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The "Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies" (SPRINTT) randomized controlled trial: Case finding, screening and characteristics of eligible participants

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ABSTRACT

Background: The ongoing "Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies (SPRINTT)" randomized controlled trial (RCT) is testing the efficacy of a multicomponent intervention in the prevention of mobility disability in older adults with physical frailty & sarcopenia (PF&S). Here, we describe the procedures followed for PF&S case finding and screening of candidate participants for the SPRINTT RCT. We also illustrate the main demographic and clinical characteristics of eligible screenees.

Methods: The identification of PF&S was based on the co-occurrence of three defining elements: (1) reduced physical performance (defined as a score on the Short Physical Performance Battery between 3 and 9); (2) low muscle mass according to the criteria released by the Foundation for the National Institutes of Health; and (3) absence of mobility disability (defined as ability to complete the 400-m walk test in 15 min). SPRINTT was advertised through a variety of means. Site-specific case finding strategies were developed to accommodate the variability across centers in catchment area characteristics and access to the target population. A quick "participant profiling" questionnaire was devised to facilitate PF&S case finding.

Results: During approximately 22 months, 12,358 prescreening interviews were completed in 17 SPRINTT sites resulting in 6710 clinic screening visits. Eventually, 1566 candidates were found to be eligible for participating in the SPRINTT RCT. Eligible screenees showed substantial physical function impairment and comorbidity burden. In most centers, project advertisement through mass media was the most rewarding case finding strategy.

Conclusion: PF&S case finding in the community is a challenging, but feasible task. Although largely autonomous in daily life activities, older adults with PF&S suffer from significant functional impairment and comorbidity. This subset of the older population is therefore at high risk for disability and other negative health-related events. Key strategies to consider for successfully intercepting at-risk older adults should focus on mass communication methods.

1. Introduction

The last decade has witnessed the proliferation of research programs aimed at testing interventions to foster independence in older adults by targeting functional impairment rather than individual diseases (Beswick et al., 2008; Puts et al., 2017). This approach is not a "betrayal" of the noble mission of medicine of reducing mortality and promoting healthiness. Indeed, functional status is the single most important measure of health in older persons, being a major determinant of well-being and survival (Studenski et al., 2011; Steptoe et al., 2015; Cesari et al., 2016; Landi et al., 2016). The "Lifestyle Interventions and Independence for Elders" (LIFE) study (Pahor et al., 2014) and the "Multi-modal Intervention in Diabetes in Frailty" (MID-Frail) study (Rodríguez-Mañas et al., 2014) have been the most notable initiatives in the field. The randomized controlled trial (RCT) conducted as part of the "Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies" (SPRINTT) project was conceived as an evolution of the pioneering LIFE study (Marzetti et al., 2015; Landi et al., 2017). The project is funded by the Innovative Medicines Initiative (IMI), a public-private partnership between the European Union and the European Federation of Pharmaceutical Industries and Associations (EFPIA). The agency is strategically equipped to foster the research in areas where there is an unmet medical or social need by supporting collaborative efforts of academic and industrial partners.

Similar to LIFE, in SPRINTT, candidate participants are considered to be eligible if presenting with functional limitations in the absence of mobility disability (Pahor et al., 2014; Landi et al., 2017). In SPRINTT, however, the functional impairment needs to be associated with low appendicular lean mass (aLM). This combination identifies a novel condition, termed physical frailty & sarcopenia (PF&S) (Cesari et al., 2017), in which muscle atrophy is envisioned as the biological substratum of physical frailty (Landi et al., 2015). Notably, at the end of an ad hoc scientific advisory procedure, PF&S has received initial endorsement by the European Medicines Agency (EMA) as a prototypical geriatric pre-disability condition.

The other major difference from LIFE is the nature of intervention administered to the active group. While LIFE adopted a unidimensional intervention (i.e., physical activity) to prevent the outcome of interest, SPRINTT participants receive a personalized combination of physical activity, nutritional counseling/dietary intervention, and an information & communication technology (ICT) intervention (Landi et al., 2017). The rationale underlying the multicomponent intervention (MCI) chosen in SPRINTT resides in the proposition that the complex framework within which PF&S develops may be more efficiently tackled through a multidomain, person-tailored intervention (Beswick et al., 2008; Cesari et al., 2017).

Here, we illustrate the procedures for PF&S case finding and screening of candidate SPRINTT RCT participants. The main demographic and clinical characteristics of older adults with PF&S who were found to be eligible for participating in the RCT are also described.

2. Methods

2.1. Overview

The SPRINTT trial is a phase III, single-blind, multicenter RCT (ClinicalTrials.gov identifier: NCT02582138) that is being conducted to compare the efficacy of a MCI program (i.e., physical activity, nutritional counseling/dietary intervention, and ICT intervention) versus a healthy aging lifestyle education (HALE) program for preventing mobility disability in older persons with PF&S. The MCI and the HALE intervention are thoroughly described elsewhere (Landi et al., 2017; Marzetti et al., 2017). Like in LIFE (Pahor et al., 2014), the primary outcome of mobility disability has been operationalized as incident inability to complete the 400-m walk test (Simonsick et al., 2001). Secondary outcomes of SPRINTT are detailed elsewhere (Landi et al., 2017).

The SPRINTT RCT is currently being conducted in 16 sites, located in 11 European countries, under the coordination of the Department of Geriatrics at the Università Cattolica del Sacro Cuore (Rome, Italy) (Table 1). As discussed later, one clinical site withdrew from the study during the recruitment phase. Trial operations are also supported by members of EFPIA (Sanofi-Aventis R&D, Novartis, GlaxoSmithKline, Servier, Astellas, Biophytis, and Boehringer-Ingelheim).

Table 1
SPRINTT study sites.

Site name	City, country
Università Cattolica del Sacro Cuore (coordinating center)	Rome, Italy
IRCCS INRCA	Ancona, Italy
University of Parma	Parma, Italy
University Hospital of Getafe	Getafe, Spain
University Hospital Ramón y Cajal	Madrid, Spain
University Hospital of Toulouse	Toulouse, France
University Hospital of Limoges	Limoges, France
Charles University	Prague, Czech Republic
Silesians Hospital	Opava, Czech Republic
Jagiellonian University Medical College	Krakow, Poland
Friedrich-Alexander Universität Erlangen-Nürnberg	Nurnberg, Germany
Maastricht University Medical Center	Maastricht, The Netherlands
University of Helsinki	Helsinki, Finland
Diabetes Frail, Medici Medical Practice	Luton, United Kingdom
Aston University of Birmingham[a]	Birmingham, United Kingdom
Medical University of Graz	Graz, Austria
Lanspitali University Hospital	Reykjavik, Iceland

[a] This site is no longer active.

2.2. Strategies for PF&S case finding

Study sites were allowed to develop their own recruitment plan to accommodate the variability of catchment area characteristics and access to the target population across the multiple European centers. In general, case finding strategies included the use of newspapers, radio and television advertisements, direct mails, and direct approach by trained personnel at health fairs, supermarkets, pharmacies, senior centers, medical clinics, civic organizations, and churches. Participants in previous studies were approached, and ineligible candidates asked for relatives or friends who might have been eligible. Special attention was paid to informing healthcare providers (in particular, general practitioners, physiotherapists, nurses, and pharmacists), medical clinics, and hospitals within the catching area of each center about the SPRINTT trial. Advertisement material, including brochures and posters, was distributed in malls, grocery stores, hobby shops, public libraries, pharmacies, post offices, train stations, etc. Direct mailing campaigns were also used to distribute study brochures and introductory letters to specific geographic areas. Telephone or in-person contacts with healthcare providers were established to seek for their assistance in recruiting older persons for the study. Early on, a dedicated website (www.mysprintt.eu) was created to promote awareness of the project among the general public as well as healthcare professionals and researchers and to foster recruitment. The study was also advertised through various older persons' organizations (e.g., retired persons' trade unions, local senior groups and third age universities). In Italy, a formal collaboration was established with Coldiretti, the largest organization of farmers at national and European level, to promote the participation in the trial among its members. Finally, a quick "participant profiling" questionnaire [the so-called "Frailty Bureau of Investigation" (FBI) questionnaire] was developed and distributed to the staff in charge of participant recruitment across SPRINTT centers (Fig. 1).

A centralized monitoring team (CMT) was appointed by the coordinating center to track the various strategies and identify those that were most successful at individual sites. To this aim, recruitment reports, containing data on the number of candidates screened from the

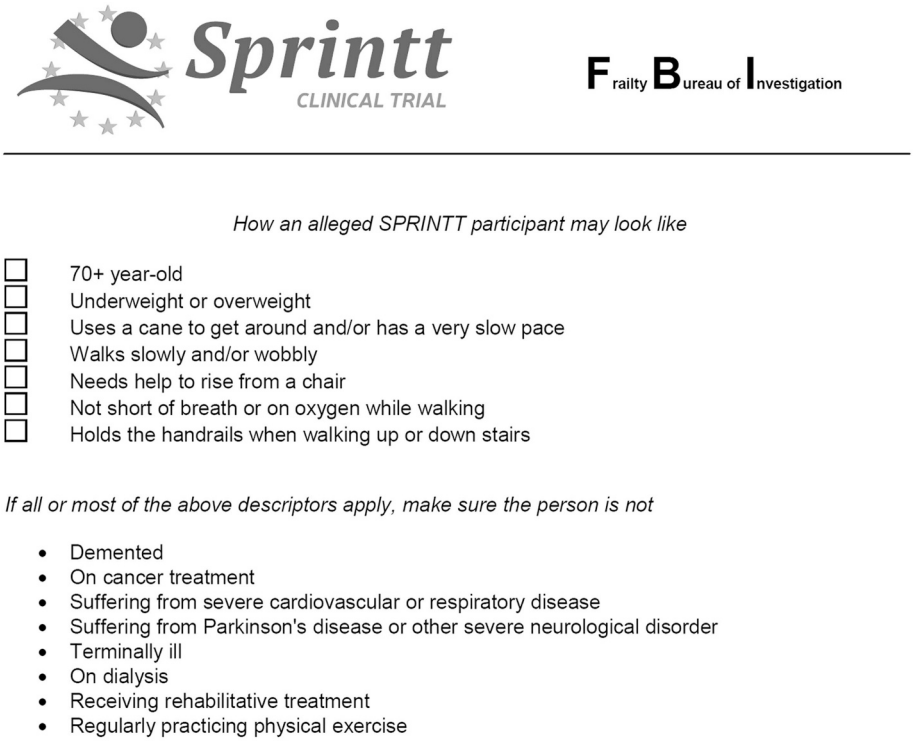

Fig. 1. FBI (Frailty Bureau of Investigation) questionnaire for quick SPRINTT participant profiling.

various case finding sources, were prepared by each clinical site and regularly forwarded to the CMT. The information was subsequently shared among the study sites, so that each of them could be informed on methods that were most successful and which were not worth pursuing.

The CMT also provided assistive responses in case of difficulties with PF&S case finding. Corrective actions were based on the recruitment shortfall and tailored to the needs of the site. Teleconferences and on-site visits were organized to discuss the reasons for the shortfall, and to implement problem-solving methods with the aim of increasing the number of eligible participants in the following month. In selected cases, the CMT cooperated with local staff members in the development of targeted strategies aimed at improving recruitment yields depending on where individuals were lost during the case finding process.

2.3. Goals and time-frame of PF&S case finding

The identification of PF&S was based on the co-occurrence of three defining elements: (1) reduced physical performance; (2) low muscle mass; 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 (Cesari et al., 2017). Briefly, the physical frailty domain of PF&S was based on a Short Physical Performance Battery (SPPB) (Guralnik et al., 1994) summary score ≥ 3 and ≤ 9. By convention, an older person with an SPPB score > 9 is considered to be robust (Studenski et al., 2003). On the other hand, a score ≤ 9 identifies frail individuals and a score ≤ 7 is commonly used to define a subgroup of frail older adults at especially high risk of adverse events (Vasunilashorn et al., 2009). The exclusion of individuals with SPPB scores < 3 is motivated by the fact that such a poor performance is, in general, not compatible with the ability to complete the 400-m walk test (primary endpoint in the SPRINTT RCT) (Vasunilashorn et al., 2009).

The identification of the sarcopenia component of PF&S (i.e., low muscle mass) relied on the cut-points for aLM recommended by the Foundation for the National Institutes of Health (FNIH) sarcopenia project (Studenski et al., 2014). Whole-body dual energy X-ray absorptiometry (DXA) scans were used to estimate aLM, and each candidate participant was considered eligible if presenting an aLM-to-body mass index (BMI) ratio (aLM_{BMI}) below < 0.789 or < 0.512 in men and women, respectively. When the aLM_{BMI} criterion was not met, candidates were tested with the alternative criterion (i.e., crude aLM $<$ 19.75 kg in men and $<$ 15.02 kg in women). Different to what is commonly done during sarcopenia assessment, no specific measures of muscle strength (e.g., handgrip strength) were obtained. The functional domain of sarcopenia was instead captured through the SPPB. However, handgrip strength is measured at the first visit after participant randomization and at all subsequent visits to further assess the impact of the MCI on muscle function.

Consistent with the LIFE RCT (Pahor et al., 2014), SPRINTT adopted incident incapacity to complete the 400-m walk test as the primary outcome. As such, participants were required to complete a 400-m walk within 15 min at the screening visit. This test was chosen for several reasons: (1) it is designed to provide a dichotomous result (i.e., capacity/incapacity to complete the task) on the specific and meaningful condition of mobility disability; (2) mobility disability has been indicated as the first clinically relevant step of the disabling process (Cesari et al., 2017), therefore representing a target condition of special interest for preventive interventions; (3) the 400-m walk test is not supposed to challenge the cardiorespiratory reserve of the individual (as, for example, the 6-min walk test), but measures his/her capacity to cover within a reasonable amount of time the distance required to remain independent in daily living (Rolland et al., 2004).

The other inclusion and exclusion criteria are detailed elsewhere (Landi et al., 2017). Briefly, a set of eligibility criteria was devised in order to select a population that would be: (1) at high risk of experiencing the mobility disability outcome during the 3-year RCT timeframe, (2) most likely to benefit from the MCI, and (3) most likely to comply with the intervention and assessment protocols. The age group was selected because persons aged 70 years and older are at increased risk of mobility disability, and are expected to have a sufficiently long life expectancy to justify participation in a 3-year preventive trial (Ferrucci et al., 2000). In addition, candidate participants needed to have sufficient cognitive abilities to both provide informed consent to the study and participate in the trial interventions. Cognitive function was measured using the Mini Mental State Examination test (MMSE) (Folstein et al., 1975) and those scoring < 24 were considered ineligible for the RCT. The evaluation of nutritional status was not obtained for participant selection. This parameter was assessed after the establishment of eligibility to properly design the dietary intervention in the MCI group.

As previously specified (Landi et al., 2017), the SPRINTT RCT aimed at recruiting a total of 1500 70+ year-old persons with PF&S, 80% of whom presenting with an SPPB score < 8, and the remaining 20% with SPPB ≥ 8. Efforts were made to maintain these proportions at each study site.

2.4. Screening of PF&S

The screening process for the identification of PF&S comprised five primary components: phone screen, SPPB, health screen, 400-m walk test, and DXA. These components were administered over two or three contacts, i.e., a phone interview (prescreening interview) and one or two clinic visits.

As already implemented in LIFE, before candidate participants were invited to attend the study site for the screening visit, a number of eligibility items were checked over the phone. This preliminary interview was a quick and inexpensive method to identify potential participants who had a high probability of being found ineligible at the screening visit. Candidates who remained eligible were subsequently invited to the clinical trial site to complete a screening visit and determine the final eligibility. The screening process could be stopped at any time if an eligibility criterion was not met. Based on the experience of LIFE, it was anticipated that the SPPB would exclude a large share of potential participants. Hence, in order to improve time- and cost-efficiency of the screening process, physical performance assessment was usually completed as the first step during the screening visit. DXA, instead, was generally performed as the last assessment in order to minimize the number of scans leading to negative results.

2.5. Training of SPRINTT staff

At each study site, staff members were requested to become familiar with their assigned activities in order to meet high quality standards. Before study commencement, key study staff at each site was trained on-site by an ad hoc established standardization team (ST), whose members were originally trained by the LIFE study staff at the University of Florida. A train-the-trainer model was adopted, such that staff members who were trained by the ST became then responsible for training and re-training other staff members. As needed, the ST provided remote or on-site support for the whole duration of participant accrual.

2.6. Statistical analysis

Descriptive statistics were used to provide the main characteristics of screenees eligible to participating in the SPRINTT RCT. Analyses were computed using the SAS software (version V9.4, SAS Institute, Cary, NC).

3. Results

3.1. Results of PF&S case finding

Case finding activities were completed in approximately 22 months. The first prescreening was conducted on January 11th 2016, whereas the last screening was completed on October 31st 2017. Project advertisement through mass communication media was generally the most rewarding strategy for PF&S case finding with the exception of the site in Helsinki. Indeed, the Finnish center relied mostly on a national registry-based method to reach out the target population. In the other countries, depending on the study site, 60–70% of eligible enrollees were gathered through TV, radio and newspaper ads. The remaining candidates were retrieved via mass mailing, presentations at senior centers, supermarkets and universities of the third age, brochures, flyers and posters placed in patient waiting areas and primary care physicians' offices, and word of mouth.

The flow of PF&S case finding, from the prescreening interview to final eligibility establishment, is shown in Fig. 2. Overall, 12,358 prescreening interviews were completed, and 6710 candidates proceeded to the screening visit. At the end of the process, 1566 participants were found eligible for the RCT, 341 (21.8%) with SPPB 8-9 and 1225 (78.2%) with SPPB 3-7. The target of 1500 participants was exceeded because some prescreened candidates whose screening visits were scheduled after the accomplishment of the recruitment target were eventually found to be eligible.

As depicted in Fig. 2, the main reason for screening failure was SPPB out of range, followed by normal muscle mass at DXA, medical conditions, and inability to complete the 400-m walk test. Less frequently, candidate participants disqualified because of safety concerns during functional testing, poor cognition (i.e., MMSE < 24), behavioral conditions (e.g., excessive alcohol consumption), nursing home residence, sensory impairments, use of drugs not permitted by the protocol (e.g., systemic corticosteroids, androgens, estrogens, growth hormone), or other conditions (e.g., participation in another clinical trial, physical activity program, or physiotherapy/cardiorespiratory rehabilitation; investigator judgment of non-safety/non-compliance).

Fig. 3 shows candidate screening and the accrual of eligible participants during the 22-month case finding period. According to one of the recruitment scenarios envisioned during the RCT planning phase (Landi et al., 2017), participant enrolment exceeded the expected goal during the first 12 months and lagged behind thereafter. The delay was due to the withdrawal of one clinical site (i.e., Aston University of Birmingham) because of administrative issues and the slower recruitment pace in other centers. In order to ensure the accomplishment of the recruitment goal and preserve the RCT integrity, the CMT and the project leadership engaged three backup clinical sites (i.e., Graz, Parma, and Reykjavik), increased the case finding target in the best-recruiting centers, and extended the accrual phase duration. The length of participant follow-up will be maintained as planned by proportionally extending the RCT operations beyond the projected closing date.

3.2. PF&S case finding across study sites

PF&S case finding was pursued in 17 clinical sites across 11 European countries (Table 1). As previously mentioned, Aston University of Birmingham withdrew from the study because of administrative issues after approximately 5 months. The number of screenings ranged from 33 in Birmingham to 1236 in Rome (Italy), whereas the number of candidates with PF&S varied from 10 in Birmingham to 224 in Rome (Fig. 4). As a whole, 4.3 people were screened for every eligible participant. The number of screenings per eligible candidate ranged from 2.2 in Opava to 9.2 in Krakow (Poland) (Table 2). This large variability was due to several factors, including differential

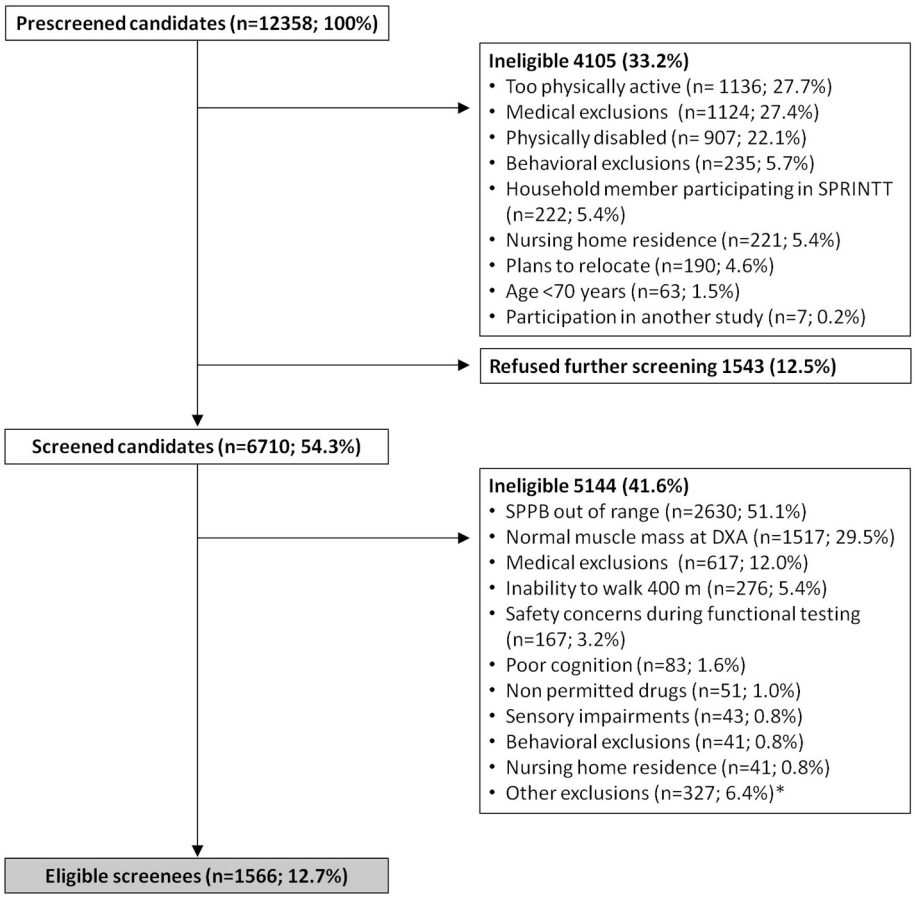

Fig. 2. Flow-chart of the PF&S case finding process. For ineligible screenees, the sum of individual items is higher than 100% because in some instances the screening process was not stopped at the first unmet eligibility criterion. *Includes: participation in another clinical trial, physical activity program, or physiotherapy/cardiorespiratory rehabilitation; investigator judgment of non-safety/non-compliance.

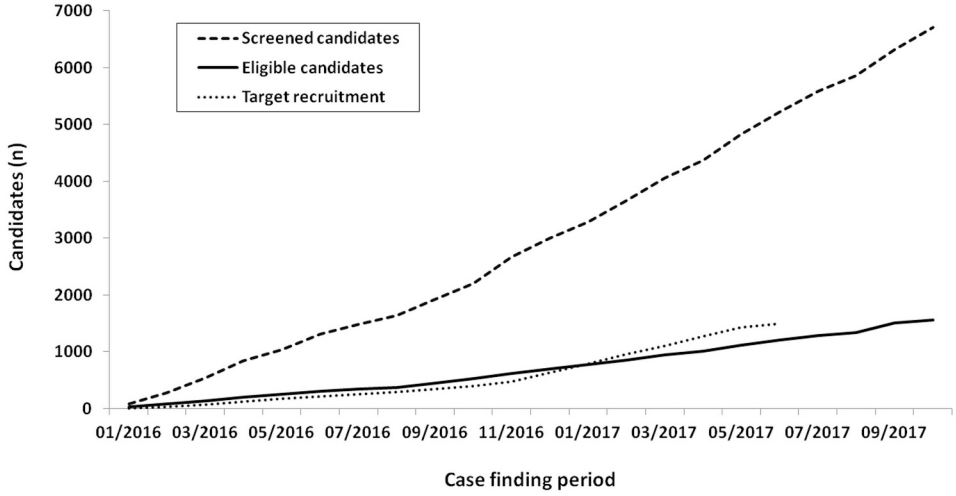

Fig. 3. Screening and accrual of PF&S candidates during the 22-month case finding period.

efficiency of the case finding strategies adopted, characteristics of the catchment areas, varying access to the target population, availability of local registries, number of staff members dedicated to PF&S case finding, number of months of active case finding. With regard to the latter point, while case finding activities were conducted for an average of 16.4 months, the number of months during which PF&S case finding was pursued by individual sites varied from 5 to 22 (Table 3). This heterogeneity has several causes, such as late ethical approval, administrative issues, early termination of activities in some centers, and late engagement of additional sites.

3.3. Characteristics of eligible screenees

The main characteristics of eligible screenees are presented in Table 4. The mean age was approximately 79 years, with over 70% women. The vast majority of participants was Caucasian (88%). In this regard, it should be mentioned that no ethnic minorities were specifically targeted. The mean BMI was higher than 28 kg/m^2, with over one third of the sample having BMI values $\geq$30 kg/m^2. Candidates were on average almost completely independent in the basic and instrumental activities of daily living. As required by the RCT protocol, eligible screenees were cognitively intact, with a mean MMSE score close to 28. The mean SARC-F score was nearly 3, which is lower than the cut-off value suggested for identifying sarcopenia (Malmstrom and Morley, 2013). Similarly, the average calf circumference was approximately 4 cm greater than the cut-point proposed to be indicative of sarcopenia (Marzetti et al., 2018). Physical performance was significantly impaired, as documented by an average score on the SPPB of 6.7 and a 4-m walk speed of 0.73 m/s. The time to complete the 400-m walk test (8.69 min on average) was also indicative of substantial functional impairment (Vestergaard et al., 2009; Deshpande et al., 2013). With regard to the sarcopenia component of PF&S, low muscle mass was more frequently captured by crude aLM in women and by the aLM_{BMI} criterion in men.

Osteoarthritis was the most prevalent comorbidity among eligible screenees, followed by cardiovascular conditions, emotional/nervous/psychiatric problems, diabetes mellitus, chronic lung disease, cancer, and cerebrovascular accidents. Almost one in two participants reported at least one fall event occurred in the previous year, and more than one in ten sustained an injurious fall within the same time-frame.

4. Discussion

In 2013, IMI launched a call seeking for "Developing innovative therapeutic interventions against physical frailty and sarcopenia as a prototype geriatric indication". The SPRINTT project was designed to provide an objective operationalization of the PF&S condition that would identify a high-risk population with unmet medical needs (Marzetti et al., 2015). PF&S was conceptualized as the co-occurrence of physical function impairment and low muscle mass in the absence of mobility disability (Cesari et al., 2017). The theoretical framework of PF&S was built on past landmark experiences in the field and was mostly inspired by the LIFE study (Pahor et al., 2014) and the FNIH project (Studenski et al., 2014). One major achievement of the SPRINTT project has been the identification and initial characterization of PF&S among older adults living in the community. This challenging task was accomplished in spite of a number of anticipated and unforeseen difficulties related to the intrinsic characteristics of the target population and the transnational and multicultural deployment of the project.

Indeed, several issues were faced related to different national ethical procedures, country-specific requirements for the use of diagnostic equipment (e.g., DXA), administrative issues, and case finding challenges due to the novelty of the PF&S condition. Furthermore, some PF&S-related attributes were learnt after the beginning of case finding. For instance, the prevalence of low muscle mass according to the FNIH criteria is relatively low in older adults with SPPB scores of 8 or 9, whereas exclusionary conditions are quite common in those scoring < 8 on the SPPB. This latter subgroup is also often reluctant to engaging in long-term prevention programs such as those proposed in SPRINTT (Picorelli et al., 2014). Lastly, tools that are commonly recommended for the rapid screening of sarcopenia (e.g., SARC-F and calf circumference) turned out not to be suitable for PF&S case finding.

Through it all, 1566 older persons were found to be eligible for the RCT across 17 clinical sites. Project advertisement through mass media was by far the most effective strategy for PF&S case finding. The screening failure rate was lower than in the LIFE study, with one eligible candidate every 4.3 screenings as opposed to one out 9.1 in LIFE (Marsh et al., 2013). This reflects a high prevalence of PF&S among community-dwelling older adults. It should, however, be acknowledged that the SPRINTT consortium took advantage from the LIFE successes and shortcomings. The proactive support received by the LIFE study

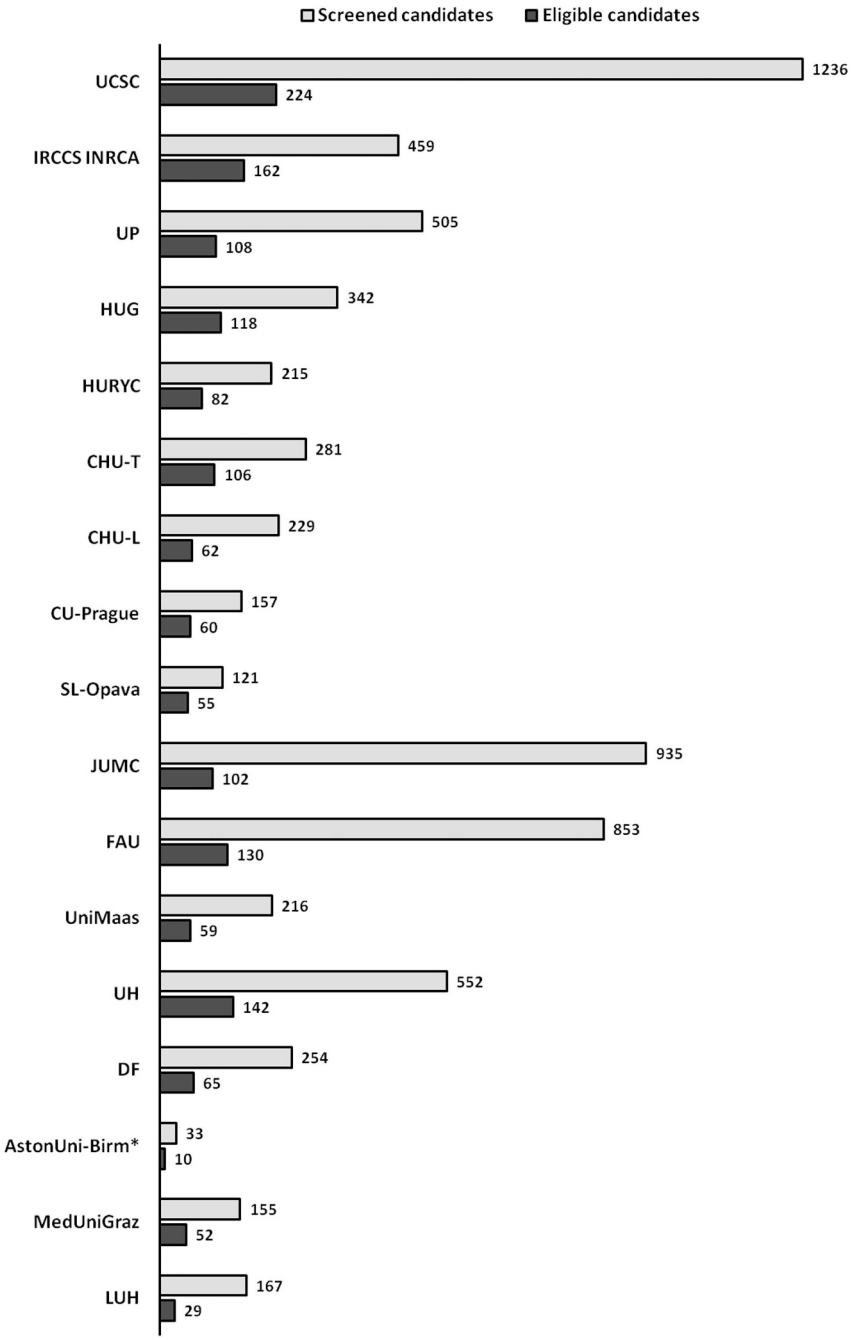

Fig. 4. Output of PF&S case finding across the 17 SPRINTT sites. *Abbreviations*: AstonUni-Birm, Aston University of Birmingham; CHU-L, University Hospital of Limoges; CHU-T, University Hospital of Toulouse; CU-Prague, Charles University; DF, Diabetes Frail Medici Medical Practice; FAU, Friedrich-Alexander Universität Erlangen-Nürnberg; HUG, University Hospital of Getafe; HURYC, University Hospital Ramón y Cajal; JUMC, Jagiellonian University Medical College; LUH, Lanspitali University Hospital; MedUniGraz, Medical University of Graz; SL-Opava, Silesians Hospital; UCSC, Università Cattolica del Sacro Cuore; UH, University of Helsinki; UniMaas, Maastricht University Medical Center; UP, University of Parma.
*This site in no longer active.

leadership and staff members also allowed SPRINTT to be implemented without the need of running a pilot trial.

The age and gender distributions of SPRINTT eligible screenees were comparable to LIFE participants (Pahor et al., 2014). PF&S older adults are usually overweight, with > 30% of them being obese. This finding (as well as the high prevalence of concurrent osteoarthritis) is consistent with the concept of sarcopenic obesity (Roubenoff, 2000), and adds to a growing literature indicating that excessive adiposity contributes to physical frailty and functional limitations in advanced age (Binkley et al., 2013; Porter Starr et al., 2014). Indeed, the adipose tissue is highly metabolically active and promotes systemic inflammation and oxidative stress (Hulsegge et al., 2016; Picca et al., 2017). In addition, excessive adiposity exacerbates the age-associated fat infiltration within muscles (Goodpaster et al., 2000), which in turn contributes to muscle dysfunction and frailty (Goodpaster et al., 2001; Visser et al., 2005). Overweight and obesity are well-known risk factors for cardiovascular disease. The latter, in turn, may favor the development of geriatric syndromes, including frailty (Strandberg et al., 2013; Atkins et al., 2018).

The prevalence of major comorbid conditions was very similar between SPRINTT eligible screenees and LIFE participants. Conversely, functional impairment was more severe among SPRINTT candidates, as reflected by the lower average SPPB score (6.7 vs. 7.4). This finding is explained by the higher proportion of participants with SPPB < 8 targeted by SPRINTT as opposed to LIFE (80% vs. 45%, respectively). It is noteworthy that older adults with PF&S were rarely recruited among people referred to outpatient clinics or hospital services. Most eligible screenees were indeed gathered among individuals who had not yet sought any specific medical advice despite their evident functional impairment. Hence, SPRINTT was able to identify a population of older adults with clearly unmet clinical needs, at least partly due to underestimation of the increased risk profile and the non-referral to clinicians

Table 2
Number of screenings per eligible participant (screening failure rate) across the SPRINTT study sites.

Site name	Screening failure rate
Università Cattolica del Sacro Cuore	5.5
IRCCS INRCA	2.8
University of Parma	4.7
University Hospital of Getafe	2.9
University Hospital Ramón y Cajal	2.6
University Hospital of Toulouse	2.7
University Hospital of Limoges	3.7
Charles University	2.6
Silesians Hospital	2.2
Jagiellonian University Medical College	9.2
Friedrich-Alexander Universität Erlangen-Nürnberg	6.6
Maastricht University Medical Center	3.7
University of Helsinki	3.9
Diabetes Frail, Medici Medical Practice	3.9
Aston University of Birmingham[a]	3.3
Medical University of Graz	3.0
Lanspitali University Hospital	5.8
All SPRINTT centers	4.3

[a] This site is no longer active.

Table 3
Number of months during which PF&S case finding was pursued across the SPRINTT study sites.

Site name	Months of active PF&S case finding (n)
Università Cattolica del Sacro Cuore	22
IRCCS INRCA	21
University of Parma	12
University Hospital of Getafe	21
University Hospital Ramón y Cajal	21
University Hospital of Toulouse	17
University Hospital of Limoges	20
Charles University	19
Silesians Hospital	17
Jagiellonian University Medical College	22
Friedrich-Alexander Universität Erlangen-Nürnberg	19
Maastricht University Medical Center	15
University of Helsinki	19
Diabetes Frail, Medici Medical Practice	15
Aston University of Birmingham[a]	5
Medical University of Graz	5
Lanspitali University Hospital	9
Average length of PF&S case finding activities	16.4

[a] This site in no longer active.

Table 4
Main characteristics of eligible screenees.

Characteristics	Eligible screenees (n = 1566)
Demographics	
Age (years), mean ± SD	78.9 ± 5.8
Gender (female), n (%)	1119 (71.5)
Race/ethnicity, n (%)	
White	1380 (88.1)
Asian	17 (1.1)
African American/black	2 (0.1)
Other	4 (0.3)
Refused/missing	163 (10.4)
Anthropometry	
BMI (kg/m^2), mean ± SD	28.6 ± 6.0
Calf circumference (cm), mean ± SD	35.0 ± 4.4
Functional ability and cognition	
ADL score, mean ± SD	5.6 ± 0.6
IADL score, mean ± SD	7.3 ± 1.2
SARC-F score, mean ± SD	2.9 ± 1.9
MMSE score, mean ± SD	27.9 ± 1.8
PF&S defining parameters	
SPPB summary score, mean ± SD	6.7 ± 1.4
Balance score, mean ± SD	2.5 ± 1.0
4-m walk score, mean ± SD	2.8 ± 0.8
Chair-rise score, mean ± SD	1.4 ± 0.8
4-m walk speed (m/s), mean ± SD	0.73 ± 0.19
Time to walk 400 m (min), mean ± SD	8.69 ± 2.45
400-m walk speed (m/s), mean ± SD	0.82 ± 0.21
aLM (kg), mean ± SD	
Men	21.13 ± 3.52
Women	14.73 ± 2.15
aLM_{BMI}, mean ± SD	
Men	0.725 ± 0.083
Women	0.529 ± 0.076
Medical conditions	
Any cardiovascular medical history, n (%)	1109 (70.8)
High blood pressure, n (%)	1027 (65.6)
Coronary artery disease, n (%)	138 (8.8)
Congestive heart failure, n (%)	102 (6.5)
Pacemaker, n (%)	44 (2.8)
Chronic lung disease, n (%)	242 (15.5)
Stroke or brain hemorrhage	106 (6.8)
Transient ischemic attack, n (%)	136 (8.7)
Cancer (excluding minor skin cancer), n (%)	217 (13.9)
Diabetes mellitus, n (%)	330 (21.1)
Osteoarthritis, n (%)	1204 (76.9)
Falls(s) in past year, n (%)	694 (44.3)
Injurious fall(s) in past year, n (%)	233 (14.9)
Previous hip fracture(s), n (%)	94 (6.0)
Previous non-femoral fracture(s), n (%)	505 (32.2)
Emotional/nervous/psychiatric problems, n (%)	354 (22.6)

Abbreviations: ADL, activities of daily living; aLM, appendicular lean mass; aLM_{BMI}, appendicular lean mass to body mass index ratio; BMI, body mass index; IADL, instrumental activities of daily living; MMSE, Mini Mental State Examination; PF&S, physical frailty and sarcopenia; SPPB, short physical performance battery.

for medical advice.

Interestingly, the two alternative FNIH criteria used to identify low muscle mass (i.e., crude aLM and aLM_{BMI}) showed a gender-specific distribution, with a greater proportion of men diagnosed with sarcopenia based on aLM_{BMI}. Low muscle mass was instead more often captured by unadjusted aLM in women. Preliminary, unpublished analyses performed on existing data during the SPRINTT preparation phase showed that aLM_{BMI} detected more instances of sarcopenia in overweight or obese older adults. Conversely, the crude aLM criterion was more effective at identifying sarcopenia in individuals with normal or low BMI. Whether the differential performance of the two FNIH criteria reflects the existence of gender-specific sarcopenic phenotypes it will be established through pre-planned secondary analyses at the end of the project.

In summary, we have described a population of non-disabled older persons with clear physical impairment specifically linked to muscle loss. These individuals with unmet medical needs are sufficiently prevalent and easy to detect in the community that may represent an ideal target for pharmacological and non-pharmacological interventions against sarcopenia and physical frailty. In this context, it is important to underline the approval that the EMA granted to the SPRINTT methodology, including the rationale underlying the PF&S defining criteria.

5. Conclusion

The global aging of our societies is posing novel and unprecedented challenges to health and social care systems. The preservation of independence in late life has therefore become an urgent need to be achieved through tailored and innovative interventions (Marzetti et al., 2016). Data presented here show the existence and main characteristics of a large European sample of older adults with PF&S that represents a prototypical population with unmet clinical needs. We have

demonstrated the feasibility of recruiting a geographically and culturally heterogeneous population of older community-dwellers at high risk for disability and other negative health-related events. Key strategies to consider for successful interception of these at-risk older adults should focus on mass communication methods (e.g., TV broadcasting, radio, newspapers).

Conflict of interest

All of the authors of the present work are partners of the SPRINTT consortium, which is partly funded by the European Federation of Pharmaceutical Industries and Associations (EFPIA).

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