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Clinical Trials on Sarcopenia: Methodological Issues Regarding Phase 3 Trials

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Keywords

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Sarcopenia was initially defined as an age-related loss of muscle mass¹ but this definition and the biological and clinical concept of sarcopenia have dramatically evolved to try to address a broader perspective on this important part of the aging process. However, current research on the plausible mechanistic pathways leading to sarcopenia and the functional consequences of sarcopenia are hampered by a lack of a consensus definition and a standardized assessment methodology.^{2,3} This issue is currently addressed by numerous international scientific and clinical groups with limited success.⁴ The lack of a clear definition of sarcopenia and an assessment methodology results in a variation in the reported prevalence across available representative epidemiologic cohorts of between 8% and 40%.² This broad range in prevalence and the absence of consensus criteria make the performance and outcomes of phase 3 clinical trials challenging. A large variability in the target population, if uncontrolled, increases the uncertainty in possible drug effects by inflating the confidence intervals, and attempts to control the variability by using a homogeneous less-representative study population reduces the generalizability of the drug effects, thus questioning the clinical efficacy of these trials. It is noteworthy to state that the challenges to conduct phase 3 trials in the elderly should not offset the opportunities for the development of new strategies to counteract sarcopenia and prevent late-life disability.

This article comprehensively reviews the methodological issues of conducting phase 3 clinical trials for sarcopenia. The current sarcopenia definition, body composition

assessment, target population, end points, the need of biologic markers, and the design of phase 3 trials are further developed throughout this article.

METHODOLOGY

A PubMed search with the MeSH terms, sarcopenia (all subheadings): clinical trial, phase 3, body composition, sarcopenia-aged-80 and over-frail elderly, was performed to retrieve relevant articles published from 2008 through 2010. Abstracts of the articles were reviewed, and selected publications were consulted in full. The reference lists of the selected articles were also perused for supportive relevant literature, and the investigators provided additional articles of interest to obtain a more comprehensive review of the literature.

DEFINING PHASE 3 CLINICAL TRIALS

Clinical trials are used to assess the performance and safety of new pharmaceutical agents, and they are classified into 4 phases, 1 to 4. Table 1 summarizes the main features of each of the phases. Before approval by government regulatory authorities and commercialization, a new drug is tested in separate trials in each of the 3 initial phases. Phase 4 is the postmarketing phase with intensive safety surveillance after a drug is commercially available. Phase 3 clinical trials are randomized controlled trials on large patient groups aimed at providing a definitive assessment of efficacy in clinical use. Because of their size and long duration, phase 3 trials are expensive, time consuming, and difficult to design and run.

DEFINITION OF SARCOPENIA

Since its first description, various definitions of sarcopenia have appeared as the knowledge and understanding of the aging process have increased. During this time, improved techniques to assess body composition and the availability of large representative epidemiologic data sets have modified the initial simple concept of a decrease in the muscle mass. Despite these enhancements in basic and clinical knowledge and technology, a consensus operational definition of sarcopenia applicable across racial groups/ethnic groups/populations has not developed.² The current definitions of sarcopenia add a loss in strength and a decline in function to the loss of muscle mass,⁴⁻⁶ but it is unclear whether muscle weakness results from the loss of muscle mass or from a qualitative histologic impairment of muscle tissue. Muscle mass declines at a rate of 1% to 2% per year after 50 years of age, but strength declines at 1.5% per year and is as much as 3% per year after the age of 60 years. Even if this decline in strength is higher in sedentary individuals, and twice as high in men than in women, less than 5% of the variance in the age-related decline in strength is explained by concurrent changes in muscle mass.⁷ Despite the actual controversies, the available data for sarcopenia are sufficient to designate that the decline in muscle mass is a primary determinant of the disabling process associated with sarcopenia. It could be less relevant than muscle strength or physical performance in predicting clinical events, but loss of lean mass is associated with major biologic and clinical outcomes.³

Most current definitions of sarcopenia are based on a cut point for low total or appendicular lean mass, and some have started to include measures of strength or physical

performance.^{8,9} This inclusion is because of recent knowledge that numerous mechanisms, beyond muscle mass, underlie the cause for muscle weakness in the elderly. Impairments in the muscular and/or nervous systems (with the possibility that cognitive decline acts as a determinant), physical inactivity, and chronic undernutrition, along with hormonal declines and immunologic changes in the physiology of older adults, contribute to this broader view of sarcopenia.^{4,9} A recent proposed diagnosis of sarcopenia required the documentation of low muscle mass and the presence of low strength as measured by grip strength or low physical performance as measured by gait speed.⁴ Walking requires muscle mass, function, and strength. Grip strength is a useful surrogate for total strength in young adults but can be compromised by arthritis and functional use in the hands. Gait speed, at the usual pace and over a short distance, is a reliable, valid, and quick physical performance assessment tool and a major predictor of adverse health outcomes with specific cut points for many diseases.⁵ These characteristics indicate that gait speed is potentially the main screening tool for the presence of sarcopenia along with low muscle mass in the elderly.⁴

TARGET POPULATIONS

The possible target populations should have a sarcopenia risk profile to provide the required clinical end points and optimize the statistical power to detect a meaningful difference between the intervention and the control group, to diminish the sample size, and to decrease the duration of the trial.¹⁰ However, the absence of a consensus definition of sarcopenia makes it difficult to determine the best target population. A broad definition of sarcopenia leads to a target population with high variability in which it is difficult to detect meaningful differences but it is easy to generalize. A restricted definition of sarcopenia leads to a target population with low variability but a low capacity of generalization of findings. In addition, the overall goal of the trial needs to be considered. For example, a primary preventive trial would require a presarcopenia stage target population with a risk profile without presenting sarcopenia. The presarcopenia stage has been recently conceptualized by low muscle mass without an effect on strength or physical performance.⁴ Table 2 summarizes the new concepts of presarcopenia, sarcopenia, and severe sarcopenia. In sarcopenia preventive trials, the variability can be large if inclusion is based solely on muscle mass assessment and large populations need to be included to power the study. If an intervention yields positive results (delays the onset of functional impairment or forces decline in the presence of low muscle mass), it could be generalized to the whole aging population. However, for clinical trials assessing an intervention, not only muscle impairment but also a decline in strength or physical performance (at a sarcopenic or severe sarcopenic stage) needs to be present. The target population must therefore be much more selective to exclude not only sarcopenic patients but also disabled older adults. Primary preventive trials should be conducted in autonomous, community-dwelling older adults who present with few disabilities, and so, strength measurements and physical performance assessment should not be impaired. Intervention trials can be conducted not only in community-dwelling autonomous older adults but also in specific communities presenting some degree of disability. The enrollment of specific populations such as institutionalized or hospitalized older adults (because of acute diseases or surgery or because of programmed elective surgery) depends on the goal of the study. If disability is present, the assessment tools need to be adapted to the degree of

dependency of the target population. Depending on the study population, slight to severe impairments should be observed in strength, physical performance, and muscle mass.

Another major challenge in selecting the target population is the presence of coexisting conditions with a wide spectrum of potential confounders able to influence skeletal muscle. Comorbidities need to be standardized to obtain a clear baseline with no confounders, but this standardization depends on the age range of the target group and increasing difficulty in the oldest age groups. Nutritional status needs to be assessed, and malnutrition should probably be considered as an exclusion criterion in the same way as the presence of severe functional impairment. The lack of careful characterization can explain why many clinical trials on sarcopenia, especially those that tested pharmacologic agents, have been disappointing.¹¹

Clearly, the first aim is to define sarcopenia (muscle mass and/or muscle weakness) depending on the overall goal of the trial, measure all possible confounders, and then decide how to account for them using design and analytic strategies. Two possible strategies, to account for confounders, are possible. The first is to state restrictive inclusion-exclusion criteria so that a homogeneous population is included in the trial. The second is to perform stratification based on previous identified confounders when analyzing the trial data. This strategy needs to be planned during the design of the study because the sample size needs to be increased.

Finally, the sarcopenia risk profile could be increased by increasing the age of the trial participants. The main manifestations of the age-related muscle loss are evident at old age; therefore, in order to evaluate whether an intervention is beneficial in the delay of sarcopenia onset or the treatment of sarcopenia, sarcopenia-related impairments must be present (for an intervention trial) or appear over a short period (for a prevention trial). Taking into account the prevalence of sarcopenia in community-dwelling older adults (about 10% in older adults aged 60–70 years and about 30% in those older than 80 years), the target population could be those aged 70 years or older.¹² In a younger population, sarcopenia would be hard to identify and too many participants will need to be screened; even more, the onset of sarcopenia-related impairments will be expected to develop over a longer period so that the duration of follow-up of this sample will be an issue.

SARCOPENIA ASSESSMENT: SKELETAL MUSCLE MASS

A wide range of techniques are available to assess muscle mass.¹³ The most commonly used, low cost, and accessible method to assess skeletal muscle mass is dual-energy x-ray absorptiometry (DXA). The accuracy of DXA for assessing muscle mass in people of different age groups and in some pathologic conditions may vary. DXA overestimates muscle mass because it does not differentiate between water and bone-free lean tissue. Despite these limitations, DXA provides valid estimates of appendicular skeletal muscle mass, and skeletal muscle measures with DXA are associated with prevalent and incident physical disability. Bioelectric impedance analysis is an inexpensive and easy-to-assess methodology but has limited accuracy and validity and is not broadly recommended for use among older adults. Similarly, anthropometric measures are not recommended for the

assessment of skeletal muscle mass in the elderly.⁴ Magnetic resonance imaging (MRI) and computed tomography (CT) are considered the gold standard and the most accurate imaging methods to assess muscle mass, muscle cross-sectional area, and muscle quality as determined by muscle density and intramuscular fat infiltration. However, the high cost and operational complexity limit their use in large clinical trials. MRI and CT also assess adipose tissue, which is directly associated with intramuscular fat infiltrates, which in turn may impair muscle function and strength.¹⁴

Skeletal muscle mass assessment should be performed by DXA in trials in which large samples are needed, such as preventive trials, when initially assessing the muscle mass as a case-finding tool; when lean, fat, and bone tissues need to be assessed at the same time; or when repeated measurements are needed (because DXA exposes to minimum radiation). MRI or CT should be reserved for more-specific trials during drug development in smaller samples but in which muscle density and fat infiltration is an issue and mainly for proof of concept. Reducing fat infiltration or increasing muscle density could result in muscle quality improvement without increases in muscle mass (therefore not detected by DXA) and therefore prove efficacy of certain interventions.

SARCOPENIA ASSESSMENT: STRENGTH AND PHYSICAL PERFORMANCE

Skeletal muscle strength is an important component for the assessment of sarcopenia and muscle quality. Several measurement methods are available, including simple dynamometers to measure isometric strength of the hand and forearm and the complex isokinetic strength measures of power and torque of the legs. Muscle strength measures of various body compartments are correlated. Grip strength measured with a hand dynamometer is a reasonable surrogate measure of skeletal muscle strength in the lower extremities,¹³ and it is a clinical marker of adverse outcomes, showing a predictive value for mortality similar to that of quadriceps strength.^{15,16} However, grip strength can be difficult to assess in many elderly because of arthritic effects on the hand and wrist and because it is not able to reflect loss of function of the lower body.

Standardized physical performance measures complement the measures of muscle mass for the assessment of sarcopenia. Physical performance measures are correlated with body composition and skeletal muscle parameters and predict relevant health-related outcomes, such as mortality, morbidity, institutionalization, and disability.^{5,13} The short physical performance battery (SPPB), gait speed at usual pace over a short distance, the long corridor walking test (400-m walk test), and the 6-minute walk test are among the most widely used and validated measures.^{5,17–20} Another useful physical performance measure is the stair climb test.¹⁹ Among this wide range of physical performance tests, SPPB and gait speed have recently been recommended for clinical trials in frail older adults.²⁰ Levels of clinically meaningful change have been established for the SPPB (1 point) and gait speed (0.10 m/s on a 4-m walking test).^{21,22} In addition, SPPB and gait speed have demonstrated excellent reliability, predictive validity for a large number of adverse outcomes, including mortality, nursing home admission, hospitalization, falls, and new onset of disability, and sensitivity to clinically important change.^{5,20}

BIOLOGICAL MARKERS IN TRIALS

Adipose tissue produces several adipokines (such as leptin) and proinflammatory cytokines (such as tumor necrosis factor α and interleukins 1 and 6), all of which are associated with aging, obesity, and sarcopenia. Several studies have shown independent associations of these factors with lower muscle strength, lower physical performance, and higher risk of disability in older persons.¹³ Assessment of antioxidants, such as intake of carotenoids and vitamin C and plasma levels of α - and γ -tocopherols, is inversely associated with measures of sarcopenia. Several other biomarkers have shown significant associations with measures of sarcopenia. Anemia is associated with lower muscle strength and physical performance in older persons, and low serum albumin levels are associated with poor grip strength in older men and women.¹³ Vitamin D plays an important role in the skeletal muscle metabolism, and persons with low serum 25-hydroxyvitamin D levels have poor muscle mass measured with DXA and diminished lower grip strength.²³ Therefore, several studies have shown that adipokines, proinflammatory cytokines, markers of oxidative damage, and a broad range of other biomarkers have strong and independent associations with several measures of sarcopenia. However, such markers are also associated with a wide range of other diseases and conditions. Depending on the overall goal of the trial, biomarkers should be included. The use of blood sampling and dosing biomarkers in large preventive trials depends on specific end points and costs.¹⁰ In the case of smaller sample sizes in intervention trials, blood sampling is possible and probably needed to eliminate possible confounders that could diminish the expected effect of an intervention.

END POINTS FOR TRIALS IN SARCOPENIA

Primary outcomes for clinical trials of interventions on sarcopenia should be highly responsive to treatment effects and clinically relevant. Functional abilities are the most clinically relevant factors affected by sarcopenia, and the primary end point of all sarcopenia trials should include the assessment of physical performances.²² Among performance-based measures of function, the best-studied measures are those that assess the function and mobility of lower extremity, which contains the largest muscles of the body. Such measures have demonstrated predictive validity for numerous critical health factors such as survival, health care use, future functional decline, and quality of life. Performance measures of mobility have also repeatedly been shown to be sensitive to changes in strength.²² After identifying a valid and reliable assessment tool as a primary end point, a clinically meaningful change detected by the tool becomes an issue and needs to be identified. Without this identified meaningful change, the intervention is considered clinically relevant even if statistically significant.¹⁰ As stated earlier, SPPB and gait speed (over a short distance at usual pace) are recommended as the primary end points in clinical trials.²⁰ However, another challenge with function-related end points is that disability fluctuates and is variable among older adults, especially among those related to transient acute illness and exacerbations of chronic illness. Investigators should cope with eventual fluctuations of end points, and the best analytic strategies should be proposed to minimize the effect of fluctuation. Although time-to-event designs with survival analyses are currently being used, analyses by linear mixed effects models have been proposed for data that are repeatedly assessed in longitudinal cohorts and might fluctuate over time.²⁴

In trials involving sarcopenia, in order to determine if the treatment worked the way it was expected to, strength and muscle mass need to be assessed as secondary end points. Clearly, all the issues that affect strength and mass measurements including validity, feasibility, and reproducibility come into play if they are to be considered as secondary end points and of particular interest in specific research areas and intervention trials.²² Investigators need to be selective in the possible secondary end points to include confounders but to avoid participant burden in old-aged population.¹⁰ Some end points are not applicable to all participants. Incapacity to perform an end point assessment (for example, in the case of disabled older adults unable to perform a physical performance assessment) automatically transforms it into an exclusion criterion, and the older adults who cannot perform the end points of the trial cannot be enrolled. In these cases, the development of new scales or end points for special subpopulations should be encouraged or the secondary end point should not be included in the trial.

Special attention also needs to be taken regarding cognition because trials involving physical activity, physical performance, and strength could affect progression of cognitive decline and adherence to the protocol, compliance with the interventions, and programmed follow-up could be influenced by cognitive status.^{25,26} In a sarcopenia trial, a general recommendation could be to assess cognition, at baseline and during follow-up, and to evaluate direct and indirect drug effects on cognitive decline over time.

Fat mass contributes significantly to functional impairment in elderly people independent of muscle mass, and sarcopenic obesity was associated with an increased mobility disability compared with sarcopenia without obesity.²⁷ It is possible that the combination of high fat mass and low muscle mass is detrimental and highly predictive of functional decline. Changes over time in the fat mass could predict increases or decreases in future sarcopenia-related impairments, and intervention could be effective by changing fat mass with no initial effects on muscle mass. Until the exact phys-iopathologic pathways are known, it is recommended to measure and take into account fat mass in analytic strategies as a confounder. Also, intramuscular adipose infiltration is related to increasing age and increasing fat mass among different racial groups, and it is associated with metabolic abnormalities, poor strength, and performance measurers, as well as incident mobility disability and higher concentrations of inflammatory markers.^{28,29} Reduction of adipose infiltration by intervention could increase performance without a significant change in muscular mass. In cases in which the expected drug effect is to reduce adipose infiltration, MRI or CT scans could be proposed as a secondary end point and as a biomarker of drug efficacy.

DESIGN OF INTERVENTIONS IN PHASE 3 TRIALS

To verify the efficacy of interventions, it is important to maximize potential benefit and minimize possible toxicity. For complex syndromes, such as sarcopenia in older populations, multidomain intervention trials are being proposed in which several combined intervention approaches in one group are compared with alternative combined interventions or controls in another group. The main issue to be resolved in such trials is the interpretation of the results because it is difficult to assess which individual intervention did or did not

work. Interventions such as drugs, nutrition, programs of physical exercising, and social interventions depend on the type of trial and its feasibility. In order for evidence in a clinical trial to determine relevant difference from an intervention, usual clinical care (present in both intervention and control groups) needs to be characterized and standardized without contaminating the control group. Interventions also need to be standardized and be strong enough to be sufficiently relevant because the usual care in the control group is enhanced due to participation in a clinical trial.³⁰ Physical activity remains an issue because it is sometimes considered usual care and sometimes an intervention depending on the trial. So whether exercise is considered usual care and should be promoted in both control and intervention groups is an unresolved issue when enrolling sedentary older participants in a trial. Therefore, assessment of self-reported physical activity by a structured questionnaire should be systematically required in all trials even if inconsistencies are associated with the assessment.

DESIGNING A PHASE 3 PREVENTIVE TRIAL ON SARCOPENIA

Many aspects of the design of a preventive trial on sarcopenia have been discussed herein. Table 3 shows the main characteristics of such trials. Briefly, presarcopenic (solely based on low muscle mass) adults older than 70 years, DXA (body composition assessment), hand grip (strength), gait speed and SPPB (physical performance), delayed sarcopenia onset (as primary end points: muscle mass, strength, or physical performance), and inclusion of all possible confounders (as secondary end points), by providing few exclusion criteria, are the basis for a preventive trial. The trial must have a randomized control design, with the control group defined as “best standard of usual clinical care.”¹⁰ Multidomain interventions (interventions in different areas at the same time) for the prevention of sarcopenia should be used based on the existence of multiple physiopathologic pathways of sarcopenia onset and progression in older adults.^{11,22} Finally, follow-up should be standardized based on the overall goal. A broad recommendation of a 6-month follow-up can be settled, with a total duration of the trial of 1 to 3 years (depending on primary end point, population characteristics, and feasibility), taking into account annual rate of decline in physical performance, muscle mass, and strength.

DESIGNING A PHASE 3 INTERVENTION TRIAL ON SARCOPENIA

Many aspects of the design of an intervention trial on sarcopenia have been discussed previously. Table 3 shows the main characteristics of such trials. Briefly, sarcopenic (low muscle mass and low physical performance or strength) adults older than 70 years, DXA, MRI or CT (for body composition assessment), complex strength and physical performance measures, treatment of sarcopenia (primary end point being physical performance), strength and muscle mass (as secondary end points), and the inclusion of the fewest possible confounders (as secondary end points) by increasing exclusion criteria are the basis of an intervention trial. The homogenization of the enrolled population powers the study, traducing a sample size reduction with an increasing chance of proving effectiveness of the intervention.

Once more, the trial must be a randomized controlled one, with the control group defined as the best standard of usual clinical care. The intervention should generally be a single intervention (mainly drug intervention). Although contamination of the control group is less probable, exercising becomes an issue if considered as usual care, and investigators will need to standardize physical activity during trial design. Specific subgroups might participate in the trial, and dependency needs to be accounted for.¹⁰

Trial duration and follow-up depend on treatment properties, but should generally be conducted over a 12- to 18-month period.

HEALTH CARE COSTS OF SARCOPENIA

The sarcopenia-related economic burden is because of the links of low muscle mass with poor physical functioning, disability onset, and mortality.^{31–33} Loss in physical function increases even more the risk of physical disability, along with increased nursing home admission and mortality.^{2,34} Therefore, sarcopenia is responsible for approximately \$18 billion annual direct health care costs in the United States.³⁵ To put this in perspective, it has been estimated that the yearly economic cost of osteoporotic fractures in the United States is \$16.3 billion.³⁶ Considering that the total number of older adults is expected to double over the next 25 years, the absolute costs associated with sarcopenia are expected to increase sharply.⁹ Conducting phase 3 clinical trials, even if challenging, could eventually generate new strategies to prevent or treat sarcopenia and its associated health consequences. These strategies could ultimately reduce the health care costs along with an increase in quality of life of the elderly.

SUMMARY

- The design of sarcopenia trials is challenging but worthwhile because progression of the disabling process of older adults can be intervened upon.
- Current research on the plausible mechanistic pathways leading to sarcopenia and the functional consequences of sarcopenia are hampered by a lack of a consensus definition and a standardized assessment methodology.
- Taking into account the prevalence of sarcopenia in community-dwelling older adults, the target population could be established at an age of 70 years or more.
- Physical performance measures should be considered as the main end points.
- Physical exercising, whether considered as usual care or intervention, remains an issue.
- The most commonly used, low cost, and accessible method to assess skeletal muscle mass is DXA.

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Table 1

Phases of clinical trials during drug development

Phase	Subjects	Main End Points
Phase 1	Trial in a small group of healthy volunteers	Safety and tolerability Pharmacokinetics and pharmacodynamics
Phase 2	Trial in a larger group of healthy volunteers or patients	2A: antidisease activity and dose assessment 2B: efficacy of the drug
Phase 3	Randomized controlled trial in a large group of patients	Assessment of the efficacy of a drug Approval to market the drug
Phase 4	Trial in drug-prescribed patients Postmarketing trial	Safety surveillance (pharmacovigilance)

Table 2

Conceptual stages of sarcopenia

Parameter Assessed	Proposed Measurement	Presarcopenia	Sarcopenia	Severe Sarcopenia
Lean Mass	DXA	Decreased	Decreased	Decreased
Strength Physical performance	Hand grip Gait speed	Normal	Decreased strength or Decreased physical performance	Decreased strength and Decreased physical performance

Abbreviation: DXA, dual-energy x-ray absorptiometry.

Data from Cruz-Jentoft A, Baeyens JP, Bauer J, et al. Sarcopenia: European consensus on definition and diagnosis: report of the European working group on sarcopenia in older people. *Age Ageing* 2010;39:414.

Table 3

Design of phase 3 trials in sarcopenia

	Preventive Trial on Sarcopenia	Intervention Trial on Sarcopenia
Overall Goal	Delay the onset of sarcopenia	Treat sarcopenia
Sarcopenia Definition	Presarcopenia: low muscle mass with normal strength and physical performance	Sarcopenia: low muscle mass with decreased strength or physical performance Severe sarcopenia: low muscle mass with decreased strength and physical performance
Muscle Mass Assessment	DXA	DXA, MRI, or CT
Strength Assessment	Hand grip	Hand grip, complex isokinetic strength measures of power and torque
Physical Performance Assessment	Gait speed, SPPB	Gait speed, SPPB, LCWT, 6-minute walking test, stair climb test
Screening Population	Adults older than 70 years Autonomous adults Community-dwelling adults Normal strength and physical performance	Adults older than 70 years Autonomous or disabled adults Community-dwelling adults or specific communities Acute conditions such as falls, hospitalization, or selective surgery Impairments in strength and physical performance
Target Population	Broad sarcopenia definition No restrictive inclusion/exclusion criteria Heterogeneous population (solely based on muscle mass measurements) Large population Generalization to whole aging population if intervention effective	Restrictive sarcopenia definition Restrictive inclusion/exclusion criteria Homogeneous population Smaller population than a preventive trial Generalization to whole aging population will be an issue
Possible Confounders	Inactivity/physical activity Nutrition Previous disability Demography (gender, age, ethnicity) Chronic conditions (diseases and drugs) Biological markers (adipokines, inflammatory markers, vitamin D, etc)	
Primary End Points	Delay the onset of decline or increase physical performance and strength Stop decline or increase muscle mass	Increase physical performance
Secondary End Points	<ul style="list-style-type: none"> Limit secondary outcomes to avoid overburden <ul style="list-style-type: none"> Onset of permanent disabilities (ADL) Onset of cognitive decline Mortality Institutionalization Hospitalization Changes in cognition Changes in fat mass Evolution of biomarkers over time (if available) Falls Quality of life 	Few secondary outcomes Increase muscle mass Increase strength Evolution of biomarkers over time Changes in cognition Changes in fat infiltration Changes in fat mass
Trial design	Randomized controlled trial Control group: best standard of care	Randomized controlled trial Control group: best standard of care

	Preventive Trial on Sarcopenia	Intervention Trial on Sarcopenia
Intervention	Multidomain intervention Single-drug intervention Standardized program of physical activity	Single-drug intervention Standardized program of physical activity
Duration	1–3 y	12–18 mo

Abbreviation: ADL, activities of daily living.