short physical performance battery (SPPB) [5]
Handgrip strength
Disability status
Pepper Assessment Tool for Disability (PAT-D) [30]
Activities of Daily Living (ADL) [31] and Instrumental Activities of Daily Living (IADL) [32]
Incidence of persistent mobility disability (operationalized as failure of completing the 400-m walk test at two consecutive 6-month visits)
Body composition [assessed using dual energy X-ray absorptiometry (DXA)]
Anthropometric parameters (body mass index (BMI), mid-arm circumference, calf circumference)
Nutritional status (Mini Nutritional Assessment-Short Form, MNA-SF) [33]
Cognitive function (assessed using the Mini Mental State Examination (MMSE) [34] and Trail Making Test (TMT) A and B [35])
Mood (assessed via the Center for Epidemiological Studies-Depression scale (CESD) [36])
Falls (assessed using self-reported questionnaire) and injurious falls
Quality of life (measured using the EuroQoL-5D instrument) [37]
Use of healthcare services (assessed through an ad hoc developed questionnaire) *Cost-effectiveness analysis*
Mortality rate



Site number	Site name	City, country	Recruitment target (n)
1	Catholic University of the Sacred Heart (coordinating center)	Rome, Italy	107
2	IRCCS-INRCA	Ancona, Italy	107
3	University Hospital of Getafe	Getafe, Spain	107
4	University Hospital Ramón y Cajal	Madrid, Spain	107
5	CHU Toulouse	Toulouse, France	107
6	CHU Limoges	Limoges, France	107
7	Charles University	Prague, Czech Republic	54
8	Silesians Hospital	Opava, Czech Republic	54
9	Jagiellonian University Medical College	Krakow, Poland	108
10	Friedrich-Alexander Universität Erlangen-Nürnberg	Nurnberg, Germany	107
11	Maastricht University Medical Center	Maastricht, The Netherlands	107
12	University of Helsinki	Helsinki, Finland	107
13	Diabetes Frail, Medici Medical Practice	Luton, United Kingdom	107
14	Aston University of Birmingham	Birmingham, United Kingdom	107
15	University of Parma	Parma, Italy	107
16	Lanspitali University Hospital	Reykjavik, Iceland	TBD*
17	Medical University of Graz	Graz, Austria	TBD*
18	JP II Geriatric Hospital of Katowice	Katowice, Poland	TBD*

* Centralized backup site

Fig. 1 SPRINTT clinical trial sites

Study population

For the SPRINTT trial, 1500 community-dwelling older persons with PF&S aged 70 years and older will be enrolled. Inclusion and exclusion criteria are summarized in Table 2. The eligibility criteria are intended to select a population that is: (1) at high risk of experiencing the mobility disability outcome, (2) most likely to benefit from the MCI, and (3) most likely to comply with the intervention and assessment protocols. The age group has been selected because persons aged 70 years and older are at increased risk of mobility disability and are expected to

Table 2 Eligibility criteria for participation in the SPRINTT clinical trial

Inclusion criteria
Age ≥70 years
Short Physical Performance Battery (SPPB) score between 3 (included) and 9 (included)
Ability to complete the 400-m walk test within 15 min without sitting, the help with another person or the use of a walker
Presence of low muscle mass based on the results of a dual energy X-ray absorptiometry (DXA) scan, according to the cut-points indicated by the Foundation for the National Institutes of Health (FNIH) Sarcopenia Project [11]
Willingness to be randomized to either intervention group and to follow the study protocol
Exclusion criteria (permanent)
Inability or unwillingness to provide informed consent or accept randomization in either study group
Plans to relocate out of the study area within the next 2 years or plans to be out of the study area for more than 6 consecutive weeks in the next year
Residence in long-term care
Household member enrolled in the study
Current diagnosis of schizophrenia, other psychotic or bipolar disorder
Consumption of more than 14 alcoholic drinks per week
Difficulty communicating with the study personnel due to speech, language, or (non-corrected) hearing problems
Cognitive impairment (i.e., MMSE score <24/30)
Severe arthritis (e.g., awaiting joint replacement) that would interfere with the ability to participate fully in either study arm
Cancer requiring treatment in the past 3 years, except for non-melanoma skin cancers or cancers that have an excellent prognosis (e.g., the early stage breast or prostate cancer)
Lung disease requiring regular use of supplemental oxygen
Inflammatory conditions requiring regular use of oral or parenteral corticosteroid agents
Severe cardiovascular disease [including New York Heart Association (NYHA) class III or IV congestive heart failure, clinically significant valvular disease, history of cardiac arrest, presence of an implantable defibrillator, or uncontrolled angina]
Peripheral arterial disease Lériche–Fontaine stage 3 or 4
Upper and/or lower extremity amputation
Parkinson's disease or other progressive neurological disorder
Renal disease requiring dialysis
Chest pain, severe shortness of breath, or occurrence of other safety concerns during baseline 400-m walk test
Current participation in a structured physical activity program
Current enrolment in another clinical trial involving lifestyle, nutrition, or pharmaceutical interventions
Other medical, psychiatric, or behavioral factors that in the judgment of the investigator may interfere with the study participation or the ability to autonomously follow either the MCI or the HALE programs
Other illness of such severity that life expectancy is expected to be less than 12 months
Clinical judgment concerning safety or non-compliance
Exclusion criteria (temporary)
Uncontrolled hypertension (systolic blood pressure >200 mmHg, or diastolic blood pressure >110 mmHg)
Uncontrolled diabetes with recent weight loss, diabetic coma, or frequent hypoglycemia
Hip fracture, hip or knee replacement, or spinal surgery in the past 6 months
Serious cardiac conduction disorder (e.g., third-degree heart block), uncontrolled arrhythmia, new Q waves within the past 6 months, or ST-segment depression (> 3 mm) on the ECG
Myocardial infarction, major heart surgery (i.e., valve replacement or coronary bypass graft), stroke, deep vein thrombosis, or pulmonary embolism in the past 6 months
Use of growth hormone, estrogens, progesterone, or testosterone supplementation in the past 3 months
Current participation in physical therapy or cardiopulmonary rehabilitation

have a sufficiently long life expectancy for justifying the participation in a 3-year preventive trial.

Eligibility criteria are aimed at identifying older persons who are physically frail and sarcopenic. At the same time, candidates participants need to be free of mobility disability at baseline, as documented by their ability to walk 400 m within 15 min without sitting, help of another person, or use of a walker. Targeting this subset of the population makes it possible to recruit a non-disabled but at-risk sample of older persons for a clinical trial of disability prevention.

Recruitment

Participant recruitment will take place during a 12- to 18-month period (see "Sample size considerations" for details). Each clinical trial site has developed specific recruitment plans to accommodate the variability across centers in catchment areas and access to the target population. In general, recruitment strategies include the use of newspapers, radio and television advertisements, and direct mailing. Special attention has been paid to informing healthcare providers, medical clinics, and hospitals within the catching area about the SPRINTT trial. Participants in the previous studies are also being approached, and ineligible participants asked about relatives or friends who might be eligible. As detailed in the statistics section, each clinical site will recruit 80% of participants with a SPPB summary score <8, to enrich the study population with higher risk older adults.

Potential participants are pre-screened over the telephone or in person. An ad hoc questionnaire is administered to screen out candidate participants who are clearly ineligible and to establish initial eligibility. Those who remain eligible are subsequently invited to the clinical trial site to complete a screening visit and determine final eligibility. After eligibility is confirmed, participants are randomly assigned (1:1 ratio) using a Web-based randomization algorithm to either the MCI or the HALE program. Randomization is stratified by study site, gender, and SPPB category (i.e., <8 or ≥8), to ensure homogeneous distribution of gender and SPPB characteristics in the two allocation groups across the recruitment sites. Stratification by center is implemented, because the cohorts recruited by the various participating sites may vary, depending on local populations and the recruitment strategies adopted. Stratification by gender is needed, because there may be differences in how women and men respond to the interventions. Finally, SPPB stratification is necessary, because the interventions are expected to have different efficacy in participants belonging to the two SPPB categories, as already shown in the LIFE study [4].

Identification of PF&S

At the screening visit, the identification of the condition of interest (i.e., PF&S) is achieved based on the co-occurrence of three defining elements: (1) low muscle mass; (2) SPPB summary score between 3 (included) and 9 (included); and (3) absence of mobility disability (i.e., ability to complete the 400-m walk test). The rationale behind each of the defining elements is provided elsewhere [10]. Here, it is worth specifying that the identification of the sarcopenia component of PF&S (i.e., low muscle mass) relies on the cut-points for appendicular lean mass (aLM) indicated by the Foundation for the National Institutes of Health (FNIH) sarcopenia project [11]. Whole-body DXA scans are used to estimate aLM, and each potential participant is considered to be eligible if presenting an aLM-to-BMI ratio (aLM_{BMI}) below <0.789 or <0.512 in men and women, respectively. When the aLM_{BMI}-based criterion is not met, the candidate is tested with the alternative criterion (i.e., crude aLM < 19.75 kg in men and <15.02 kg in women). This approach facilitates participants' recruitment and also allows for the conduct of pre-planned and post-hoc analyses to refine the operational definition of PF&S at the end of the SPRINTT project. Indeed, the combination of the two FNIH criteria will lead to the recruitment of participants with a wide spectrum of body composition profiles. Within this range, it will then be possible to identify those individuals who benefit more (or less) than others from the MCI.

Study interventions

The primary aim of the SPRINTT trial is to evaluate the effect of a MCI compared with a HALE program on the hazard rate of incident mobility disability in non-disabled older people with PF&S. Interventions will be administered for up to 36 months. Participants in both groups receive an individual 45-min introductory session by a SPRINTT investigator, during which the program is described and questions are answered.

MCI program

The intervention consists of a combination of moderate-intensity physical activity and nutritional counseling/dietary intervention, with ICT support.

Physical activity intervention The physical activity component is based on the exercise protocol implemented in the LIFE study [4], which has been shown to be safe and effective at preventing mobility disability [4] and improving physical frailty status [12]. Physical activity is recommended at moderate intensity and consists of aerobic, strength, flexibility, and balance training [4, 13]. Walking

is the primary mode of physical activity for preventing the onset of mobility disability, given its widespread popularity and ease of administration across a broad segment of the older adult population [14]. The target duration of walking is 150 min per week. This goal will be gradually approached on the basis of perceived exertion, according to the Borg's scale [15]. Other forms of endurance activity (e.g., stationary cycling) may be utilized on a limited basis when regular walking is medically or behaviorally contraindicated. Each session is preceded by a brief warm-up and followed by a brief cool-down period. In light of current clinical guidelines, participants are instructed to complete flexibility exercises following each bout of walking [16]. Moreover, two times per week, following a bout of walking, participants are instructed during the initial phase of the program to complete a 10-min routine focused on strength exercises for lower extremity muscle groups using adjustable ankle weights. This is followed by a brief lower extremity stretching routine. Balance training is introduced during the initial phase of the program as a complement to the aerobic and strength components. Supplementary instructional materials are provided to participants to reinforce the physical activity training occurring during center-based sessions, so that it can be generalized to the home environment. The intervention also involves encouraging participants to increase all forms of physical activity throughout the day (e.g., leisure sports, gardening, use of stairs as opposed to escalators/elevators, and leisurely walks with friends).

Participants are introduced to the physical activity intervention in a structured way, such that they begin at lighter intensity and gradually increase the intensity over the first 2–3 weeks of the intervention. Walking for exercise is promoted at a moderate intensity. Accordingly, participants are asked to walk at an intensity of 13 on the Borg's scale, corresponding to an activity perception "somewhat hard". Lower extremity strength exercises are performed at an intensity of 15 to 16 for the strength training component of the program ("hard").

The physical activity program is designed to be performed both at the center and at home. During the intervention, participants train at the center twice a week under direct supervision of instructors. The supervised setting allows instructors to better tailor the program to individual needs and abilities, so as to prevent the early dropout and facilitate the building of self-efficacy and support, which are key to maintaining physical activity over the long term. Center-based sessions are supplemented, in a progressive fashion, with home-based exercises as a means of facilitating physical activity in multiple settings, adopting healthier behavior, and promoting long-term adherence.

Based on the previous long-term trials of physical activity in older adults [4, 17–19], the adherence to the physical exercise training in SPRINTT is expected to range between 70 and 80%. As a means of optimizing participant compliance to the intervention, the total amount of physical activity is monitored via actimetry devices which allows the study staff to provide personalized feedback/tips to the participant (see ICT section for details).

Nutritional counseling/dietary intervention The nutritional component of the MCI has been designed to maximize the benefits of physical activity. Indeed, nutrition represents an important and potentially modifiable factor that impacts muscle health and the frailty status of an older person [20, 21]. As such, nutrition is not only involved in the direct assessment of frailty, but may also play a role in the definition of interventions aimed at restoring robustness and contrasting sarcopenia [20, 22, 23]. Notably, the combination of nutritional interventions and physical exercise appears to be the most effective strategy presently available for the management of sarcopenia [20].

For a nutritional intervention to be effective against frailty and sarcopenia, it should: (a) provide an adequate caloric intake; (b) ensure the provision of appropriate nutrients, considering age, sex, health status, physical activity level, and comorbidities; and (c) provide an adequate quantity and quality of nutrients at the right time, that is, when physiologically needed [20, 23].

In SPRINTT, the multifactorial properties of nutrition to support the beneficial effect of physical activity on PF&S is exploited through a combination of nutritional assessment and personalized dietary recommendations. SPRINTT aims to achieve two main predefined nutritional targets: (1) a daily total energy intake of 25–30 kcal/kg body weight [24]; and (2) an average protein daily intake at least in the range of 1.0–1.2 g/kg body weight [25]. These nutritional goals are based on expert recommendations on the topic [24, 25]. Nutritional targets are adjusted according to the participant's current nutritional status and eventual comorbidities that may deserve specific dietary strategies (e.g., severe kidney dysfunction, obesity, diabetes, and cardiovascular disease). Nutritional targets may be achieved through dietary advice, including supplements if deemed necessary [24, 25].

Vitamin D supplementations is recommended to participants in both groups in whom serum levels of 25-hydroxy-vitamin D (25-OH-D) are deficient or insufficient, in accordance with their primary care physician. As recommended by the American Geriatrics Society Consensus Statement on Vitamin D for Prevention of Falls and Their Consequences [26], a serum concentration of 25-OH-D of 30 ng/mL (75 nmol/L) is considered the minimum goal to achieve in SPRINTT participants.

At each study center, a dietician/nutritionist (D/N) trains participants randomized to the MCI group on how to complete a 3-day dietary record. The 3-day dietary record is

collected at baseline and every 12 months and any time the D/N deems it necessary to optimize the dietary intervention. In the case of incomplete data collection or implausible data reported on the diary, the D/N performs a plausibility-check to ensure the accuracy of the information. The macro- and micronutrient composition of the diet is determined locally by the D/N through the use of nutritional software or national dietary databases, consistent with standard clinical practice. This assessment then supports the elaboration of personalized nutritional recommendations by the D/N, in agreement with national and international guidelines. The D/N regularly monitors adherence to dietary prescription, eventually proposing additional in itinere assessments according to clinical needs.

ICT intervention Actimetry data are collected in both intervention groups. Specifically, a 7-day physical activity recording is obtained using the activPAL™ device (PAL Technologies Ltd., Glasgow, UK) within 2 weeks before or after each scheduled clinical visit. At specified timeframes (at baseline and every 6 months) as well as on-demand by the investigators, the study staff monitors adherence to physical activity in the MCI group and uses this information to provide personalized feedback/tips to the participant.

HALE program

Participants allocated to the control group are offered an health educational program. The HALE program arm meets in small groups (approximately 10–20 participants per group), once or twice a month, with required participation at least once per month. The program is based on a workshop series concerning a variety of topics of relevance to older adults (e.g., recommended vaccinations, management of acute and chronic pain, urinary incontinence, constipation, and diarrhea, etc.). As undertaken in the LIFE study [4], the program also includes a short instructor-led routine (5–10 min) of upper extremity stretching exercises or some relaxation techniques that will be performed at the end of each class. The rationale for this "placebo exercise" activity is that it helps foster adherence to this arm of the study and increases the perceived benefit of the HALE workshop series to the participants without directly affecting the major study outcomes.

Establishment of the SPRINTT biobank

Biological samples (i.e., blood and urine) for future assessment of PF&S biomarkers are collected in the early morning, after an 8-h fast at baseline, at the 12-, 24-, and 36-month visits. Biological samples are processed locally according to standardized procedures and stored at −80 °C. At regular intervals, specimens are transferred to the central repository site (University of Göttingen, Göttingen, Germany). The biomarkers to be measured will be selected based on the scientific knowledge at the time of study completion.

Sample size considerations and statistical analysis

Sample size considerations

The primary efficacy endpoint is the time from randomization to the first occurrence of inability to complete the 400-m walk test. The sample size calculation was based on the LIFE study database [4]. Specifically, survival analyses were run according to different baseline levels of SPPB score (<8 vs. ≥ 8) for the primary endpoint. The effect of the physical activity program on mobility disability was negligible in participants with baseline SPPB score ≥ 8 (hazard ratio = 0.94). Conversely, the hazard ratio was clinically and statistically significant in enrollees with baseline SPPB < 8 (hazard ratio = 0.75; 95% CI 0.59–0.94, $p = 0.012$).

In SPRINTT, a total of 434 events are required to provide 85% power to detect a 25% reduction in the hazard of mobility disability using a log-rank test performed at a two-sided alpha level of 5%. To achieve the 434 targeted events, 1200 older persons with baseline SPPB < 8 need to be randomized over a 12-month accrual period, with a maximal follow-up time of 36 months and a common exponential dropout rate of 25% over 24 months.

The inclusion of participants with a baseline SPPB score <8 would decrease the study power and, hence, the probability of success of the trial. On the other hand, restricting the enrolment to older people with SPPB < 8 would limit the aim of characterizing the whole spectrum of PF&S, as operationalized in the SPRINTT project. Hence, a convenience sample of 300 older persons with baseline SPPB 8 or 9 will still be included in the study. An ad hoc hierarchical testing procedure has been formulated to conduct secondary analyses taking advantage of this subgroup of healthier individuals.

Three different plans have been developed, based on recruitment efficiency, incidence of events, and length of follow-up. A blinded sample size reassessment based on the number of events is planned after 11 months from the beginning of recruitment to ensure that 434 events will be reported by the end of study (36 months after the first participant has been enrolled). This *interim* evaluation will allow immediate action to be taken to preserve the study power, in case the efficiency of enrolment or the number of observed events is not consistent with the original assumptions.

Scenario 1 recruitment starts at a rate of 125 participants/month (8 participants/center/month). Based on a log-rank test with a 5% two-sided alpha level, a sample size of 1500 participants (750 per treatment arm; 80% participants with SPPB < 8 and 20% with SPPB ≥8), with a total number of 35 events at 11 months and 43 at 12 months, will provide 83% power to detect a 30% reduction in the hazard rate over 24 months of follow-up (247 events).

Scenario 2 recruitment progresses as outlined above, but the number of events recorded at month 11 is lower than expected. A follow-up extension (up to 36 months) should assure that the study power is preserved (at least 80%) to detect a 30% reduction in the hazard rate with a sample size of 1500 participants. An additional power reassessment may be performed 12 months after the end of recruitment to establish the optimal length of follow-up, based on the number of events recorded thus far.

Scenario 3 recruitment efficiency is suboptimal at the very beginning and increases over time (from 6 to 160 participants/month). The duration of the recruitment will be extended by 6 months and the follow-up of participants enrolled earlier continued beyond 24 months, up to 36 months. A sample size of 1,500 participants will provide 85% power to detect a 30% reduction in the hazard rate of mobility disability, with an expected 281 total number of events at the end of the trial. At the 11-month *interim* evaluation, the number of enrollees is expected to be around 475, with around nine events recorded.

Statistical analysis

Analyses of intervention effects will be based on the intent-to-treat principle. This implies that data from participants allocated to a treatment group will be analyzed as part of that group irrespective of their compliance. First-approach analyses will always be dedicated to the evaluation of the subsample of participants with SPPB < 8 (in agreement with results from the LIFE study [4] and the present sample size calculations). Secondary analyses will subsequently be conducted considering the overall sample of the SPRINTT population including the 300 participants with SPPB ≥ 8. All tests of significance will be two-sided with a maximal type I error risk of 5%.

The primary comparison of intervention groups with respect to the distribution of time until the first post-randomization occurrence of the primary outcome will be based on log-rank stratified by study site and gender. The primary comparison will be conducted only in study participants with baseline SPPB < 8. If this primary analysis is statistically significant (i.e., $p < 0.05$), the comparison will be extended to include the remaining 300 participants with baseline SPPB ≥ 8. An additional binary indicator variable will be introduced denoting a baseline SPPB score <8 or ≥8 and its interaction with the intervention group. Hazard ratios and confidence intervals will be computed for the whole population only if this interaction term can be ignored (i.e., if it is not statistically significant). The hazard ratio between intervention groups and the corresponding confidence interval will be computed using a Cox proportional hazard model with study site and gender as co-variables for comparison in participants with a SPPB score <8 and by adding the SPPB score ≥8 flag and corresponding interaction terms as co-variables for comparison in the whole study population.

The time-to-event is defined as the time from randomization to the date of the first occurrence of mobility disability. Participants who do not meet this criterion will be censored at the time of their last primary outcome evaluation. In secondary analyses, to consider additional covariates, Cox proportional hazard models will be used if the underlying assumptions appear warranted. The proportional hazard assumption will be verified by testing the treatment-by-time interaction in the Cox model.

For the assessment of secondary efficacy endpoints, specific models will be used for continuous outcomes (e.g., physical performance, nutritional status, functional status, cognitive function, mood, and quality of life). Specifically, changes over time between groups will be assessed by repeated-measure mixed models with terms for intervention, time, baseline score, baseline score by intervention interaction, and time-by-intervention interaction. For outcomes, such as incidence of falls and mortality rate, the analysis defined for the primary efficacy outcome will be replicated (except for the secondary analysis with competitive risk for the mortality rate). Additional analyses (e.g., subgroup composite endpoint analyses) will be defined in agreement with the Managing Board (steering committee) and the data safety monitoring board (DSMB), and specified in the statistical analysis plan that will be produced prior to the beginning of the analyses.

Participant's safety

Safety of participants is of the highest priority in SPRINTT. Potential participants are screened to determine whether it is safe for them to participate in the planned interventions. Medical problems that would increase the risk from participation in the study are assessed through structured interviews, physical examinations, and ECG during the initial evaluation, prior to randomization. Participant's safety is monitored on a continuous basis during study assessments. Specific monitoring procedures have been designed to ensure participant's safety during physical activity, both supervised and unsupervised. If a participant presents a medical or surgical illness, the safety of continuing or

resuming participation in interventions is ascertained by the medical staff at the local center in cooperation with the participant's primary care physician. Finally, adverse events are closely tracked to assess their potential relationship to the intervention. The DSMB regularly reviews adverse events and provides recommendations as needed.

Discussion

Given the ongoing demographic transition, healthcare services dedicated to older adults are projected to rapidly expand, substantially impacting public health costs and creating the need for novel preventive strategies. This foreseeable emergency, indeed, requires a strategic plan based upon a sound scientific approach to devise efficient public health interventions and develop preventive strategies for the promotion of successful aging. The SPRINTT project is geared to produce significant advancements in the management of frail elders by promoting a consensus among academia, regulators, industry, and patients' representatives over: (1) a clear operationalization of the presently vague concept of frailty; (2) identification of a precise target population with unmet medical needs; (3) evaluation and validation of a new methodology for implementing preventive and therapeutic strategies among frail elders at risk of disability; (4) definition of an experimental setting serving as a template for regulatory purposes and pharmaceutical investigations; and (5) identification of biomarkers and health technology solutions to be implemented into clinical practice.

Apart from small-scale RCTs, such as the FRAilty Screening and Intervention (FRASI) study [27], and a recently published Dutch trial [28], no intervention studies specifically targeting frail older persons have yet been conducted. In this scenario, SPRINTT represents the first attempt to identify a precise subset of frail elderly with unmet medical needs and implement a MCI aimed at preventing incident mobility disability and other major negative health-related events. The implementation of a preventive MCI program in older persons is particularly useful when dealing with age-related syndromic conditions requires an immediate translation into clinical practice. Indeed, the simultaneous targeting of the multiple and heterogeneous mechanisms underlying the disabling cascade may enhance the intervention effects [29]. Conversely, a mono-dimensional intervention may be insufficient at reversing the complex frailty status. At the same time, MCIs allow the study results to be more easily translated into clinical practice for the overall older population, thus reducing the well-known limited generalization of "evidence-based studies".

It is noteworthy that the MCI that is tested in SPRINTT resembles what is commonly done in usual clinical practice, in which the intervention is designed around the needs and resources of the individual. Such an innovative approach will, therefore, greatly support the development of initiatives, procedures, and therapeutic interventions aimed at modifying and adapting the current clinical practice to the necessities of older persons.

Data collected will allow non-responding participants to be described in the MCI group by identifying variables predictive of poor response to the intervention to characterize the subgroup of participants who might be eligible for additional treatment(s), including drugs. It is also noteworthy that SPRINTT will produce novel and meaningful data on a large sample of "real practice" older adults allowing for the definition of reference values specific to the European population to be used for regulatory and research purposes.

Another major objective of SPRINTT will be the identification and validation of biomarkers that could serve to estimate muscle mass and function and track their changes over time as well as in response to specific interventions. Such biomarkers may greatly enhance the incorporation of PF&S in standard practice and may also serve as useful surrogate endpoints in future RCTs, especially if they turn out to have a causal link to the predicted clinical endpoint.

In summary, SPRINT will provide meaningful data on the newly operationalized PF&S condition. Results from the RCT will allow the validation and eventual implementation of practical therapeutic interventions against PF&S to prevent its clinical consequences (i.e., falls, disability, hospitalization, institutionalization, and death). Finally, the establishment of clear functional and imaging endpoints will pave the way for major investments by relevant stakeholders as well as for future investigations in the field.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study, informed consent is not required.

APPENDIX

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