IMI1 Final Project Report Public Summary

Project Acronym: SPRINTT

Project Title: Sarcopenia And Physical Frailty In Older People: Multi Component Treatment Strategies

Grant Agreement: 115621
Project Duration: 07/2014 - 10/2020

1. Executive summary

1.1. Project rationale and overall objectives of the project

SPRINTT aims to develop scientific and regulatory consensus over the strategic objectives of therapeutic indication, biomarkers and development of clinical methodology and health economic model for the condition of physical frailty and sarcopenia (PF&S) in a "real life" setting.
Amongst other important elements, the project intends to address these tasks by reaching a clinical consensus, developing a regulatory work-stream, and sponsoring an ad hoc randomised clinical trial (RCT).
The RCT is aimed at testing the effects of a multicomponent intervention (MCI), based on physical exercise, nutritional counselling, and information & communication technology (ICT) solutions, in community-dwelling older persons with PF&S in comparison with a healthy ageing lifestyle education (HALE) programme.
The trial should allow clear characterisation of the PF&S condition and provide the basis for supporting the identification of those individuals who may most benefit from future pharmacological and non-pharmacological interventions.
The trial will randomly allocate 1,500 participants recruited in eleven European countries to one of two groups undergoing the following interventions:

- MCI
- HALE

The ultimate goals of SPRINTT are to offer efficient treatment options to older persons with PF&S, foster their independence, and improve their quality of life.

1.2. Overall deliverables of the project

In this 76-month programme of work, there were 9 active work packages.
The overall deliverables were :

- Achieve an objective, standardised, and easy-to-apply operational definition of the geriatric condition of PF&S
- Achieve scientific and regulatory consensus on target population, state and efficacy biomarkers, and clinical trial methodologies
- Qualify biomarkers for the specific condition of PF&S
- Conduct an RCT to validate interventions aimed at preventing the adverse outcomes of PF&S (1,500 participants)
- Realise an ICT infrastructure enabling the creation of a Clinical Knowledge Hub (CKH)
- Develop a health economic model evaluating the intervention on PF&S

The SPRINTT team, through its nine work-packages, has paved the way for the RCT implementation across pre-identified European clinical centres.

1.3 Summary of progress versus plan since last period

In the last reporting period, the SPRINTT Project activities were focused on a) the completion of the SPRINTT RCT; b) database cleaning; c) data analysis, and d) dissemination of preliminary results.

As for the SPRINTT RCT, the last follow-up visits were completed on 31/10/2019. Notably, more than 75% of participants enrolled in the study completed the expected two years of follow-up. In particular, in the SPPB 3-7 stratum, 453 participants randomized in the multicomponent intervention (MCI) group (74.9%) and 451 participants in the successful aging (HALE) control group (75.2%) were followed-up for a period of 2 to 3 years, while 31 older adults in the MCI group (5.1%) and 37 (6.2%) of HALE participants completed the maximum follow-up set at 3 years. In participants with a better physical performance (Short Physical Performance Battery, SPPB, 8 and 9), 87 participants randomized in the MCI group (56.1%) and 105 participants in the HALE group (65%) were followed-up for a period of 2 to 3 years, while 37 older adults in the MCI group (23.9%) and 26 (16.4%) of HALE participants completed the 3-year follow-up. These figures are an impressive result, since collectively 75% of frailer participants and over 80% of "healthier" older adults with PF&S were engaged in the trial for more than 2 years.

Centralised and external processes were put in place in order to check and confirm the primary outcome adjudication. A specific algorithm was developed by the SPRINTT industrial partners to automatically adjudicate the incident mobility disability outcome when participants could not attend the visits at study sites. An external adjudication committee was appointed by the Managing Entity to review the outcome packet and related forms and provide a standardised and unbiased adjudication process. A dedicated platform in the SPRINTT application was developed to assist adjudicators in review and decision processes. The Adjudication process was finalised in March 2020.

Major efforts were devoted to database cleaning. Approximately 7000 queries were checked and closed through the collaboration between EFPIA monitors and academic investigators. Database was successfully locked on April 2nd 2020. The database is now available to Consortium researchers for analysis.

As for the analytical plan, a vast number of outcome variables were analysed in the first and second round of analyses conducted up to now.

The primary outcome of the RCT was incident mobility disability, operationalized as the loss of ability to complete a 400-m walk test during the follow-up. Secondary outcomes included time to first occurrence of persistent mobility disability, operationalized as the failure to complete the 400-m walk test in two consecutive occasions. Other secondary outcomes included changes from baseline in functional, cognitive, nutritional, mood, and quality of life parameters, including SPPB, Mini Mental State Examination (MMSE), Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL), and the Center for Epidemiological Studies-Depression (CES-D) scale.

The SPRINTT RCT results will be thoroughly described in the next sections. However, it should be mentioned that all of the primary objectives of the SPRINTT RCT were met. We showed that: a) a population of older adults with PF&S exists across Europe; and b) an MCI based on physical activity, nutrition counseling and ICT reduced major mobility disability up to 36 months of follow up in older adults with PF&S.

A second round of analyses was also conducted to identify the baseline characteristics of older adults with PF&S associated with a higher risk of developing mobility disability. This allowed predicting models to be

built that could be used to develop healthcare strategies against loss of independence and disability for European citizens.

A centralised biobank was populated with more than 4200 biosample boxes. Biomarker studies are ongoing and will shortly provide validated biomarkers for PF&S. Preliminary results from SPRINTT ancillary studies have showed that candidate biomarkers for PF&S exist and pertain to different biological processes, including inflammation, protein/amino acid metabolism perturbations, redox imbalance and stress responses.

Due to the COVID-19 pandemic that has impacted the majority of SPRINTT researchers, most of the dissemination activities were postponed and are still currently ongoing.

However, some relevant activities were finalised, including the drafting of the official SPRINTT Intervention Booklets. These two Booklets, entitled “SPRINTT Physical Exercise Booklet” and “SPRINTT Nutrition Booklet – Nutritional recommendations for active and healthy aging” were drafted in English and then translated in the local languages by the SPRINTT study sites investigators. SPRINTT Booklets will be distributed to European and National Geriatric Medicine Societies, stakeholders as well as to local GPs to convey the most important recommendations to preserve physical function in old age.

Several papers were drafted under the auspices of SPRINTT. In particular, in the last reporting period, two papers describing the implementation of the two main intervention of the SPRINTT RCT (i.e. physical activity and nutrition) were published on peer-reviewed journals. The first paper “Preserving Mobility in Older Adults with Physical Frailty and Sarcopenia: Opportunities, Challenges, and Recommendations for Physical Activity Interventions” (Clin Interv Aging. 2020 Sep 16;15:1675-1690. doi: 10.2147/CIA.S253535. PMID: 32982201; PMCID: PMC7508031) was drafted by all SPRINTT physical activity instructors. The rationale and implementation of nutritional intervention in SPRINTT were described in a paper entitled "The Sarcopenia and Physical frailty in older people: multi-component treatment strategies (SPRINTT) project: description and feasibility of a nutrition intervention in community-dwelling older Europeans", published in the European Geriatric Medicine, the official journal of the European Geriatric Medicine Society (EuGMS).

The manuscript reporting the SPRINTT RCT main results (i.e. primary outcome and most relevant secondary outcomes) will be submitted to JAMA in the next weeks.

Additional high-impact manuscripts have been planned to 1) report the effects of MCI on established parameters of physical performance in older adults (e.g., 4-m gait speed, handgrip strength); 2) report the effects of MCI on popular measures of disability (e.g., basic and instrumental activities of daily living); 3) report the effects of MCI on mood, cognition, and perceived quality of life; 4) describe the cost-effectiveness of MCI; 5) describe the characteristics of older adults with PF&S at greater risk of negative health-related events; 6) describe the characteristics of non-responders to MCI who might, therefore, be eligible for enrolment in trials on investigational drugs. A major impact is expected from the SPRINTT biomarker study, which will produce ground-breaking results on screening, diagnostic, prognostic, and predictive biomarkers. Findings from the SPRINTT biomarker study have indeed the potential of producing a paradigm shift in diagnosing PF&S, developing personalized treatments, and monitoring treatment effects over time. It is worth mentioning that the SPRINTT biomarker discovery plan has been inspired by concepts of contemporary geroscience, which ensures a solid scientific basis and a sweep translation of findings to the clinical arena.

In addition, the Scientific Advisory Board (SAB) met two times during the last period : in November 2018 and in November 2019. During both meetings, SAB experts reviewed status of the SPRINTT Clinical Trial progress with methodological and safety data indicators and received the conclusions of the DSMB.
SAB experts considered the information received about the study operations and achievements satisfactory and acknowledged that most of the previous recommendations were taken into consideration and advice effectively applied. The SAB had convene for its 6th meeting in early 2020 (at ICFSR, scheduled on March 11 in Toulouse, France). Due to the COVID pandemic the event was cancelled and postpone to a better time.

1.4. Significant achievements since last report

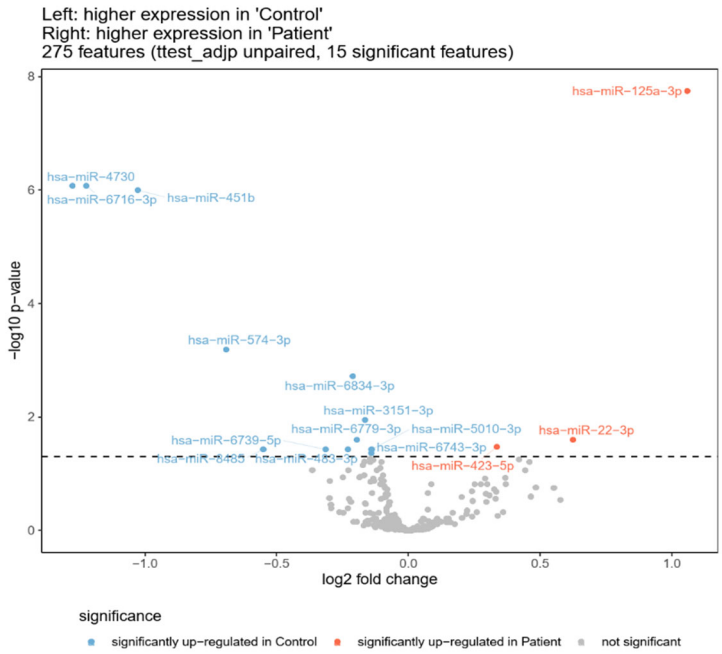
The last period of the SPRINTT project has been dedicated to the conduct and the finalisation of the SPRINTT RCT. A total of 1519 participants were randomised in the RCT, the original target of 1500 participants was exceeded because some pre-screened candidates whose screening visits were scheduled after the accomplishment of the recruitment target were eventually found to be eligible.
Participants retention in the study was another challenge; yet, more than 75% of participants enrolled in the study completed the expected minimum two years of follow-up. The monitoring team established in collaboration between EFPIA monitors and Academics monitors was a success.

Exercises with SPRINT-T participants

The Central Biobank continued receiving blood samples from 16 recruiting centers of the SPRINT-T Study. The standardized platform created for the labelling, short-term storage, and archiving of serum, EDTA plasma, whole blood, and urine samples proved to be efficient. The last shipment was done in March 2019, when the maximal capacity of the freezers was reached. With this, it was possible to store a total of 2526 biosample boxes corresponding to different follow up periods at all recruiting sites.

During the closure of the study, the team obtained several offers for shipment of the biobank from Göttingen to Rome, Università Cattolica del Sacro Cuore. Only one company was able to offer a secure transport, temperature conservation as close as possible at -80° C during shipment, collection of remaining samples at the peripheral sites under the same standards as from Göttingen and appropriate arrival at the biobank in Rome. At the last moment, the shipment was postponed by Rome site due to unexpected need of storage for SARS-CoV-2 patient samples. We now wait for confirmation to fix a shipment date, presumably in the first half of 2021.

In addition, and in order to gain a first insight into the expression of microRNAs related to sarcopenia, the team conducted an exploratory analysis. Through a microarray analysis, 275 out of 2749 miRNAs were detected in at least 75% of samples and 15 miRNAs showed a significant difference between cases and controls (see Figure 1). The analysis was done using samples of 31 cases and 29 controls from Friedrich-Alexander-Universität Erlangen-Nürnberg biomaterials.



A further analysis was performed on a selected set of 8 miRNAs out of those 15. Using qPCR method, miRNA 22-3p presented the highest fold expression in cases and was the only target revealing statistically significant difference between cases and controls. However, the majority of miRNAs showed a very low expression, as shown by very high or unmeasurable Ct values. Therefore, qPCR unfortunately did not yield conclusive results.

During that period, the WP5 team published three peer-reviewed articles (Sicsic, Ravesteijn, and Rapp 2020; Sicsic and Rapp 2019; Sirven, Dumontet, and Rapp 2020)**,** and completed all its deliverables for the SPRINTT project. The UP (Descartes) team also produced 9 presentations at seminars and conferences. In addition, the UP (Descartes) team ran additional analyses to better understand the socioeconomic impact of frailty and sarcopenia in European older populations, and identify the potential socioeconomic benefits of PF&S interventions for European citizens. Finally, the UP team is currently finishing drafting an article that explores the impact of the SPRINTT intervention on care use.

The ICT Team had, during this last phase, carried out many important tasks to support the accomplishment of RCT activities in close collaboration with WP4, WP7, WP8 and WP9 teams. The ICT supported data managers to obtain high-quality data cleaning and successfully locked the database. Through the use of efficient and advanced reporting tools, real-time reports were generated, which helped and speeded up the work of the Data Managers and all the Clinical Operations necessary to follow the completion and cleaning of data entry in the most effective way. A dashboard was created, where it was possible to check the progress of all the parameters that indicate the completion of the forms of the eCRF.

Periodic meetings were held with the DMs and WP7 to check the filling status of the eCRF and CKH, and a fruitful work was done with WP7 to complete the source data recorded in the Clinical Knowledge Hub DXA, Nutrition and Patient Reported Outcomes (external to the eCRF). WP6 also developed specific procedures to allow verification of specific data by the Members of an Adjudication committee, who accessed the eCRF with ad hoc profiles to only visualize some data and type the response directly in the eCRF.

The entire ICT System (Clinical Knowledge Hub) was developed and managed following GCPs, the European GDPR and the ICH. The Biobank sub-study was also implemented, and specific training and support activities were carried out.

In addition, the SPRINTT living labs had the goal to develop and validate different technologies that could enrich the main SPRINTT study. As such, the included technologies were focused on the assessment of an older adult's status of (pre)frailty and the training of the older adult to improve their physical and/or cognitive condition. The Living Labs team started the project by developing Standard Operation Procedures for the usability tests in the Living Lab and that could be used in the subsequent SPRINTT living lab studies. Next, alongside with the SPRINTT consortium, different technologies were selected to be tested in the living labs. The living labs team also sent out calls requesting technologies to be tested by the SPRINTT consortium. Each test was aligned with the SPRINTT board, so as to align with the general SPRINTT working procedures and eligibility criteria.

Three different studies were set up to evaluate different innovative approaches

1. In study 1, a social robot (the NAO humanoid robot, see Figure 1) was developed to administer a test to screen for sarcopenia (SARC-F) and to instruct older adults on how to perform physical exercises (taken from the OTAGO program). We tested whether a social robot could discuss with an older adult about his or her health. This discussion could then be used by doctors as an intake. Additionally, we tried to see whether the robot could act as an instructor for explaining exercises to train an older adult's physical health. Older adults appreciated these robots, but saw room for improvement as well. The robot could not always interpret correctly what the older adult said (especially if the older adult talked in dialect) and older adults has difficulty with understanding what exercise the robot wanted them to perform

Figure 1. The NAO humanoid robot used in Study 1.

2. In study 2, we tested whether administering frailty assessment tests via tablet PCs yielded reliable scores (by comparing them to results obtained via administration on paper). We tested if we could use tablets to administer medical tests to score the health of older adults. Normally this is done on paper. We wanted to see if using tablets would yield the same results. We asked a set of older adults to do the exact same tests on paper and on a tablet. With regard to the test results, it did not matter whether older adults used paper and pen, or a tablet. However, most older adults preferred to use the tablet, as it was easier
3. In study 3, we explored how a virtual agent could administer frailty assessment tests in a more engaging manner and to improve compliance (see Figure 2).

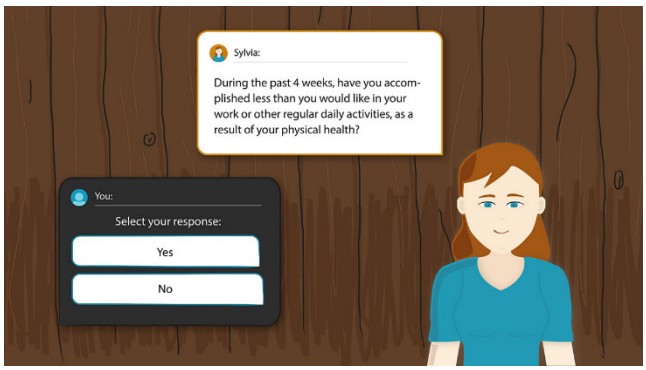


Figure 2. The virtual agent used in Study 3.

we studied how we can use a virtual agent (a cartoonlike figure on a website) to make medical tests more engaging. This, in turn, could improve the number of older adults who complete medical check-ups. We found that virtual agents are accepted by this group of people. Having an agent with the correct gender and age (in this case the participants preferred an older, male agent) appeared to be important for making people start a medical check-up.

All these efforts in the project were complemented by the expertise of WP8 in conducting analyses. The main objective of WP8 was the provision of statistical support for the design and conduct of the clinical trial. This objective was pursued through (1) performing sample size calculation for the RCT based on primary endpoint analysis, (2) the design and implementation of a statistical analysis plan agreed upon with EMA for the analysis of primary and secondary outcomes, (3) providing statistical and methodological support for data collection, management and quality monitoring, (4) completing the statistical section for the RCT technical protocol, and (5) performing statistical analyses on the primary efficacy endpoint and selected secondary endpoints at the end of the clinical study. It is worth mentioning that the adaptive recruitment and follow-up plan of the SPRINTT RCT was exploited by WP8 to reassess the study power at the end of the recruitment phase. Through the review of the information concerning the number of events experienced by the enrolees during the first 22 months, this interim evaluation allowed immediate action to be taken to preserve study power (i.e., extension beyond 24 months of the follow-up duration of participants enrolled during the first months of the trial). This decision was agreed upon with the other Consortium members, in particular with the WP7 team, and was supported by the External Scientific Advisory Board.

The WP8 team designed a complete plan for data analysis for the clinical study. The plan was designed through interaction with the WPs in charge for RCT design and implementation (WP2 and WP7) and WP6, in order to ensure that the study outcome measures would be adequately captured. The plan included the list of variables to be used to assess baseline comparability of the two randomised groups and the format in which these would be reported (e.g., means, standard deviations, medians, proportions, etc.). A detailed plan for statistical analysis of primary and selected secondary endpoints was also produced and shared with the Consortium as a whole and the WP7 team, in particular. At the end of the clinical study, following appropriate data cleaning and the database lock, statistical analyses were conducted as planned and results were reported using certified reference material (tables, listings and graphs). A separate set of analyses were performed in collaboration with WP2 to refine the initial operationalization of PF&S. These analyses aimed at identifying the characteristics of RCT participants randomised in the HALE arm who experienced the major mobility outcome. Analyses were also performed to identify variables predictive of incident disability in the intervention group in order to characterise the subgroup of participants who might be eligible from additional

treatment(s), including drugs.
Because of unforeseen technical difficulties with the ICT device initially proposed to collect physical activity and fall data, the analysis plan that was planned in collaboration with WP6 to explore associations between accelerometry data and physical function outcomes could not be produced.

WP8 provided statistical and methodological support during the whole duration of the clinical study to ensure high data quality standards. To accomplish this objective, a data surveillance plan was designed in cooperation with WP7 to ensure consistency, adequacy and quality of the aggregated data with the study objectives and assumptions. Safety tables were also compiled for safety surveillance. Data quality was ensured through the routine review of submitted data to identify and follow-up on missing data, inconsistent data, data outliers, and potential protocol deviations. Statistical analyses were conducted to identify data trends not easily detectable by onsite monitoring, such as standard checks of range, consistency and completeness of data, and checks for unusual distribution of data within and between study sites. Study site characteristics, performance metrics (e.g., screen failure, withdrawal rates, frequency of eligibility violations, correctness of forms completion, etc.), and clinical data were monitored to identify trial sites with characteristics potentially indicative of low performance or adherence to the study protocol. All the collected information was compiled in regular data surveillance reports. Separate reports were produced for the regular meetings with the Data Safety Monitoring Board. Finally, WP8 provided methodological support to the WP7 team for the production of training material on RCT operative procedures, including data collection and assessment of outcome measures.

Lastly, the activities of WP9 were performed following the original project and the description of work. A great deal of work was devoted during the entire duration of the SPRINTT study to disseminate the information and project findings first among the Consortium members and subsequently to the scientific community, the lay public, industry and other stakeholders.

The dissemination started with the production of a stakeholders inventory and a detailed plan defining the aims of the dissemination, the target groups, the specific means of communication to be used in each different group, and formulate the steps of dissemination to be implemented in a coordinated sequence (dissemination plan).

A very detailed publication policy was elaborated to provide transparent rules and procedures to prepare materials and papers describing any finding generated under the SPRINTT project. The policy applied to any means for disclosing information, in written or oral form, to the public, including any publication in journals, web communications, talks/lectures, presentations, etc. A Publication Committee was established that had the overall responsibility to guarantee that all scientific publications met the highest standard of quality and integrity and the principles of authorship were respected.

The website (http://www.mysprintt.eu/) was also a key accomplishment for the project. The website was regularly updated and expanded to take into account the progress of SPRINTT research activities as well as scientific advances concerning physical frailty and sarcopenia. A great work wasdone behind the scenes, in collaboration with WP6 and specifically with Caretek, in order to improve the SPRINTT website indexing on Google (for example, keywords, description for blind people, tags, etc.). During the 4th year of the project, WP9 developed a **subscription form** for the website (translated in all the 7 languages of participating countries), in order to collect email addresses of SPRINTT users, and send emails on website updates, tailor-made for healthcare providers, researchers and citizens. Furthermore, emails were written in English for all users, except for Italian citizens. On 2 October 2020 the following items were collected:

- 85 email addresses of citizens

- 33 email addresses from researchers (from Italy and from other 13 EU countries, but also USA, India, Turkey and New Zealand)
- 37 email addresses from healthcare providers (from Italy and from other 8 EU Countries, but also from USA, Mexico, Guatemala, Chile and Australia)

1.5. Scientific and technical results/foregrounds of the project

The SPRINTT project aimed at:

1) Identifying a precise subset of frail older adults with unmet medical needs;

2) Achieving an objective, standardised, and easy-to-apply operational definition of the geriatric condition of PF&S

3) Achieving scientific and regulatory consensus on target population, state and efficacy biomarkers, and clinical trial methodologies

As for the first 2 objectives, the SPRINTT Consortium was able to demonstrate the existence of a specific population of vulnerable older adults at risk of developing negative outcomes. The operational definition of PF&S developed by the SPRINTT Project members intercepts older adults in a critical but still reversible step of the disabling cascade. At this stage, different interventions (either lifestyle modifications, multicomponent or pharmacologic strategies) may be implemented to preserve the mobility and, therein, an independent life to an increasing share of older adults.

People with PF&S may be easily spotted in everyday life. The SPRINTT researchers have developed an easy-to-use identikit to find them in the community. A prototypical person with PF&S is an old woman/man that walks with a slow pace and/or may use a cane, needs help to rise form a chair, and often holds the handrails while walking up and down stairs. People with PF&S may be overweight or underweight but have a low muscle function that somewhat impairs their way of moving freely and enjoying their life. Unwittingly, people with PF&S are at high risk of incurring medical problems that may lead to hospitalization/institutionalization and more care use. PF&S thus identifies a subset of frail older adults with unmet medical needs. The defining criteria of PF&S are objective and measurable. In particular, the physical function domain of PF&S is assessed through the use of SPPB, a well-known, standardised, easy-to-apply and highly reproducible battery of functional tests. It is worth mentioning that European Medicines Agency identified the SPPB as the preferred option to characterise functional performance and physical frailty in clinical trials in vulnerable geriatric patients at risk of adverse outcomes (https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-physical-frailty-instruments-baseline-characterisation-older-populations-clinical_en.pdf). This choice was based on its *"prognostic value of disability and mortality; validation status; feasibility of use across all therapeutic areas; ease of use; time required; ease of investigator's training; cost"* that make the SPPB a full-fledged functional biomarker of ageing.

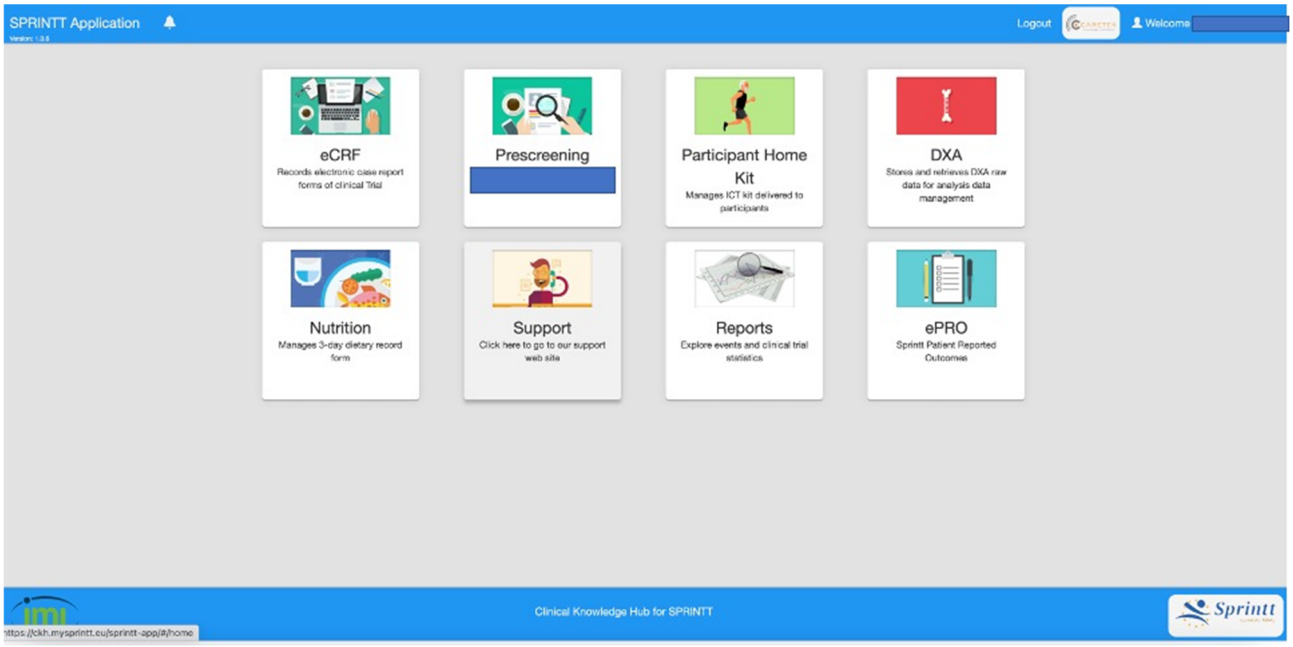
As for objective 3, the clinical trial methodologies received a preliminary positive feedback by regulators and PF&S was preliminarily endorsed by EMA as a prototypical geriatric condition. Both the results from the SPRINTT RCT and the biomarker (sub)studies will be presented to regulators to receive acknowledgement of their clinical relevance and suitability for future trials in older people. Due to COVID-19 pandemic, these activities were not finalized and are currently ongoing.

4) Conducting an RCT to test the efficacy of interventions at preventing the onset of mobility disability as well as other relevant negative health outcomes in older adults with PF&S (1,500 participants)

5) Realising an ICT infrastructure to enable the creation of a Clinical Knowledge Hub (CKH)
6) Developing a health economic model evaluating interventions in older adults with PF&S.

As for objective 4, methods and results of the SPRINTT RCT were thoroughly described in the present report sections.

The SPRINTT Clinical Knowledge Hub (CKH) (object 5) is an ICT infrastructure that was developed specifically for the SPRINTT Project. CKH was designed as a web application to incorporate the different tools (eCRF, DXA module, etc.) needed to collect SPRINTT data in a secure and user-friendly environment. The result was a an-easy-to use robust platform that helped the SPRINTT researchers in the trial deployment. SPRINTT CKH may embed a great variety of tools and allow real-time monitoring of trial activities. A dedicated report section was also implemented to assist in monitoring activities. For its characteristics, CKH may represent a useful tool for future trials in which complex interventions are applied and "non conventional" outcomes are measured. For instance, modules collecting data directly from wearable sensors may easily be implemented in the platform and remotely monitored by researchers to give advice/recommendations about different types of interventions (e.g. physical activity prescriptions).



The activities related to objective 6 are currently ongoing.

Most of the objectives were achieved by the SPRINTT Project Consortium. Due to the COVID-19 pandemic that impacted all SPRINTT investigators, some activities, including the achievement of final regulatory consensuses, are still ongoing and will be finalized within the coming months.

The most relevant scientific results obtained by the SPRINTT consortium are related to the SPRINTT RCT that took place from January 11th 2016 through October 31st 2019 in 16 clinical sites across 11 European countries. As previously described, the SPRINTT RCT was designed as a phase III, multicentre, single-blind, randomised controlled trial which tested the efficacy of an MCI based on physical activity, nutritional

counselling and information & communication technology (ICT) at preventing incident major mobility disability (MMD), operationalized as the failure to complete the 400m walk test, and other negative health-related events in a large sample of European seniors with PF&S compared with a healthy aging educational programme (HALE).

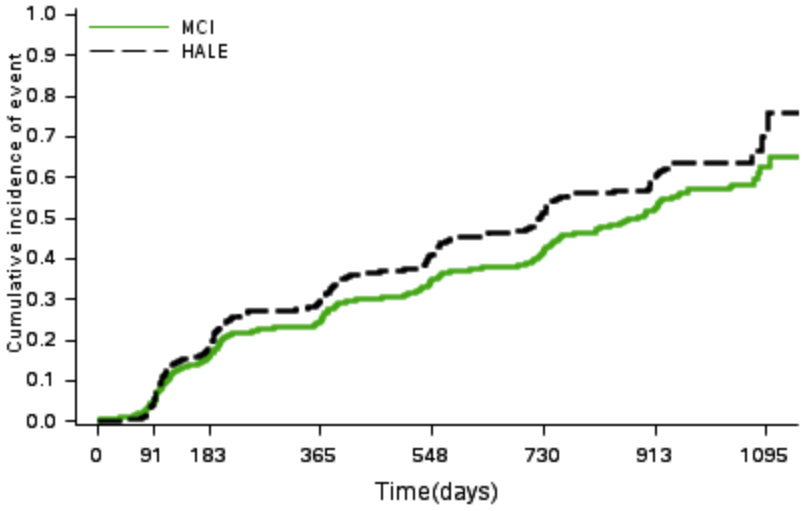
Among 12,358 prescreened candidates, 6710 proceeded to the screening visit. Of them, 1566 candidates met the eligibility criteria for the RCT, 1225 (78.2%) with SPPB 3–7 and 341 (21.8%) with SPPB 8 or 9. The original target of 1500 participants was exceeded because some prescreened candidates for whom screening visits were scheduled after the accomplishment of the recruitment target were found to be eligible. Eventually, 1519 participants accepted to be randomized, 760 to MCI and 759 to the HALE group. Of them, 1205 (79.3%) had an SPPB <8, while 314 (20.7%) had a score of 8 or 9.

The mean age was 78.9 years, with 1088 (71.6%) women, and the average body mass index (BMI) was 28.6 kg/m^2. As for the PF&S defining criteria, the average baseline SPPB score was 6.9, crude appendicular lean mass (aLM) was 21.1 kg in men and 14.6 kg in women, and aLM_{BMI} was 0.73 in men and 0.53 in women. Interestingly, the low muscle mass criterion was more often captured by crude aLM in women and by aLM_{BMI} in men, regardless of SPPB category. The average length of follow-up from randomization was 26.3 months (median=28.3 months; interquartile range [IQR]=10 months).

In the MCI group, participants attended on average 67.0% (SD=22.8%; median=71.8%; IQR=33%) and 73.5% (SD=36.5%; median=78.2%; IQR=48.9%) of center-based and home-based physical activity sessions, respectively, after excluding medical leave and other circumstances that prevented participants from exercising. Free-living walking activity, sitting and lying time, and standing activity time were captured through a wearable actimeter as proxies of physical activity and as a measure of intervention adherence. Actimetry parameters were indicative of a more active lifestyle in the MCI group compared with HALE participants during the first two years of the RCT. Differences between groups were no longer evident after 24 months, when, however, the number of observations was substantially reduced. Through the RCT, an average of 78.6% of full nutritional assessments, including collection of 3-day dietary records, was completed (SD=9.3%; median=76.2%; IQR=6.0%). In the HALE group, participants attended on average 65.9% (SD=26.4%; median=70.8%; IQR=39.4%) of scheduled meetings, after excluding medical leave and other circumstances that prevented participation.

Over the follow-up, a total of 683 MMD events (45.0%) were observed, 329 in the MCI group (43.3%) and 354 in the HALE group (46.6%). Of all MMD events, 374 (56.2%) resulted from failure to complete the 400-m walk test, while 291 (43.8%) were independently adjudicated.

As previously mentioned, the primary efficacy endpoint involved comparison between the two intervention arms in participants with baseline SPPB <8. MMD occurred in 283 (46.8%) participants of the MCI group and in 316 (52.7%) participants of the HALE group (HR=0.79; 95% CI=0.67–0.93; p=0.0051). Results were consistent when death was not included in the computation of the primary outcome (HR=0.79; 95% CI=0.67–0.93; p=0.0055).



Number at Risk

MCI	605	547	474	413	346	259	106	18
HALE	600	537	452	378	299	196	98	13

Because a significant interaction was determined between group assignment and SPPB category, participants with SPPB ≥8 were not included in the primary analysis and were analyzed separately. In this subset, MMD occurred in 46 (29.7%) participants of the MCI group and 38 (23.9%) of those in the HALE group (HR=1.25; 95% CI=0.79–1.95; p=0.3366). Subgroup analyses showed that the effects of interventions on incident MMD did not differ significantly across sexes, races, age groups, history of cardiovascular disease, history of diabetes, and baseline 4-m gait speed.

Among participants with SPPB <8, PMD occurred in 127 (21%) in those in the MCI group and 150 (25%) participants in the HALE group (HR=0.79; 95% CI=0.62–1.01; p=0.056). In participants with SPPB 8 or 9, PMD was experienced by 16 (10.3%) participants in the MCI group and 16 (10.1%) of those assigned to HALE (HR=1.14; 95% CI=0.55–2.36; p=0.7187).

Over the follow-up, a greater increase in SPPB scores was observed in the MCI group compared with the HALE group in participants with baseline SPPB <8. At 36 months, participants in the MCI group had improved their SPPB score by 2 points (SE=0.21; 95% CI=1.64–2.45), while a 1-point increase was experienced by those in the HALE group (SE=0.19; 95% CI=0.66–1.42). An increase in SPPB scores over time was also observed in participants with SPPB 8 or 9. However, the magnitude of changes was smaller (approximately 1 point in the MCI group and 0.5 points in the HALE group) and SPPB scores were not different between intervention groups at 36 months.

Changes in aLM were observed in the two intervention groups during the follow-up with sex-specific patterns. In women, declines in crude aLM and aLM_{BMI} over time were greater in those allocated to HALE than in their MCI counterparts. In women with SPPB <8, mean differences in aLM and aLM_{BMI} between MCI and HALE participants at 36 months were 0.49 kg (SE=0.12; 95% CI=0.26–0.73) and 0.02 (SE=0.01; 95% CI=0.01–0.03), respectively. In women with SPPB 8 or 9, at the end of the follow-up, differences in aLM and aLM_{BMI} between intervention groups were 0.60 kg (SE=0.15; 95% CI=0.30–0.90) and 0.02 (SE=0.01; 95% CI=0.00-0.03), respectively. In men, aLM and aLM_{BMI} declined over time with no clear differences between intervention groups or baseline SPPB categories.

Interestingly, mood also improved significantly in MCI participants compared with HALE counterparts. Indeed, the average difference in the Center for Epidemiological Studies-Depression scale (CES-D) score between groups was a remarkable reduction of 2.7 points (SE=0.86; 95% CI=-4.36 to -0.97) in MCI compared with HALE participants.

Data related to safety were analyzed by intervention arm in the whole randomized population as well as according to SPPB categories. During the RCT, 416 (54.7%) participants in the MCI group and 376 (49.5%) participants in the HALE group experienced at least one AE (RR=1.10; 95% CI=1.00−1.22). Serious AEs, including death, life-threatening illnesses or accidents, hospitalizations, permanent disability or incapacity, and other serious illnesses, were experienced by 282 (37.1%) and 264 (34.8%) participants in the MCI and HALE group, respectively (RR=1.07; 95% CI 0.93−1.22). Reasons for hospitalization and emergency room or urgent care visits were highly heterogeneous and unrelated to study procedures. Fall events were reported by 350 (46.1%) and 348 (45.8%) MCI and HALE participants, respectively (RR=1.00; 95 CI=0.90−1.12).

Collectively, the SPRINTT RCT showed that an MCI based on physical activity, nutrition counseling and ICT reduced major mobility disability over 26 months in older adults with PF&S. Implementation of such an intervention in community-dwelling older adults may represent a feasible strategy to reduce burdensome age-related mobility impairments in people at risk of disability

Another major milestone achieved by the SPRINTT Consortium was the SPRINTT Clinical Knowledge Hub (CKH), the ICT infrastructure developed for the project. The CKH has been finalised and presented to the Annual Conference of the EUGMS. Due to its versatility and the easy integration with popular eCRF platforms, the SPRINTT CKH may represent a prototypical tool to conduct new-generation clinical trials.

1.6. Potential impact and main dissemination activities and exploitation of results

On 14 December 2020, the United Nations General Assembly proclaimed the Decade of Healthy Ageing (2021-2030) to promote initiatives aimed at preserving functional ability and engagement in advanced age. Disease-oriented care models are inapt to extend healthspan and promote optimal longevity.
A shift was therefore invoked from pursuing the treatment of single diseases toward holistic, person-centered approaches to maximize functional abilities. In this scenario, mobility is regarded as a primary target to foster active aging. This view is supported by the observation that, in advanced age, reduced physical performance is associated with higher risk of disability, hospitalization, nursing-home placement, and death as well as with greater healthcare costs.
In particular, it was estimated that (physical) frailty has an incremental effect on ambulatory health expenditures of roughly €750 and €1500 for pre-frail and frail individuals, respectively.
Conversely, improvements in habitual walking speed are associated with increased survival. The relevance of physical performance in late life is further highlighted by the fact that the ongoing pandemic has disproportionately impacted older people with impaired functional status.
The disabling trajectory of mobility-limited older adults may be deflected by lifestyle interventions. In this scenario, the SPRINTT projected was conceived to specifically target older adults with functional limitations without mobility disability. One of the main strengths of SPRINTT is the clinical relevance of the condition of interest.
As conceptualised by the project consortium and preliminarily endorsed by EMA, PF&S intercepts older adults in a critical step of the disabling cascade, therefore identifying a specific population with unmet medical needs. Indeed, preliminary analysis on baseline SPRINTT dataset have shown PF&S was associated with greater odds of emergency room and hospital admission as well as formal and informal long-term care use. The primary outcome of SPRINTT, MMD, reflects a critical and potentially reversible pre-disability stage. Failure to complete the 400-meter walk test predicts major negative health-related events (including disability and mortality) independent of comorbidities. This test is indeed crucial and discriminative for the functional assessment of apparently well-functioning, yet at-risk older adults, and frames a multisystem dysfunction amenable for person-tailored, multidimensional interventions, such as the MCI implemented in SPRINTT.
The SPRINTT RCT showed that, compared with a HALE program, an MCI based on physical activity with ICT support and nutritional counselling significantly reduced the risk of incident MMD in older adults with PF&S and baseline SPPB <8 over an average of 26 months of follow-up. MCI elicited substantial improvements in SPPB scores in frailer older persons with PF&S and, in women, attenuated declines in aLM regardless of baseline SPPB score. These findings indicate that the MCI tested in SPRINTT is an effective strategy to reduce the burden of mobility impairment in community-dwelling older adults at risk of disability.
While the LIFE study was the first and largest RCT showing beneficial effects of physical activity in older adults over a long follow-up, SPRINTT may be considered a relevant step forward in the field. First of all, participants were recruited in 11 European countries. Therefore, the study sample was composed by a geographically and culturally heterogeneous cohort of frail older people across Europe. In addition, the study population was among the larger and frailer cohorts ever included in an RCT and followed up for more than 2 years. Indeed, SPRINTT participants recapitulate the characteristics of a vulnerable population that is increasingly prevalent in modern societies, but typically excluded from RCTs.

The SPRINTT RCT also showed that MCI produced significant improvements in the other two PF&S defining elements, i.e., poor physical performance and low muscle mass. In particular, in participants with baseline SPPB <8, at the end of the trial, the SPPB score increased by 2 points in the MCI group compared with baseline. This result is remarkable, since changes of 1-1.5 points in the SPPB summary score impact on clinical status and overall quality of life of older adults. It is worth mentioning that, in participants with SPPB <8, the average baseline score was 6.2 which increased to 8.2 in the MCI group at the end of the trial. As shown by LIFE and confirmed by SPRINTT, older adults with an SPPB score >8 have a reduced risk of developing MMD.

Older adults with baseline SPPB <8 allocated to HALE improved their SPPB summary score by 1 point relative to baseline. Recent evidence supports that social engagement may positively influence physical function in older persons. Participation to meetings, socialization with HALE group companions as well as regular medical contacts offered older adults the opportunity to move from their home and practice functional tasks in the community, which may have beneficially impacted their functional status. This view is supported by findings from the LIFE pilot study in which the SPPB score increased by more than 1 point in over 50% of participants in the control group after 12 months of a successful aging intervention. This gain was lost 2 years after the end of the intervention. Our findings supports the recommendations by WHO Global strategy on ageing and health to promote social engagement, inclusion, and participation

MCI had a positive effect on muscle mass in women, but not in men, irrespective of baseline SPPB category. Different trajectories in body composition have been described in older men and women, with men experiencing greater losses of lean mass over time. Sex also influences the relation between body composition and physical function in older adults, such that physical performance appears to be more dependent on lean mass in women than in men. In addition, sex-specific associations between protein intake and changes in muscle mass and physical function were described in older persons. Overall, our findings suggest that the MCI implemented in SPRINTT may be more effective in older women with PF&S. This is also apparent from the subgroup analysis showing a substantial benefit experienced by older women with SPPB<8.

SPRINTT has relevant strengths. Major efficacy endpoints are reliable, standardized, and well-validated clinical and public health outcomes for older people. Both retention and adherence to RCT interventions were remarkably high and comparable with other major non-pharmacological trials in frail older adults. MCI proved to be feasible, safe, and effective in a highly vulnerable population, although no reductions in falls, hospitalizations, or deaths were observed in the active group.

Findings from the SPRINTT Project may have a major impact on the health and socio-economic status of European citizens. The condition of interest, PF&S, has received initial endorsement by EMA as a prototypical geriatric condition amenable for preventive interventions against disability. SPRINTT RCT clearly showed that older adults with PF&S respond positively to MCI and improve their physical function, mood and quality of life as well as reduce their risk of mobility disability. People with PF&S who are non-responders to MCI may be eligible to pharmacological interventions targeting muscle mass and function. It is worth mentioning that PF&S in its conceptualization has all the characteristics for a rapid implementation in the clinics and for easy acceptation by health care professionals, public health authorities, and regulatory bodies. Indeed, PF&S has a biological substratum at the level of muscle, easily and objectively measurable with available techniques. At the clinical level, the manifestations of the PF&S, such as slow gait speed, impaired balance, and weakness, are also measurable in an objective manner with specific assessment scales, such as the SPPB. This renders PF&S similar to other common age-related degenerative conditions, such as congestive heart failure, chronic obstructive pulmonary disease, and peripheral artery disease.

Moreover, the ongoing biomarker studies will identify possible biological mediators that characterize PF&S and its progression, and define people who will respond or not to MCI. The invaluable amounts of biological samples and data collected as well as the SPRINTT CKH infrastructure are notable means

to attract both academic and biopharmaceutical R&D departments interested in the preservation of physical function and wellbeing of the growing European older population with unmet medical needs.

To complement this overall view, we would like to pick up countries specific examples:

- In Czech Republic

The SPRINTT project dissemination activities increased awareness regarding physical frailty, sarcopenia and their adverse and costly consequences such as falls, disability and long-term care use. It stimulated discussion in scientific communities and organizations. (medical, nursing, public health, health care management) on how to improve screening and recognition of frailty/sarcopenia and started negotiations with health care insurance companies to reimburse diagnostic procedures (e.g., DXA). With project results dissemination, the implementation activities will focus on beneficial potential of multimodal intervention to prevent, slow down or reverse frailty/sarcopenia. Other stakeholders, such as NGO and social care providers and representatives of older people (LIFE 90, University of the 3rd age participants) were invited to participate in broader dissemination of project results and increase of its overall impact.

- In Finland

In an ageing society, like Finland, maintaining function and wellbeing of older citizens is of utmost importance from societal and economical perspectives. A substantial proportion of older people are at esspecially high risk for mobility disability after the 2020 COVID-19 pandemic and lockdowns related to it. Therefore, the results from SPRINTT will give tools to cope with the socioeconomic complications of Covid-19.
SPRINTT results will help organize and implement more effective methods to preserve function of vulnerable and frail older people, a substantial proportion of the older population and at special risk after the Covid-19 pandemic.

- In Germany

A local Sportsclub intergrates the SPRINTT program into its official program. The team trained several of its exercise trainers on the SPRINTT MCI program.
At the national level, as sarcopenia has also received an ICD code (M62.50), there will be in the future the possibility to integrate sarcopenic older persons into rehabilitation exercise programs (including 50 sessions per year). The rehabilitation program in Germany consists of several arms (neurological, orthopedic, COPD, CVD, and diabetes, as well as functional rehab), and is regulated by law.
Furthermore, together with Michael Drey and colleagues, the team has translated and validated the SARC-F into German (Drey et al., 2020). This validated German SARC-F will help identify in the future “at risk of sarcopenic older persons” in clinical and community settings.

- In Italy

Awareness on the PF&S condition was raised at multiple levels. The lay public was thoroughly informed through participation of SPRINTT investigators in local and national mass communication media. SPRINTT booklets were produced in which the benefits of physical activity and optimal nutrition on PF&S were explained in a plain, yet rigorous manner. A fruitful collaboration was established between SPRINTT investigators and the governance of “Coldiretti”, the largest European federation of retired farmers. The concept of PF&S and possible interventions to prevent physical disability in advanced age were illustrated to Coldiretti associates in meetings organized ad hoc by

the federation. A FaceBook page ("SPRINTTItalia") was created and regularly updated to offer tips on how to keep active and in good health throughout the life course. The same concepts were promoted through the "Longevity check-up 7+" project, an initiative developed by the Deptartment of Geriatrics at the UCSC to raise awareness on the importance of healthy lifestyle habits to reach optimal longevity. The campaign received additional media attention by sponsoring the "Longevity run" initiative, a series of mass-gathering events organized across Italy to promote physical activity as a means to foster successful aging.

The Italian scientific community was kept updated on the progresses of SPRINTT through the participation of SPRINTT investigators in national conferences of geriatrics, internal medicine, physiotherapy, and translational science. It is worth mentioning that the dissemination of the SPRINTT concepts has substantially benefited from the fact that many SPRINTT investigators are board members of the Italian Society of Gerontology and Geriatrics (SIGG). Dr. Landi, leader of WP7, is currently the President of the SIGG.

- In Poland

The first stage of using the results of the SPRINTT project is an extensive information and education campaign, targeted to seniors and healthcare professionals, presenting the possibility of preventing mobility disability by implementing a multimodal intervention involving increasing physical activity and nutrition. This campaign is the basis for raising awareness among seniors and healthcare professionals and will enable widespread implementation of intervention aimed at reducing the prevalence of mobility disability resulting from sarcopenia. This will translate into a longer preservation of physical function among older persons. Physical activity and adequate nutrition can help improve the overall health of older people. In turn, reducing the number of disabled elderly people will contribute to reduce the need for care services, which may decrease the costs associated with the care.

- In Spain

Reversing or slowing sarcopenia in the course of physical frailty could decrease the risk of mobility disability and other complications and thereby generate important societal cost savings, together with improvements in wellbeing and quality of life and reduced need for informal care
- Detecting sarcopenia and frailty and including both conditions in mainstream clinical medicine will contribute to early detection and treatment. As both conditions are determinants of poor prognosis in many other chronic conditions, this will lead to improved prognosis.
- As soon as the final results are published they will be actively promoted, to both professionals and decision makers, with the help of the Spanish Geriatric Society
The Region of Madrid plans to implement in older people living in nursing homes (around 50,000 persons) an integrated physical activity program following the main conceptual approach of SPRINTT. This implies a major logistic development which will involve hundreds of physiotherapists (new

contracts) based in Primary Care and a strong coordination with the Geriatric Teams based at the hospitals. The Directorate in charge of that task in the Regional Ministry of Health has contacted with us in order to provide support and, hopefully, training based in both Vivifrail and SPRINTT.
In a second step, the Spanish team has planned to promote this intervention in older people at home.

The website (http://www.mysprintt.eu/) was a major mean of dissemination of available and newly produced knowledge during the project and therefore it was created at a very early stage, before the anticipated delivery date. It has been constantly updated and expanded to take into account the progress of SPRINTT research activities as well as scientific advances concerning PF&S.

The Dialogue platform of SPRINTT was a board of external advisors who supervised the project and its progress, and tackled issues that raised from the different perspectives involved. This board provided advice on the set up and conduct of the clinical study, dedicated communication strategies and aimed at ensuring that the project adequately met the needs of patients and caregivers. In the website specific educational contents were produced for researchers, health care professionals, older people and their caregivers. The layout and style of the information was different and specific for each type of stakeholder respecting health literacy principles. In particular, for contents specific for the lay public, the WP9 collaborated with the Dialogue platform. In order to promote health literacy concerning the topic of frailty and sarcopenia, several leaflets for the public were developed on the following topics: frailty, sarcopenia, dietary protein, aerobic exercise, balance exercise and strength training. These flyers, which were freely downloadable from the website, were translated into English, Italian, French and German, whereas some of the six flyers were also translated in Polish (n=2), Spanish (n=4) and Finnish (n=3). For the lay public, scientific articles concerning PF&S, and a healthy lifestyle (physical activity and nutrition) were written in a less technical and simplified language.

Throughout the course of the project, the section dedicated to health professionals and that dedicated to researchers was constantly updated, including about 300 articles on PF&S.

General practitioners (GPs) were identified as key stakeholders, as they provide medical care to older persons, including those with physical frailty and sarcopenia. However, GPs often do not have familiarity with the concepts of PF&S. The SPRINTT team developed specific material for GPs that fell under three major categories. First, conventional, mainly paper based, dissemination materials (e.g. leaflets, flyers, posters, newsletters, publications, etc.) were produced, presenting clinical manifestations, health consequences, prevention and treatment of patients with PF&S. Then, in the SPRINTT website, a specific section was developed for health care professionals, including primary care physicians, which provided easy, accessible and well-structured information about the project, structure, objectives and expected results. Finally, to facilitate the illustration of the SPRINTT project and its activities during various events and specific workshops, a standard power point presentation was prepared in English. The PowerPoint presentation for GPs was released in three different formats with increasing complexity. The basic power point presentation included essential background and a core concepts of the SPRINTT project, the second presentation included had a more complete background and a full explanation of the SPRINTT project, finally, the third presentation included an expanded scientific rationale of the SPRINTT project and the current state of the art of scientific knowledge. These power point presentations were prepared in close collaboration with the Dialogue platform.

In the **multimedia section**, several videos were uploaded, including presentations of the project at major international scientific meetings. The **events area** collected the main international events in the geriatric field. The **news section** was a tool used by WP9 to communicate information about the project status outside the project. The official mail address of the project was activated and available on the SPRINTT website since the creation of the website (sprintt-Info@mysprintt.eu and sprintt-press@mysprintt.eu). Many older people, caregivers and health care professional contacted the SPRINTT staff to ask some information using the official mail address of the project. All the pictures uploaded on the website respected the rules of copyright. The website was linked with a range of other websites including those of the partner institutions of SPRINTT, national and international organisations in the field of gerontology and geriatrics, nutrition and physical activity for older adults, older persons' representative organizations, and social media, in order to maximize the diffusion of the project's findings. An efficient system of monitoring page views was created. on 8 October 2020 the counter reported 890,403 website visits

1.7. Lessons learned and further opportunities for research

The collaboration within a public-private partnership has been an added value to achieve the project objectives. The open and continuous dialogue between industry, academia and stakeholders resulted in a) the identification and characterization of a condition of interest that frames an older population with unmet medical needs; b) the design and conduction of an RCT compliant with International and National Rules, and consistent with recommendations from European Regulatory Agencies; c) regulatory recognition of the sarcopenia definition and endpoints used in SPRINTT; d) the development of an ICT infrastructure to be used in future studies.

The SPRINTT project may open several venues in the field of research on aging. PF&S was preliminarily endorsed by EMA as a prototypical geriatric condition. The results from the SPRINTT RCT will be presented to regulators to show the actual clinical relevance of PF&S and its suitability for future trials in older people.

The SPRINTT biobank is one of the largest repositories of biosamples from older, community-dwelling adults with a range of frailty severity available in Europe. Its establishment and exploitation are a remarkable legacy of the project.

Besides the biobank, the SPRINTT Consortium developed innovative strategies for biomarker discovery that encompass the complexity of the biology of aging. Several projects were built based on the "SPRINTT Biomarker" tenets, including the "BIOmarkers associated with Sarcopenia and PHysical frailty in ElderRly pErsons" (BIOSPHERE) study, the "develOpment of metabolic and functional markers of Dementia IN Older people" (ODINO) Study, and the "EXosomes in PArkiNson Disease" (EXPAND) study, among others. All these projects lay on the founding concept of "geroscience", i.e. a specific age-related condition develops based upon different "signature" perturbations in one or more of the fundamental biological mechanisms of aging, the so-called "hallmarks of aging".

SPRINTT Consortium Members are leading and/or collaborating to International Projects aimed at implementing multicomponent interventions in frail older adults across Continents. For example, HUG is coordinating the EU-funded DIABFRAIL-LATAM study that aims at scaling up a multimodal intervention in frail older people with diabetes in 5 Latin-American countries across different settings of care. UCSC and DiFrail are part of this Consortium.

The common concepts that inspired SPRINTT and LIFE studies have reinforced a bidirectional collaboration with US partners. For instance, Dr. Pahor, PI of LIFE, acted as the leader of the External

Scientific Advisory Board of SPRINTT. Furthermore, studies have been planned to exploit the SPRINTT and LIFE databases, which will be provide an unprecedented amount of data on a vulnerable population typically excluded from "traditional" RCTs.

The involvement of Dr. Renuka Visvanathan, Clinical Director of the Aged & Extended Care Services at the Queen Elizabeth Hospital & Basil Hetzel Institute (Adeleide, Australia), as a member of the Data Safety and Managing Board of SPRINTT has laid the ground for additional collaborations between SPRINTT investigators and their Australian peers on topics related to sarcopenia, frailty, and development of clinical pathways for vulnerable older adults.

The demonstration that large numbers of older adults with sarcopenia and physical frailty can be identified, recruited, diagnosed, and treated is not to be underestimated. This sort of feasibility is of direct importance to industry sponsors. Moreover, the participating centers form the core of a potential clinical trial network for testing emerging interventions for sarcopenia and physical frailty.