Multicomponent intervention to prevent mobility disability in frail older adults: randomised controlled trial (SPRINTT project)

Roberto Bernabei,1,2 Francesco Landi,1,2 Riccardo Calvani,1 Matteo Cesari,3,4 Susanna Del Signore,5 Stefan D Anker,6 Raphaël Bejuit,7 Philippe Bordes,7 Antonio Cherubini,8 Alfonso J Cruz-Jentoft,9 Mauro Di Bari,10 Tim Friede,11,12 Carmen Gorostiaga Ayestarán,13 Harmonie Goyeau,7 Pålmi V Jónsson,14 Makoto Kashiwa,15 Fabrizia Lattanzio,8 Marcello Maggio,16,17 Luca Mariotti,18 Ram R Miller,18 Leocadio Rodriguez-Mañas,19 Regina Roller-Wiinbergser,20 Ingrid Rýznarová,21 Joachim Scholpp,22 Annemie M W J Schols,23 Cornel C Sieber,24 Alan J Sinclair,25 Anna Skalska,26 Timo Strandberg,27,28 Achille Tchalla,29 Eva Topinková,30 Matteo Tosato,1 Bruno Vellas,31 Stephan von Haehling,12,32 Marco Pahor,33 Ronenn Roubenoff,34 Emanuele Marzetti,1,2 on behalf of the SPRINTT consortium

For numbered affiliations see end of the article

Correspondence to: E Marzetti
Centre for Geriatric Medicine (CeMI), Fondazione Policlinico Universitario “Agostino Gemelli” IRCCS, Università Cattolica del Sacro Cuore, Rome, 00168, Italy emanuele.marzetti@policlinicogemelli.it (or @Emanuele00962649 on Twitter;
ORCID 0000-0001-9567-6983)

Additional material is published online only. To view please visit the journal online.

Cite this as: BMJ 2022;377:e068788
http://dx.doi.org/10.1136/bmj-2021-068788
Accepted: 22 March 2022

ABSTRACT

OBJECTIVE
To determine whether a multicomponent intervention based on physical activity with technological support and nutritional counselling prevents mobility disability in older adults with physical frailty and sarcopenia.

DESIGN
Evaluator blinded, randomised controlled trial.

SETTING
16 clinical sites across 11 European countries, January 2016 to 31 October 2019.

PARTICIPANTS
1519 community dwelling men and women aged 70 years or older with physical frailty and sarcopenia, operationalised as the co-occurrence of low functional status, defined as a short physical performance battery (SPPB) score of 3 to 9, low appendicular lean mass, and ability to independently walk 400 m. 760 participants were randomised to a multicomponent intervention and 759 received education on healthy ageing (controls).

INTERVENTIONS
The multicomponent intervention comprised moderate intensity physical activity twice weekly at a centre and up to four times weekly at home. Actimetry data were used to tailor the intervention. Participants also received personalised nutritional counselling. Control participants received education on healthy ageing once a month. Interventions and follow-up lasted for up to 36 months.

MAIN OUTCOME MEASURES
The primary outcome was mobility disability (inability to independently walk 400 m in <15 minutes). Persistent mobility disability (inability to walk 400 m on two consecutive occasions) and changes from baseline to 24 and 36 months in physical performance, muscle strength, and appendicular lean mass were analysed as pre-planned secondary outcomes. Primary comparisons were conducted in participants with baseline SPPB scores of 3-7 (n=1205). Those with SPPB scores of 8 or 9 (n=314) were analysed separately for exploratory purposes.

RESULTS
Mean age of the 1519 participants (1088 women) was 78.9 (standard deviation 5.8) years. The average follow-up was 26.4 (SD 9.5) months. Among participants with SPPB scores of 3-7, mobility disability occurred in 283/605 (46.8%) assigned to the multicomponent intervention and 316/600 (52.7%) controls (hazard ratio 0.78, 95% confidence interval 0.67 to 0.92; P=0.005). Persistent mobility disability occurred in 127/605 (21.0%) participants assigned to the multicomponent intervention and 150/600 (25.0%) controls (0.79, 0.62 to 1.01; P=0.06). The between group difference in SPPB score was 0.8 points (95% confidence interval 0.5 to 1.1 points; P=0.001) and 1.0 point (95% confidence interval 0.5 to 1.6 points; P=0.001) in favour of the multicomponent intervention at 24 and 36 months, respectively. The decline in handgrip strength at 24 months was smaller in women assigned to the multicomponent intervention than to control (0.9 kg, 95% confidence interval 0.1 to 1.6 kg; P=0.028). Women in the multicomponent intervention arm lost 0.24 kg and 0.49 kg less appendicular lean mass than controls at 24 months (95% confidence interval 0.10 to 0.39 kg; P=0.001) and 36 months (0.26 to 0.73 kg; P=0.001), respectively. Serious adverse events occurred in 237/605 (39.2%) participants assigned

What is already known on this topic

Mobility is a primary target to maintain function and foster active ageing
Lifestyle interventions (eg, physical activity alone or with nutritional counselling/supplementation) are feasible, safe, and effective for improving physical function in older adults at risk of mobility disability
The identification of a condition encompassing reduced physical function and target organ damage (ie, muscle failure) might stimulate the development of preventive interventions against disability in older people who are at risk

What this study adds

Physical frailty and sarcopenia is a novel, objectively measurable condition that identifies a subset of the older population at risk of adverse health related events, including mobility disability, whose medical needs are currently unmet
A multicomponent intervention based on moderate intensity physical activity with technological support and nutritional counselling was associated with a reduction in the incidence of mobility disability over 36 months of follow-up in older adults with physical frailty and sarcopenia

the bmj | BMJ 2022;377:e068788 | doi: 10.1136/bmj-2021-068788
to the multicomponent intervention and 216/600 (36.0%) controls (risk ratio 1.09, 95% confidence interval 0.94 to 1.26). In participants with SPPB scores of 8 or 9, mobility disability occurred in 46/155 (29.7%) in the multicomponent intervention and 38/159 (23.9%) controls (hazard ratio 1.25, 95% confidence interval 0.97 to 1.61; P=0.14).

CONCLUSIONS
A multicomponent intervention was associated with a reduction in the incidence of mobility disability in older adults with physical frailty and sarcopenia and SPPB scores of 3-7. Physical frailty and sarcopenia may be targeted to preserve mobility in vulnerable older people.

TRIAL REGISTRATION
ClinicalTrials.gov NCT02582138.

Methods
Study design
The SPRINTT trial was a multicentre randomised controlled trial conducted from January 2016 to 31 October 2019 at 16 sites across 11 European countries. The European Medicines Agency accepted the trial methodology and analytical strategy during an ad hoc scientific advice procedure that was completed in early 2015. A summary description of the protocol is available on ClinicalTrials.gov (NCT02582138). Details were provided in a dedicated publication and are included in the supplementary appendix. The Università Cattolica del Sacro Cuore in Rome, Italy, coordinated trial activities. Trial sites are listed in the supplementary appendix. As part of the Innovative Medicines Initiative Joint Undertaking of the EU (www.imi.europa.eu), member companies of the European Federation of Pharmaceutical Industries and Associations gave in-kind support. The academic members provided an independent interpretation of results. An independent statistician replicated and verified the analyses.

Participants
Participants were men and women aged 70 years or older with physical frailty and sarcopenia, defined as having a short physical performance battery (SPPB) score of 3 to 9 points (scores range from 0 to 12, with lower scores indicating poorer physical function), low appendicular lean mass according to sex-specific cut-points recommended by the Foundation for the National Institutes of Health sarcopenia project, and the absence of mobility disability, operationalised as being able to complete a 400 m walk test in less than 15 minutes without sitting, stopping for more than one minute, receiving help, or using a walker.

This operational definition of physical frailty and sarcopenia was discussed and agreed with EMA. Main exclusion criteria were self-reported walking speed less than one minute, receiving help, or using a walker. This operational definition of physical frailty and sarcopenia was discussed and agreed with EMA. Main exclusion criteria were self-reported walking speed less than one minute, receiving help, or using a walker.

Interventions
The multicomponent intervention and the healthy ageing lifestyle educational programme are extensively described elsewhere. Both interventions were administered for up to 36 months, depending on when participants were recruited during the trial. The multicomponent intervention comprised a combination of moderate intensity physical activity with technological support and nutritional counselling. Physical activity included aerobic, strength, flexibility, and balance exercises. The intervention was divided into an adoption phase (weeks 1-52) and maintenance phase (week 53 to end of the trial). During the adoption phase, two centre based physical activity sessions were conducted weekly. These sessions were

doi: 10.1136/bmj-2021-068788 | BMJ 2022;377:e068788 | the bmj
used to initiate the aerobic programme and safely introduce participants to the strength, stretching, and balance components. Centre based sessions were progressively supplemented by home based physical activity sessions: once weekly during weeks 1-4, twice weekly during weeks 4-8, and up to four times weekly during weeks 9-52. The maintenance phase involved two centre based physical activity sessions and up to four home based sessions weekly. Training intensity was adapted through assessment of perceived exertion by the Borg scale (ratings range from 6 to 20, with 6 representing no exertion at all and 20 representing maximal exertion). Participants were asked to walk at an intensity of 13 (somewhat hard). Lower extremity strengthening exercises were performed at an intensity of 15 or 16 (hard). Adherence was ascertained by registering centre attendance and participant completed diaries on frequency of home based sessions. The total amount of physical activity was monitored for seven consecutive days at baseline and every six months using the activPAL3 actimeter (PAL Technologies, Glasgow, UK) worn on the thigh. Instructors could request additional seven day actimetry recordings anytime if indications suggested participants were not complying with physical activity prescriptions. Instructors used the information to provide participants with personalised feedbacks on their performance goals to be reached as part of behavioural strategies to maximise adherence and remove possible disincentives. The nutritional component was designed to support the effects of the physical activity programme. The intervention involved individualised nutritional assessments and prescription of personalised dietary plans with two main targets: a daily energy intake of 25-30 kcal/kg bodyweight and a daily protein intake of at least 1.0-1.2 g/kg bodyweight. A three day dietary record was collected at least once a year, followed by an individualised dietary interview. Adherence to nutritional prescriptions was ascertained through regular contacts with study staff during which participant feedback was collected and dietary plans reviewed. Additional dietary assessments could be performed at the discretion of the interventionist to maximise adherence.

The healthy ageing lifestyle educational programme consisted of seminars and workshops on topics relevant to older adults (eg, vaccinations, chronic pain management, gastrointestinal and urological problems, technological devices, personal safety). Meetings were offered in groups of 10-20 participants once or twice a month, with required participation of at least once a month. A short instructor led programme (5-10 minutes) of upper extremity stretching exercises or some relaxation techniques was offered at the end of each meeting.

Outcomes
The primary outcome was mobility disability, operationalised as the inability to complete the 400 m walk test in less than 15 minutes without sitting, stopping for more than one minute, requiring help, or using a walker. For the test, participants were asked to complete 10 laps around a 20 m course at their usual pace without overexerting themselves. The 400 m walk test was administered after three months of randomisation and every six months from baseline.

If the 400 m walk test was not performed, a stepwise procedure was devised for outcome adjudication. A predefined algorithm was applied to automatically adjudicate mobility disability based on a 4 m gait speed ≤0.4 m/s or >0.4 m/s if participants needed a walking aid other than a single straight cane, medical records, or self-reported or proxy reported walking disability. Those participants who did not perform the 400 m walk test and could not be automatically adjudicated were evaluated by an independent committee based on clinical variables, functional tests, and adverse events.

Participants were censored at their last successful 400 m walk test if the mobility disability criterion was not met at the end of the trial, at their first consecutive visit when more than nine months had elapsed between two consecutive successful tests, or at the date of the randomisation visit when no post-baseline 400 m walk test was available. Mobility disability was considered to be present at the date participants failed the 400 m walk test, were unable to attempt the test, did not attempt the test and were classified as mobility disabled through the adjudication process, did not attempt the test and mobility disability could not be adjudicated, or died.

The SPRINTT trial includes several prespecified secondary outcomes (supplementary appendix). Here we report the secondary outcomes of persistent mobility disability, operationalised as failure to complete the 400 m walk test on two consecutive occasions or inability to complete the test followed by death, and changes from baseline to 24 and 36 months in measures of physical performance, muscle strength, and appendicular lean mass.

Sample size calculation
The size of the study population was determined to address the main requirements of the Innovative Medicines Initiative Joint Undertaking to evaluate whether a multicomponent intervention would reduce the risk of incident mobility disability in older adults with physical frailty and sarcopenia, and to characterise the physical frailty and sarcopenia condition and obtain information on intervention effects across its whole SPPB range (scores 3-9). To meet the first requirement, we performed a sample size estimation based on information retrieved from the Lifestyle Interventions and Independence for Elders (LIFE) study database by running survival analyses for mobility disability according to different baseline SPPB score categories (<8 v 8 or 9). In LIFE, the hazard of incident mobility disability was observed to be significantly reduced by physical activity only in participants with SPPB scores <8 (hazard ratio 0.75, 95% confidence interval 0.59 to 0.94; P=0.012). We therefore estimated that a sample of 1200 older
people with an SPPB score of 3 to 7, enrolled over 12 months, would provide 85% power (434 mobility disability events) to detect a 25% reduction in the hazard of mobility disability over a maximum follow-up of 36 months, considering a dropout rate of 25% over two years and a log-rank test with a 5% two-sided \( \alpha \) level.\(^7\) To address the second objective, we chose to enrol an exploratory sample of 300 participants with low appendicular lean mass and an SPPB score of 8 or 9.\(^8\) The size of this subsample was determined based on feasibility and resource availability. A hierarchical testing procedure was devised to control type I error rate by testing the primary endpoint in the whole study population only in case of a significant result (P<0.05) in participants with SPPB scores of 3 to 7.\(^9\)

Based on a blinded interim sample size reassessment at 11 months, we prolonged the accrual period by six months. A second blinded power reassessment at 29 months revealed a number of mobility disability events that were lower than expected. We extended the follow-up by seven months to maximise the probability of reaching the required number of events and to allow participants recruited during the last phase of accrual to receive intervention and be followed-up for 24 months. The maximum length of interventions and follow-up was kept at 36 months.

**Randomisation and blinding**

Eligible participants were invited to the study sites for an in-person meeting, during which trial procedures and requirements were mentioned again. Participants were then randomised 1:1 to the multicomponent intervention or lifestyle education using a web based randomisation system with permuted block algorithm, stratified by study site, sex, and SPPB score category (3-7 and 8 or 9). An evaluator blinded approach was used to preserve the trial integrity. Accordingly, outcome assessors were unaware of group assignment, clinic and laboratory measurements, and intervention adherence.

**Safety**

All study staff monitored participant safety and reported three categories of adverse events: serious adverse events, unexpected adverse events (those potentially related to study procedures or activities and not listed in the informed consent form or study protocol), and adverse events that occurred while the participant was under the supervision or guidance of study staff either onsite or offsite. Some adverse events were further flagged as of special interest if falling into prespecified categories (ie, abnormal test results requiring medical attention, emergency department visits, fractures, outpatient surgery, and restricted activity possibly due to study procedures). An independent committee reviewed safety data once a year.

**Statistical analysis**

All analyses were performed according to a predefined statistical analysis plan (supplementary appendix). Baseline characteristics of participants allocated in the two intervention arms are described as means (standard deviations) for continuous variables and absolute numbers (percentages) for categorical variables. Analyses of intervention effects were based on the intention-to-treat principle. For the analysis of the primary efficacy endpoint (time to the first occurrence of mobility disability or death from any cause) we compared intervention arms using a two sided 5% \( \alpha \) level log-rank test procedure stratified by randomisation factors of site and sex. The primary comparison was conducted in randomised participants with baseline SPPB scores of 3 to 7. We used a Cox proportional hazard model stratified by randomisation factors of site and sex to estimate the hazard ratio of mobility disability between intervention groups and the corresponding 95% confidence interval. The Kaplan-Meier method was used to summarise cumulative incidence functions. If the findings of this primary analysis were statistically significant (P<0.05), we would perform an additional analysis to include the exploratory group of participants with SPPB scores of 8 or 9 only if no interaction was observed between SPPB category and intervention arm. We used the Kaplan-Meier method to compare the cumulative incidence functions for the two intervention arms between the two SPPB categories. Prespecified subgroup analyses based on Cox proportional hazard models were conducted to determine whether intervention effects were influenced by baseline personal, clinical, or functional characteristics.

We analysed secondary efficacy endpoints in the two SPPB categories separately. A Cox proportional hazard model stratified by randomisation factors of site and sex was used to estimate the hazard ratio of persistent mobility disability between intervention groups and the corresponding 95% confidence interval. Changes from baseline to 24 and 36 months in SPPB score, handgrip strength, and appendicular lean mass were analysed by mixed effect models with repeated measures. Models included the fixed categorical effects of intervention arm, the planned time point, the randomisation factors of site and sex, the intervention×time point interaction, and the continuous fixed covariates of baseline value and baseline value×time point interaction. For all analyses, a two sided P<0.05 was considered to be statistically significant.

We analysed safety data by intervention group in the two SPPB categories separately. Risk ratio with 95% confidence interval was used to estimate the probability of experiencing an adverse event.

All analyses were run using SAS version 9.4 (Cary, NC).

**Patient and public involvement**

A dialogue and knowledge platform was established at the beginning of the project through the mapping of stakeholders (older adults’ representatives, healthcare professionals, and experts in bioethics, data security, privacy, storage and use, and bioinformatics), and
their invitation to conference calls and in-person meetings focused on the operational definition of physical frailty and sarcopenia, treatment protocols, strategies for participant recruitment and engagement, health literacy plans, and dissemination activities. The platform was subsequently extended to include regulatory experts from the EU to reach a consensus on the definition of the target population and trial methodology. After trial commencement, quarterly teleconferences were held with EMA to discuss progress of the project, emerging problems, safety aspects, and other relevant events in the trial.

Educational contents were produced for older people and their caregivers. In particular, to promote health literacy on the topics of frailty and sarcopenia, we developed leaflets that were freely downloadable from the project website.

Participants were actively involved in recruitment by advertising the trial among their peers. In addition, the dialogue and knowledge platform provided recommendations on strategies to reach out to the target population and maximise participant engagement in the trial activities. Participants were regularly asked to provide feedback on the intervention burden and other issues that might affect their motivation to participate in the trial. Local study staff evaluated the information collected and forwarded it to the coordinating centre in Rome for further evaluation with assistance of the dialogue and knowledge platform. No corrective actions were required.

**Results**

**Participants**

Participants were recruited from January 2016 to November 2017. Randomisation began on 3 February 2016 and enrolment finished on 15 November 2017. The final follow-up visit was on 31 October 2019. Details on screening, recruitment strategies, and characteristics of eligible participants are reported elsewhere. Of 12358 screened candidates, 1519 were eligible and agreed to be randomised: 760 to the multicomponent intervention group and 39/759 (5.1%) in the lifestyle education group. In participants with an SPPB score of 3 to 7, during the first two years of the trial (supplementary appendix, fig S1). Differences in actimetry data between intervention groups were no longer evident 24 months after randomisation, when the number of observations was substantially lower. Overall, 78.6% of participants completed full nutritional assessments, including dietary records over three days. Relative to baseline daily energy intake (23.3 SD 7.4 kcal/kg/day), values increased by 6.8% at 24 months (24.1 (SD 7.1) kcal/kg/day) and 10.7% at 36 months (26.1 (SD 7.5) kcal/kg/day). A similar pattern was observed for daily protein intake, the values of which increased from baseline (0.98 (SD 0.32) g/kg/day) by 10.9% at 24 months (1.10 (SD 0.32) g/kg/day) and by 14.8% at 36 months (1.15 (SD 0.32) g/kg/day).

Participants in the lifestyle education group attended on average 65.9% (SD 26.4%) of scheduled meetings, after medical leave and other circumstances that prevented participation had been excluded. A mean of 7.9 meetings were excluded.

**Primary outcome**

Post-baseline 400 m walk tests were unavailable for 36/760 (4.7%) participants in the multicomponent intervention group and 39/759 (5.1%) in the lifestyle education group. In participants with an SPPB score of 3 to 7, mobility disability occurred in 283/605 (46.8%) in the multicomponent intervention group (six deaths, 1.0%) and 316/600 (52.7%) in the lifestyle education group (seven deaths, 1.2%) (hazard ratio 0.78, 95% confidence interval 0.67 to 0.92; P=0.005) (fig 2). Results were consistent when death was removed from the primary outcome (0.79, 0.67 to 0.93; P=0.006).

As a qualitative interaction between SPPB category and intervention arm was found when the cumulative event curves for participants with SPPB scores of 3-7 and a score of 8 or 9 were compared, we analysed those with an SPPB score of 8 or 9 separately. In this subset, mobility disability occurred in 46/155 (29.7%) participants in the multicomponent intervention group (three deaths, 1.9%) and 38/159 (23.9%) in the lifestyle education group (two deaths, 1.3%) (hazard ratio 1.25, 95% confidence interval 0.79 to 1.95; P=0.34) (supplementary appendix, fig S2). Subgroup analyses in participants with an SPPB score of 3 to 7 showed that the effects of interventions on incident mobility disability were comparable across sexes.
Fig 1 | Flow of participants through study. *Sum of individual items is higher than number of ineligible participants because screening was not always stopped at the first unmet eligibility criterion. Some entries are different from those previously published8 because of data updates after database cleaning. DEXA=dual energy x ray absorptiometry; SPPB=short physical performance battery; SPRINTT=Sarcopenia and Physical Frailty in older people: multi-component Treatment strategies

Races, age groups, history of cardiovascular disease, history of diabetes, and 4 m gait speed <0.8 m/s or ≥0.8 m/s (fig 3). The gait speed cut-point was chosen based on previous findings, which showed that a walking speed at usual pace slower than 0.8 m/s identifies older adults at risk of adverse outcomes.2 18

Secondary outcomes
Table 2 and table 3 show the results for secondary outcomes. In participants with an SPPB score of 3 to 7, persistent mobility disability occurred in 127/605 (21.0%) in the multicomponent intervention group (seven deaths, 1.2%) and 150/600 (25.0%) in the lifestyle education group (four deaths, 0.7%) (hazard ratio 0.79, 95% confidence interval 0.62 to 1.01; P=0.06). The SPPB score increased more in the multicomponent intervention group than lifestyle education group at both 24 months (least squares mean difference 0.8 points, 95% confidence interval 0.5 to 1.1 points; P<0.001) and 36 months (1.0 point, 0.5 to
### Table 1 | Baseline characteristics of study participants according to short physical performance battery (SPPB) score category and group allocation. Values are number (percentages) unless stated otherwise

| Characteristics | SPPB score 3-7 | SPPB score 8 or 9 |
|----------------|---------------|------------------|
|                | Multicomponent intervention (n=605) | Lifestyle education (n=600) | All (n=1205) | Multicomponent intervention (n=155) | Lifestyle education (n=159) | All (n=314) |
| **Personal characteristics** | | | | | | |
| Mean (SD) age (years) | 79.3 (5.9) | 79.2 (5.8) | 79.2 (5.8) | 78.3 (5.7) | 77.1 (5.4) | 77.7 (5.6) |
| Women | 434 (71.7) | 425 (70.8) | 859 (71.3) | 113 (72.9) | 116 (73.0) | 229 (72.9) |
| **Ethnicity** | | | | | | |
| White | 535 (88.4) | 526 (87.7) | 1061 (88.0) | 136 (87.7) | 138 (86.8) | 274 (87.3) |
| Others | 7 (1.2) | 8 (1.3) | 15 (1.2) | 3 (1.9) | 2 (1.3) | 5 (1.6) |
| Not available | 63 (10.4) | 66 (11.0) | 129 (10.7) | 16 (10.3) | 19 (11.9) | 35 (11.1) |
| **BMI** | | | | | | |
| Mean (SD) BMI | 28.7 (5.4) | 28.7 (5.9) | 28.7 (5.7) | 28.2 (5.6) | 28.3 (6.1) | 28.2 (5.9) |
| **Physical frailty and sarcopenia defining criteria** | | | | | | |
| Mean (SD) SPPB summary score | 6.2 (1.1) | 6.2 (1.1) | 6.2 (1.1) | 8.6 (0.5) | 8.6 (0.5) | 8.6 (0.5) |
| Men | 20.94 (3.55) | 20.88 (3.52) | 20.91 (3.53) | 21.18 (3.17) | 22.06 (3.99) | 21.62 (3.61) |
| Women | 14.61 (2.00) | 14.74 (2.20) | 14.68 (2.10) | 14.54 (1.85) | 14.47 (1.85) | 14.50 (1.93) |
| **Mean (SD) appendicular lean mass (kg):** | | | | | | |
| Men | 0.72 (0.08) | 0.72 (0.07) | 0.72 (0.07) | 0.74 (0.09) | 0.72 (0.07) | 0.73 (0.08) |
| Women | 0.52 (0.07) | 0.52 (0.07) | 0.52 (0.07) | 0.54 (0.08) | 0.54 (0.08) | 0.54 (0.08) |
| **Clinical characteristics** | | | | | | |
| Osteoarthritis | 466 (77.0) | 463 (77.2) | 929 (77.1) | 122 (87.7) | 117 (73.6) | 239 (76.1) |
| Any cardiovascular medical history | 443 (73.2) | 423 (70.5) | 866 (71.9) | 114 (73.5) | 100 (62.9) | 214 (68.2) |
| Hypertension | 413 (68.3) | 392 (65.3) | 805 (66.8) | 105 (67.7) | 91 (57.2) | 196 (62.4) |
| Myocardial infarction | 46 (7.6) | 50 (8.3) | 96 (8.0) | 16 (10.3) | 16 (10.1) | 32 (10.2) |
| Congestive heart failure | 42 (6.9) | 45 (7.5) | 87 (7.2) | 4 (2.6) | 9 (5.7) | 13 (4.1) |
| Chronic lung disease | 99 (16.4) | 88 (14.7) | 187 (15.5) | 20 (12.9) | 26 (16.4) | 46 (14.6) |
| Stroke or brain haemorrhage | 46 (7.6) | 41 (6.8) | 87 (7.2) | 8 (5.2) | 6 (3.8) | 14 (4.5) |
| Diabetes mellitus | 131 (21.7) | 139 (23.2) | 270 (22.4) | 26 (16.8) | 30 (18.9) | 56 (17.8) |
| Cancer (excluding minor skin cancer) | 79 (13.1) | 82 (13.7) | 161 (13.4) | 25 (16.3) | 25 (15.7) | 50 (15.9) |
| Falls in past year | 28 (4.5) | 27 (4.5) | 55 (4.5) | 62 (40.0) | 62 (39.0) | 124 (39.5) |
| Injuries in past year | 102 (35.9) | 86 (31.9) | 188 (33.9) | 25 (41.0) | 20 (32.3) | 45 (36.6) |
| Previous hip fracture | 35 (5.8) | 34 (5.7) | 69 (5.7) | 12 (7.7) | 10 (6.3) | 22 (7.0) |
| Previous non-femoral fracture | 198 (32.7) | 191 (31.8) | 389 (32.3) | 48 (31.0) | 53 (33.3) | 101 (32.2) |
| Emotional, nervous, psychiatric problems | 130 (21.5) | 128 (21.3) | 258 (21.4) | 39 (25.2) | 40 (25.2) | 79 (25.2) |
| At least one drug at time of screening | 578 (95.5) | 578 (96.3) | 1156 (95.9) | 147 (94.8) | 150 (94.3) | 297 (94.6) |
| ±5 drugs at time of screening | 358 (59.2) | 340 (56.7) | 698 (57.9) | 76 (49.0) | 80 (50.3) | 156 (49.7) |

**BMI** = body mass index; **MMSE** = mini-mental state examination.

1.6 points; P<0.001). The decline in handgrip strength at 24 months was smaller in women assigned to the multicomponent intervention than those assigned to lifestyle education (0.9 kg, 95% confidence interval 0.1 to 1.6 kg; P=0.028). No significant between group differences were observed in men. Women in the multicomponent intervention group lost less appendicular lean mass than women in the lifestyle education group at both time points (24 months 0.2 kg, 0.10 to 0.39 kg; P<0.001; 36 months 0.49 kg, 0.26 to 0.73 kg; P<0.001). No significant between group differences were observed in men.

In participants with an SPPB score of 8 or 9, persistent mobility disability occurred in 16/155 (10.3%) in the multicomponent intervention group (one death, 0.6%) and 16/159 (10.1%) in the lifestyle education group (one death, 0.6%) (hazard ratio 1.14, 95% confidence interval 0.55 to 2.36; P=0.72). A 0.5 point difference in the SPPB score in favour of the multicomponent intervention was observed at 24 months (95% confidence interval 0.1 to 1.0 points; P=0.027). No significant between group differences were observed for handgrip strength at any time point in either men or women. At 36 months, women in the multicomponent intervention lost less appendicular lean mass than women in the lifestyle education group (0.60 kg, 95% confidence interval 0.30 to 0.90; P<0.001).

**Safety**

Table 4 shows the results for safety. In participants with an SPPB score of 3 to 7, 337/605 (55.7%) in the multicomponent intervention group and 297/600 (49.5%) in the lifestyle education group experienced at least one adverse event during the trial (risk ratio 1.13, 95% confidence interval 1.01 to 1.25). Serious adverse
In the SPRINTT trial, an intervention based on physical activity with technological support and nutritional counselling in participants with physical frailty and sarcopenia and an SPPB score of 3 to 7 was associated with a reduction in the risk of incident mobility disability during 36 months of follow-up, compared with an intervention comprising lifestyle education. Participants with an SPPB score of 3 to 7 assigned to the multicomponent intervention showed greater improvements in physical performance than participants assigned to lifestyle education. Women with an SPPB score of 3 to 7 in the multicomponent intervention group lost less muscle strength and appendicular lean mass than women in the lifestyle education group. In participants with an SPPB score of 8 or 9, the multicomponent intervention did not affect the risk of developing mobility disability, had marginal effects on physical performance, and, in women, attenuated the loss of appendicular lean mass.

**Comparison with previous studies**

Several investigations have tested the impact of lifestyle interventions on frailty, disability, and other health outcomes in community dwelling older adults. In LIFE, a physical activity intervention was associated with a reduction in the risk of mobility disability over 2.6 years of follow-up compared with a health education programme in 1635 older adults with an SPPB score of ≤9. In participants with an SPPB score of <8 (731, 44.7%), mobility disability developed in 38.2% of those in the physical activity intervention group and 46.8% in the control group. In participants with an SPPB score of 8 or 9, mobility disability occurred in 1.62, 1.16 to 2.27. Deaths occurred in 31/605 (5.1%) participants in the multicomponent intervention group and 25/600 (4.2%) in the lifestyle education group (1.23, 0.74 to 2.06).

In participants with an SPPB score of 8 or 9, 79/155 (51.0%) in the multicomponent intervention group and 79/159 (49.7%) in the lifestyle education group experienced at least one adverse event during the trial (1.03, 0.82 to 1.28). Serious adverse events occurred in 45/155 (29.0%) participants in the multicomponent intervention group and 48/159 (30.2%) in the lifestyle education group (0.96, 0.68 to 1.35). Falls were recorded in 9/155 (5.8%) participants in the multicomponent intervention group and 16/159 (10.1%) in the lifestyle education group (0.58, 0.26 to 1.27). Deaths occurred in 5/155 (3.2%) participants in the multicomponent intervention group and 3/159 (1.9%) in the lifestyle education group (1.71, 0.42 to 7.03).

The proportion of participants who were admitted to hospital or to the emergency department was comparable between intervention groups within SPPB categories. Reasons for hospital admission and emergency department or urgent care visits were highly heterogeneous and were considered unrelated to study procedures.

**Discussion**

In the SPRINTT trial, an intervention based on physical activity with technological support and nutritional counselling in participants with physical frailty and sarcopenia and an SPPB score of 3 to 7 was associated with a reduction in the risk of incident mobility disability during 36 months of follow-up, compared with an intervention comprising lifestyle education. Participants with an SPPB score of 3 to 7 assigned to the multicomponent intervention showed greater improvements in physical performance than participants assigned to lifestyle education. Women with an SPPB score of 3 to 7 in the multicomponent intervention group lost less muscle strength and appendicular lean mass than women in the lifestyle education group. In participants with an SPPB score of 8 or 9, the multicomponent intervention did not affect the risk of developing mobility disability, had marginal effects on physical performance, and, in women, attenuated the loss of appendicular lean mass.

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The proportion of participants who were admitted to hospital or to the emergency department was comparable between intervention groups within SPPB categories. Reasons for hospital admission and emergency department or urgent care visits were highly heterogeneous and were considered unrelated to study procedures.
23.9% of those in the physical activity intervention group and 25.7% in the control group. In SPRINTT, the proportion of participants with an SPPB score of 3 to 7 who experienced mobility disability was 46.8% (283/605) in the multicomponent intervention group (45.8% excluding deaths) and 52.7% (316/600) in the lifestyle education group (51.5% excluding deaths). In those with an SPPB score of 8 or 9, incident mobility disability occurred in 29.7% of participants (46/155) in the multicomponent intervention group and 23.9% (38/159) in the control group. These findings suggest that in older adults with an SPPB score of <8 the presence of reduced appendicular lean mass might identify a subset of mobility limited adults at especially high risk of disability. This observation might also explain why the effect size of the multicomponent intervention was lower than expected (22% v 25%). The estimation was based on the results of LIFE, in which only a portion of participants presumably had low appendicular lean mass. In the exploratory sample of older adults with moderate reduction in physical function, the primary outcome was observed more frequently in those assigned to the multicomponent intervention than those assigned to lifestyle education. This finding is unexpected and in contrast with results from LIFE; owing to insufficient power and wide confidence intervals, however, no meaningful interpretations can be provided.

Participants with an SPPB score of 3 to 7 assigned to the multicomponent intervention had a 2 point higher score at 36 months relative to baseline. The SPPB score in those in the lifestyle education group had increased by 1 point at 36 months. A 0.5 point increase in SPPB score was observed at 36 months in participants with an SPPB score of 8 or 9, regardless of group allocation. The improvement experienced by participants with an SPPB score of 3 to 7 equals or exceeds clinically meaningful changes of the test (1.0-1.5 points). The between group difference in SPPB score in favour of the multicomponent intervention (0.8 points at 24 months and 1.0 point at 36 months) is consistent with previous studies that tested lifestyle interventions in frail older people.

The multicomponent intervention showed a positive effect on appendicular lean mass in women, irrespective of SPPB category. Studies have shown that sex influences body composition changes in response to exercise in old age, with women experiencing greater benefits than men. In addition, sex specific associations between protein intake and longitudinal changes in appendicular lean mass have been described in older people.

### Strengths and limitations of this study

The SPRINTT trial has several strengths. The physical frailty and sarcopenia construct, albeit original, relies on validated tests and assessments. SPPB is a comprehensive test that captures limitations in lower extremity function. For its validity, sensitivity to changes, reproducibility, feasibility, and predictive value for disability and mortality across healthcare settings, the EMA indicated SPPB as the preferred option to characterise physical frailty for intervention trials in older adults. Indeed, changes in SPPB scores are increasingly used as key efficacy endpoints in clinical trials on sarcopenia, physical frailty, and other age related conditions. The presence of low appendicular lean mass was determined according to the cut-points recommended by the Foundation for the National Institutes of Health as the best predictors of mobility disability. Study participants were followed for up to 36 months, confirming the feasibility of identifying, enrolling, and retaining frail older adults on a large scale. Finally, the multicomponent intervention proved to be feasible, safe, and effective in a highly vulnerable population. The risk of adverse events was, however,
greater among participants with a baseline SPPB score of 3 to 7 assigned to the multicomponent intervention than those assigned to lifestyle education (table 4). A similar finding was reported in LIFE17 and in the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability trial,32 and is consistent with the results of a recent systematic review and meta-analysis of clinical trials on exercise interventions.37 Participants in the multicomponent intervention had more frequent contacts with study staff, potentially resulting in a higher rate of adverse event recognition and reporting. The incidence of serious adverse events was, however, comparable between the intervention groups.

SPRINTT has limitations. Almost all participants were white, which impedes generalising findings to other ethnic groups. Older adults with important cognitive deficits were not included in the trial. Owing to the need for frequent in-person contacts, most participants resided within a short distance of the study sites. Therefore, they might not be fully representative of people from the community or those living in rural areas. Differences between intervention groups in the frequency of interactions with their peers and the study staff could have influenced outcomes. The composite nature of the multicomponent intervention does not allow the relative contribution of its individual components to the overall effect to be established. However, previous studies have shown that physical activity conveys most functional benefits of multidomain interventions in frail older adults.38 The confidence interval of the primary outcome analysis was wide, which is consistent with major trials on lifestyle interventions in frail older adults.37 22 24 25 32 This might be explained—at least partly—by the heterogeneity of frail older people and might reflect various degrees of responsiveness to interventions.39 Finally, although outcome assessors were blinded to group assignment, it was not possible to blind participants to their intervention allocation.

### Unanswered questions and future research

The multicomponent intervention showed no effect on mortality or other major outcomes, such as risk of severe illnesses and admission to hospital. The trial design does not allow inference about whether this was due to the duration of the intervention or its characteristics. Future, ad hoc designed studies are warranted to establish whether interventions involving physical activity and nutritional counselling improve survival and overall health in vulnerable older adults. Although regular physical activity might be beneficial for preventing falls and fall related fractures in older people,40 rates of falls were greater in participants with SPPB scores of 3 to 7 in the multicomponent intervention group than in participants in the lifestyle education group (table 4). These findings are in line with those of LIFE17 41 and suggest that the SPRINTT training programme may not be adequate for preventing falls in frail older adults. Physical activity routines mostly based on walking, such as those tested in SPRINTT and LIFE, may paradoxically expose participants to a greater risk of falling, possibly through increasing confidence in daily activities.42 43 Studies are needed to identify the optimal characteristics of physical activity programmes (eg, duration, frequency, volume, type of exercises) that allow prevention of disability and falls in vulnerable older adults. The technological support part of the multicomponent intervention was based on the use of a research grade actimeter. Future studies are warranted to explore whether increasingly available, user friendly, and reliable activity monitoring systems and e-health platforms could enable frail older people to better adhere to physical activity recommendations and be regularly monitored for safety.

### Policy implications

US and EU data indicate that about 13% of community dwelling adults aged 70 years and older have mobility disability.1 44 Almost half of participants in SPRINTT developed mobility disability over 36 months, indicating that the condition of interest is clinically relevant and identifies an important public health problem. This may support the recognition of physical frailty and sarcopenia as a new clinical entity by regulatory agencies. The multicomponent intervention was associated with a decrease in the risk of incident mobility disability in those with SPPB scores of 3 to 7, which may help overcome the therapeutic nihilism that has so far surrounded low physical function and muscle failure in old age. This, in turn, is expected to

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**Table 3 | Secondary outcomes in participants with baseline short physical performance battery (SPPB) score 8 or 9 according to group allocation**

| Outcomes | Multicomponent intervention (n=155) | Lifestyle education (n=159) | Effect size (95% CI) | P value |
|----------|-----------------------------------|----------------------------|----------------------|--------|
| Changes from baseline in physical performance (SPPB summary score) | | | | |
| 24 months | 1.0 (0.2) | −0.5 (0.3) | 0.5 (0.1 to 1.0) | 0.027 |
| 36 months | 0.5 (0.3) | 0.5 (0.3) | −0.0 (−0.8 to 0.7) | 0.94 |
| Changes from baseline in handgrip (muscle) strength (kg) | | | | |
| 24 months | −0.2 (1.2) | −0.4 (1.1) | −1.7 (−5.0 to 1.7) | 0.33 |
| 36 months | −3.7 (1.9) | −2.4 (1.6) | −1.2 (−6.2 to 3.8) | 0.65 |

**Changes from baseline in appendicular lean mass**

| 24 months | −0.1 (0.4) | −0.2 (0.4) | 0.2 (−0.8 to 1.2) | 0.70 |
| 36 months | −1.2 (0.5) | 0.0 (0.6) | −1.2 (−2.7 to 0.3) | 0.12 |

| 24 months | −0.1 (0.0) | −0.1 (0.0) | 0.1 (−0.1 to 0.2) | 0.33 |
| 36 months | −0.0 (0.0) | −0.0 (0.0) | 0.0 (−0.0 to 0.1) | 0.22 |

**CI= confidence interval. Values are least squared means (standard errors), except for persistent mobility disability.**

*Hazard ratio (95% CI). For all other secondary outcomes, effect size is shown as least squared mean difference (95% CI) between multicomponent intervention and lifestyle education.
Table 4 | Adverse events experienced by study participants throughout the trial according to short physical performance battery (SPPB) score category and group allocation

| Type of event                        | SPPB score 3-7 Multicomponent intervention (n=605) | SPPB score 8 or 9 Multicomponent intervention (n=155) | SPPB score 3-7 Lifestyle education (n=600) | SPPB score 8 or 9 Lifestyle education (n=159) |
|--------------------------------------|--------------------------------------------------|-----------------------------------------------------|------------------------------------------|---------------------------------------------|
|                                      | No (%) of participants | No of events | No (%) of participants | No of events | Risk ratio (95% CI) | No (%) of participants | No of events | No (%) of participants | No of events | Risk ratio (95% CI) |
| Any adverse event                   | 337 (53.7)            | 832 (0.66)  | 297 (49.3)            | 678 (0.53)  | 1.13 (1.01 to 1.25) | 79 (51.0)            | 176 (0.49)  | 79 (49.7)            | 163 (0.43)  | 1.03 (0.82 to 1.28) |
| Serious adverse events              | 237 (39.2)            | 451 (0.36)  | 216 (36.0)            | 393 (0.31)  | 1.09 (0.94 to 1.26) | 45 (29.0)            | 83 (0.23)  | 48 (30.2)            | 72 (0.19)  | 0.96 (0.68 to 1.35) |
| Death                               | 31 (5.1)              | 31 (0.02)   | 25 (4.2)              | 25 (0.02)   | 1.23 (0.74 to 2.06) | 5 (3.2)              | 5 (0.01)   | 3 (1.9)              | 3 (0.01)   | 1.71 (0.42 to 7.03) |
| Life threatening illness            | 24 (4.0)              | 29 (0.02)   | 16 (2.7)              | 23 (0.02)   | 1.49 (0.80 to 2.78) | 4 (2.6)              | 4 (0.01)   | 2 (1.3)              | 4 (0.01)   | 2.05 (0.38 to 11.04) |
| Hospital admission                  | 204 (33.7)            | 378 (0.30)  | 196 (32.7)            | 352 (0.27)  | 1.03 (0.88 to 1.21) | 40 (25.8)            | 65 (0.18)  | 43 (27.0)            | 63 (0.17)  | 0.95 (0.66 to 1.38) |
| Permanent disability                | 11 (1.8)              | 13 (0.01)   | 6 (1.0)               | 6 (0.01)    | 1.82 (0.68 to 4.88) | 2 (1.3)              | 2 (0.01)   | 2 (1.3)              | 2 (0.01)   | 1.03 (0.17 to 7.19) |
| Other serious illness               | 28 (4.6)              | 31 (0.02)   | 17 (2.8)              | 22 (0.02)   | 1.63 (0.90 to 2.95) | 6 (3.9)              | 12 (0.03)  | 3 (1.9)              | 3 (0.01)   | 2.05 (0.52 to 8.06) |
| Unexpected events possibly related to study procedures | 33 (5.5)              | 60 (0.05)   | 38 (6.3)              | 65 (0.05)   | 0.86 (0.55 to 1.35) | 7 (4.5)              | 13 (0.04)  | 14 (8.8)             | 29 (0.08)  | 0.51 (0.21 to 1.24) |
| Falls                               | 80 (13.2)             | 108 (0.09)  | 49 (8.2)              | 61 (0.05)   | 1.62 (1.16 to 2.27) | 9 (5.8)              | 13 (0.04)  | 16 (10.1)            | 19 (0.05)  | 0.58 (0.26 to 1.27) |
| Events under supervision or guidance of study staff | 26 (4.3)              | 27 (0.02)   | 10 (1.7)              | 10 (0.01)   | 2.58 (1.25 to 5.30) | 7 (4.5)              | 8 (0.02)   | 2 (1.3)              | 2 (0.01)   | 3.59 (0.76 to 17.01) |
| Adverse events of special interest  | 169 (27.9)            | 345 (0.27)  | 135 (22.5)            | 252 (0.20)  | 1.24 (1.02 to 1.51) | 51 (32.9)            | 89 (0.25)  | 38 (23.9)            | 72 (0.19)  | 1.38 (0.96 to 1.97) |
| Abnormal test results requiring medical attention | 28 (4.6)              | 30 (0.02)   | 18 (3.0)              | 21 (0.02)   | 1.54 (0.86 to 2.76) | 7 (4.5)              | 10 (0.03)  | 2 (1.3)              | 2 (0.01)   | 3.59 (0.76 to 17.01) |
| Emergency department visits         | 102 (16.9)            | 191 (0.15)  | 84 (14.0)             | 156 (0.12)  | 1.20 (0.92 to 1.57) | 30 (19.4)            | 53 (0.15)  | 26 (16.4)            | 41 (0.11)  | 1.18 (0.74 to 1.91) |
| Fractures                            | 33 (5.5)              | 43 (0.03)   | 30 (5.0)              | 37 (0.03)   | 1.09 (0.67 to 1.77) | 9 (5.8)              | 10 (0.03)  | 9 (5.7)              | 10 (0.03)  | 1.03 (0.42 to 2.51) |
| Outpatient surgery                   | 29 (4.8)              | 40 (0.03)   | 34 (5.7)              | 46 (0.04)   | 0.85 (0.52 to 1.37) | 4 (2.6)              | 6 (0.02)   | 11 (6.9)             | 21 (0.06)  | 0.37 (0.12 to 1.15) |
| Restricted activity possibly due to study procedures | 49 (8.1)              | 71 (0.06)   | 13 (2.2)              | 15 (0.01)   | 3.74 (2.05 to 6.82) | 18 (11.6)            | 20 (0.06)  | 2 (1.3)              | 2 (0.01)   | 9.23 (2.18 to 39.12) |

CI = confidence interval. Sum of individual items is higher than number of participants who experienced at least one adverse event because single events may fall into more than one category. Event rate was calculated as ratio between total number for whom an event was recorded and participant years. In the multicomponent intervention arm, participant years were 1265.96 for SPPB scores 3-7 and 361.85 for SPPB score 8 or 9. In the lifestyle education arm, participant years were 1282.88 for SPPB scores 3-7 and 378.05 for SPPB score 8 or 9.

**Conclusions**

Older adults with physical frailty and sarcopenia represent a subset of the older population at risk of adverse health related events and whose medical needs are currently unmet. A multicomponent intervention based on physical activity with technological support and nutritional counselling was associated with a reduction in the incidence of mobility disability over 36 months of follow-up in older adults with physical frailty and sarcopenia and SPPB scores of 3 to 7. Therefore, such an intervention may be proposed as a strategy to preserve mobility in older people at risk of disability.

**AUTHOR AFFILIATIONS**

1Fondazione Policlinico Universitario “Agostino Gemelli” IRCCS, Rome, Italy
2Department of Geriatrics and Orthopaedics, Università Cattolica del Sacro Cuore, Rome, Italy
3Department of Clinical Sciences and Community Health, Università di Milano, Milan, Italy
4Geriatric Unit, IRCCS Istituti Clinici Scientifici Maugeri, Milan, Italy
5Bluecompanion, London, UK
6Department of Cardiology and Berlin Institute of Health Centre for Regenerative Therapies, German Centre for Cardiovascular Research (DZHK) partner site Berlin, Charité Universitätsmedizin Berlin, Berlin, Germany
7Sanofi-Aventis R&D, Chilly-Mazarin, France
8IRCCS INRCA, Ancona, Italy
9Servicio de Geriatría, Hospital Universitario Ramón y Cajal-IRYCIS, Madrid, Spain
10Department of Medical Statistics, University of Goettingen Medical Centre, Goettingen, Germany
11Department of Geriatrics, Landspitali University Hospital, Faculty of Medicine, University of Iceland, Reykjavik, Iceland
12German Centre for Cardiovascular Research (DZHK) partner site Goettingen, Goettingen, Germany
13International Clinical Trial Research Department, Servier, Madrid, Spain
14Department of Geriatrics, Landspitali University Hospital, Faculty of Medicine, University of Iceland, Reykjavik, Iceland
15Astellas Pharma, Tokyo, Japan
16Department of Medicine and Surgery, Università degli Studi di Parma, Parma, Italy
data collection, data analysis, data interpretation, writing of the report, or decision to submit the article for publication.

Competing interests: All authors have completed the ICJME uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: The present work was funded by a grant from the Innovative Medicines Initiative Joint Undertaking (AC, AJC-J, AJS, AMWJS, AT, BV, CCS, EM, ET, Fal, FrL, IR, LM, LR-M, MC, MDB, MM, MT, PJV, RB, RC, RR-W, SDA, Svh, and TS received in-kind support from the European Federation of Pharmaceutical Industries and Associations as part of the Innovative Medicines Initiative Joint Undertaking for the submitted work; GSA is a full time employee of Server; HG, PB, and RaB are full time employees of Sanofi-Aventis; JS is a full time employee of Boehringer Ingelheim Pharma; MK is a full time employee of Astellas Pharma; RR and RM are full time employees of Novartis; Ali-C received grant support from Abbott Nutrition, Frenesius Kabi, and Nutricia outside of the submitted work, and personal fees from Abbott Nutrition, Frenesius Kabi, Nestlé, Nutricia, Pfizer, and Sanofi-Aventis; EM received personal fees from Abbott, Nestlé, Nutricia, and Thermofisher outside the submitted work; MC received personal fees from Nestlé outside the submitted work; RC received personal fees from Abbott and Nutricia outside the submitted work; SDA received grant support from Abbott and Vifor Pharma outside of the submitted work, and personal fees from Abbott, Bayer, Boehringer Ingelheim, Cardiac Dimension, Cordis, Impulse Dynamics, Novartis, Occlutech, Servier, and Vifor Pharma outside of the submitted work; SDS has a pending US patent; Svh received grant support from Angénieux, Boehringer Ingelheim, and ZS Pharma outside of the submitted work; personal fees from AstraZeneca, Bayer, Brahms, Chugai, Grunenthal, Helsinn, Hexal, Merck Sharp and Dohme, Novartis, Pharmacosmos, Respicardia, Roche, Servier, and Sorin outside the submitted work; TF received personal fees from Bayer, Biosense Webster, CSL Behring, Coherex Medical, Fresenius Kabi, Galapagos, Janssen, Livio Nova, Minoprio, Novartis, Parexel, Penumbra, Roche, and Vifor Pharma outside the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: The study protocol was approved by the ethics committees of the Università Cattolica del Sacro Cuore, Rome, Italy (protocol No 15611/15), and was subsequently ratified by the ethics committees of all participating institutions.

Data sharing: Anonymous raw trial data can be shared on request to Luca Maniotti (luca.maniotti1@unicatt.it). A data access agreement needs to be signed.

The lead authors (EM, FrL, RC, RR, and RoB) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained.

Dissemination to participants and related patient and public communities: The study results will be disseminated to the public through press release, broadcasts, newspapers, and the SPRINTT website (http://www.mysprintt.eu/en/public).

Provenance and peer review: Not commissioned, externally peer reviewed.

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