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DESIGNING PHASE II B TRIALS IN SARCOPENIA *THE BEST TARGET POPULATION*

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Abstract

Despite the existing limitations and controversies regarding the definition of sarcopenia and its clinical consequences, the current scientific evidence strongly suggests that muscle decline is a primary determinant of the disabling process (and likely of other major health-related events). In fact, the muscle loss (in terms of mass as well as strength) occurring with aging has been growingly associated with mobility impairment and disability in older persons. Unfortunately, current evidence is mainly from observational studies. Times are mature to begin testing interventions aimed at modifying the sarcopenia process through the design and development of specific clinical trials. Considering the emergence of many promising interventions towards this age-related condition (e.g., physical exercise [in particular, resistance training], testosterone, antioxidant supplementations), the need for Phase II trial designs is high. In the present report, we discuss which are the major issues related to the design of Phase II clinical trials on sarcopenia with particular focus on the participant's characteristics to be considered as possible inclusion and exclusion criteria.

THE STUDY OF SARCOPENIA

Sarcopenia is the age-related phenomenon characterized by loss of muscle mass and strength which may consequently determine loss of function. Since its origins in 1988, when Rosenberg during a meeting in Albuquerque (New Mexico, USA) pointed out the importance of focusing more research efforts to this major feature of the aging process(1), many steps forward have been done in the understanding of this condition. Unfortunately, the exploration of this topic has not been easy as initially might have been expected. Despite of the steadily increasing number of studies targeting sarcopenia over the years (Figure 1), up to date, several major clinical and research issues are still present and debated(2, 3). In fact, results are not always been encouraging: while preliminary evidence suggested muscle mass decline as a crucial factor for determining the disabling process (primary outcome of geriatric medicine)(4–6), later studies have been raising some concerns about the predictive value of muscle mass for major health-related events(7–9). These controversial results have been explained by several weaknesses of current evidence on the topic. In particular, the

major limitation resides in the lack of a clear, standardized, and objective definition of sarcopenia(10, 11). Clarifying the defining criteria for sarcopenia means:

1. Distinguishing the age- versus the disease-related muscle decline. This issue is not trivial, because implicitly linked to the nature of the studied phenomenon. Is sarcopenia a physiological pathway or a manifestation of disease(s)? It is noteworthy that answering to this question poses the cornerstones for the development of adequate inclusion/exclusion criteria to be considered when designing clinical studies on the topic.
2. Determining the assessment method to measure skeletal muscle (both in its quantitative as well as qualitative characteristics). This point does not only involve the choice of a "gold standard" methodology, but the identification of relevant cut-points for the implementation of the measure in the clinical and research settings.
3. Agreeing about which are the expected results from interventions aimed at modifying the sarcopenia process. In other words, considering sarcopenia as a condition worth to be studied (because detrimental for the health status) implies setting reasonable outcomes in terms of prevention, treatment, and/or cure of it.

Why is it difficult to define sarcopenia? Mainly because it is not yet clear what should be included in this term. A recent position paper from the European Working Group on Sarcopenia in Older People(12) has proposed to base the sarcopenia definition on the loss of muscle mass combined with the reduction of muscle strength or physical performance. On the other hand, as pointed out by Clark and Manini(13), sarcopenia (from Greek *sarx* "flesh", and *penia* "loss") is different from dynapenia (i.e., loss of strength).

This controversial issue requires special attention. It is true that muscle strength is a stronger outcome with a clearer impact on physical impairment and disability (consequently, on clinical practice). For example, clinical trials testing physical exercise (in particular, resistance training) or anabolic agents (e.g., testosterone) have consistently found that strength improves before mass increases. But why we need to call the "muscle strength decline" with an inappropriate term (i.e., sarcopenia)? Altering the innate meaning of the term "sarcopenia" shifting it from a pure quantitative description of the phenomenon towards a sort of "comprehensive muscular outcome" may be potentially confusing. Conversely, muscle mass *per se* may have limited clinical relevance (especially if considering the huge initial expectations for this condition as a potential determinant of major health-related outcomes). However, the skeletal muscle mass decline still represents the most dramatic age-related body modification and a benchmark for studies on the aging process.

In a previous paper, Studenski reported the main considerations from an International Work Group held at the Baltimore Longitudinal Study of Aging in 2008(11). Among the statements provided to guide the definition of sarcopenia for future studies, there was the realization that:

1. Muscle mass alone is not a strong predictor of (current or future) function;

2. Muscle strength is a strong predictor of function, and weakness should be considered as a key clinical indicator;
3. Muscle impairment is determined by multiple potential concurrent pathophysiological contributors.

Considering geriatrics as specifically focused on preventing the onset of disability in older persons, the choice of low muscle strength (or weakness) as primary component of sarcopenia may seem more reasonable, and possibly facilitate its implementation in clinical and research settings. Even in this case, there are some difficulties with definitions. In fact, there are no standardized and validated criteria defining low muscle strength or weakness.

Another issue limiting the definition of sarcopenia is related to the wide spectrum of potential confounders able to (positively and negatively) influence the skeletal muscle (both in its amount and functionality)(10). In fact, numerous behavioral, biological, and clinical factors are able to significantly modify the sarcopenia process. An optimal definition should be able to capture the inner nature of this age-related decline by implicitly excluding (or taking care of) all the potential confounders/modifiers. In a previous paper(10), we provided a detailed description of the main factors to evaluate when recruiting participants for clinical trials on sarcopenia. In this context, it is worth to be mentioned the important role played by the adipose tissue. With aging, muscle mass decline is not an isolated phenomenon, but parallels the age-related increase of fat mass (till the worst case scenario of sarcopenic obesity(14–16)). Thus, there are in literature sarcopenia definitions which simultaneously consider muscle and fat mass(17, 18).

Although the limitations and controversies on the topic, the amount of data on sarcopenia is currently more than adequate to formally indicate muscle mass decline as a primary determinant of the disabling process. It may be less relevant of muscle strength and physical performance in predicting clinical events, but several studies have demonstrated that lean mass is associated with major biological (e.g., apoptosis(19), mitochondrial modifications(20), inflammation(17, 21), insulin resistance(22)) and clinical outcomes (e.g., lower extremity performance(5)). Nevertheless, most of available data are coming from observational studies. The limited findings from the few available clinical trials are negatively affected by 1) having sarcopenia as a secondary outcome, 2) small sample sizes, 3) recruitment of special populations (e.g., cancer patients), and/or (last, but for sure not least) 4) the lack of clinically-oriented outcomes to which interventions are targeted.

Times are mature to begin studying sarcopenia in a more structured way, that is through the design and development of specific clinical trials aimed at modifying this age-related process. Considering the emergence of many promising interventions towards this age-related condition, the need for Phase II trial designs is high.

DESIGNING PHASE IIB CLINICAL TRIALS ON SARCOPENIA

After a Phase I trial determines the safety and tolerability (plus pharmacokinetics and pharmacodynamics if a drug is tested) of an intervention on healthy volunteers, Phase II trials are called to provide the basis to make an informed and rational decision whether the

tested intervention should or not proceed to the following Phase III testing. Since Phase III trials are extremely time- and resource-consuming, the conduction of high-quality Phase II trials is crucial. Briefly, Phase II trials (usually enrolling more participants than Phase I trials, but still far less than Phase III trials) include healthy volunteers as well as patients, and specifically verify the activity of a new intervention. In particular, early Phase II trials (or Phase IIA trials) are aimed at determining the anti-disease activity of the tested intervention, assessing its required dosing. The following Phase II trials (or Phase IIB trials) are then conducted to estimate the degree of activity of the intervention, that is how well the intervention is effective at the established doses. Independently of their design (as single-arm study, or including the presence of alternative arms of patients), Phase II clinical trials are comparative(23).

The standard Phase II trial design is a single-arm study testing a null hypothesis (i.e., no efficacy of the intervention) versus an alternative hypothesis (i.e., the intervention is effective, and consequently worth to be further studied in Phase III trials). Sometimes, Phase II trials include a randomization to multiple single-arm studies (which may consider or not a control group). The main advantages of planning several randomized arms reside in the reduction of participants' selection bias and the uniform evaluation of the separate interventions(24).

During the Phase II trials, interim analyses are performed to verify that a specific group of participants is not receiving an intervention that is clearly inferior to others (in this case, the study is stopped). On the other hand, if an intervention is more effective than expected, the trial is not usually stopped because does not raise ethical concerns and there is interest in evaluating how far the novel intervention may be effective(25).

Moving back the discussion to the theme of sarcopenia, it is evident (as mentioned above) that the design of clinical trials is particularly hampered by the lack of a standardized definition serving as primary outcome. It is obvious that the inclusion and exclusion criteria to select the study population need to be chosen considering the final outcome. However, Phase II clinical trials can also rely on surrogate measures to determine the activity of the proposed intervention(26).

TARGET POPULATION FOR PHASE II CLINICAL TRIALS

A Phase II clinical trial is aimed at determining the activity of an intervention for a specific condition (or surrogate of it). Muscle strength and mass reach their peaks in the twenties, and start declining in the thirties with a progressive acceleration over time. However, the main clinical manifestations of the age-related muscle loss are usually evident only at old age. The study of a condition taking so long to become clinically relevant might be impossible without proper adaptations. Therefore, in order to evaluate whether an intervention is beneficial to stop or delay the age-related muscle decline, selected populations (serving as models of accelerated aging) may be considered.

Some examples of populations experiencing an "accelerated aging" are provided in Table 1. Young healthy volunteers restrained from physical activity may represent a first choice. This type of population may be characterized by a relatively easy recruitment, in particular if the

study is conducted in academic settings (with students as primary target). Moreover, by selecting healthy volunteers the burden of comorbidities potentially influencing the skeletal muscle will likely be irrelevant. Nevertheless, this option may rise some ethical concerns, especially if the study (and, consequently, the intervention [i.e., limitation of physical activity]) will be conducted over a long time. In fact, to develop the model of induced sarcopenia, participants should be encouraged to do less physical activity as possible, implicitly promoting a well-established risk factor (i.e., sedentary lifestyle) for a multitude of negative clinical outcomes. Moreover, this selection will likely exclude older persons who, besides of usually presenting a number of chronic diseases, may have explicit clinical contraindications to be sedentary (e.g., chronic venous insufficiency, cardiovascular disease, diabetes, neurological disorders).

The enrollment of patients with progeroid syndromes (characterized by a genetically-driven accelerated aging) might be extremely interesting, but the rarity of these conditions as well as ethical concerns (the patients are children) makes this option not easily doable. Moreover, the accelerated aging occurring in these syndromes is still not exactly the same kind of aging process physiologically experienced at a slower rate over decades. The genetic component of these diseases represents an important (and difficult to measure) confounder for the study of the aging muscle.

Alternatively, a possible model of sarcopenia in humans may be provided by patients with limited physical activity due to a temporary and specific acute condition. In this context, orthopedic older patients may represent an optimal type of study population to consider. More than patients having experienced a post-traumatic fracture (which may be more likely to present chronic clinical conditions or acute consequences of the trauma), older subjects undergoing elective surgery (e.g., knee or hip replacement intervention for arthritis) may represent excellent candidates for sarcopenia trials. In fact, besides of generally experiencing an overall healthy status (otherwise the surgical intervention could not be considered), they usually follow a pre-intervention *iter* (to assess their functional and biological reserves) which may facilitate their enrollment in clinical studies. Then, after the intervention, they usually reduce their physical exercise, limiting it to the rehabilitation activities. The major issue with this type of participants is represented by the consequences that the chronic condition to be surgically treated may have caused over years (e.g., walking impairments, postural modifications, local muscular changes due to the chronically inflamed site, muscular atrophy due to the previous long-lasting limited use or misuse).

Given the close relationship existing between inflammation and sarcopenia, some Authors have proposed to study the age-related muscular phenomenon in specific clinical conditions characterized by an inflammatory phenotype (e.g., rheumatoid arthritis, osteoarthritis)(27–30). If this opportunity might surely be biologically valid, major limitations are represented by the cumbersome (and potentially misleading) presence of the peculiar high inflammatory status. Moreover, some inflammatory diseases may not be particularly frequent at old age (e.g., acquired immune deficiency syndrome [AIDS]), thus potentially limiting the recruitment of older persons.

The best option (which is also the most commonly pursued) is to study sarcopenia by particularly focusing on physical function. In other words, the selection of a target population for sarcopenia trials among older persons experiencing some physical impairments is likely to represent the easiest and more efficient choice. Of course, this may pose the risk of ending with a too heterogeneous group of participants, characterized by different comorbidities. However, defining inclusion and exclusion criteria aimed at limiting those clinical conditions that more than others are able to affect skeletal muscle mass and function (e.g., stroke, Parkinson's disease) may reduce this potential bias. It is also noteworthy that, considering the lack of clinically relevant cut-points defining sarcopenia on the basis of skeletal muscle mass, the adoption of physical performance and muscle strength measures may bypass this issue. In fact, preliminary studies have already defined possible cut-points for physical function measures to be used for distinguishing normal versus abnormal values(31–34).

When evaluating all the possible opportunities in the designing phase of a sarcopenia trial, it is important to keep in mind that by choosing a specific population rather than another may lead to significantly different results. In fact, if the study population presents a condition influencing the skeletal muscle, results may be enhanced (if some muscle reserve is "freed" by the intervention), or attenuated (if the muscle is unable to react to the intervention because severely damaged or limited by the underlying condition).

As mentioned above, the easiest and more convenient way to conduct a Phase II trial on sarcopenia might be by selecting older persons which are already experiencing signs of muscle impairment or at an early stage of the disabling process. But what can be defined as initial muscle impairment? Likely something that is not yet clinically relevant. The definition of clinical relevance is closely related to the determination of cut-points identifying a certain condition. In nature, there are no categorical variables. The continuum experienced by all living beings needs categorizations which are often arbitrary and based on epidemiological studies distinguishing what is good from what is bad. So, in the context of determining clinical thresholds for muscle function, it is of extreme interest the analysis performed in the Health Aging and Body Composition (Health ABC) study database identifying cut-points for knee extensor strength able to predict the risk of mobility limitation in this sample of community-dwelling well-functioning older persons aged 70–79 years(35). The importance of a study like this resides in the provision of cut-points distinguishing normal from abnormal values, health from impairment. Unfortunately, to our knowledge, this is the only work proposing clinically-oriented cut-points for a muscle strength parameter. Although even better established cut-points are available for other physical function tests (e.g., Short Physical Performance Battery(33, 34)), the need to isolate the muscle function (as appropriate when considering sarcopenia) requires the choice of measures (as muscle strength) which are minimally influenced by other systems and apparati.

If there is a lack of established muscle strength cut-points to define a clinically relevant improvement (or worsening), the comparison between pre- and post-intervention muscle strength is still possible. This kind of evaluation presents two main limitations: 1) it is unknown whether a reported beneficial (or detrimental) effect is important from a clinical

standpoint of view, and 2) selection bias may influence the study findings. As mentioned above, the inclusion of a control group (with the design of a randomization phase) may (at least partially) solve both issues(24). In fact, if an alternative group testing another treatment (non necessarily a placebo) is available, researchers will be able to determine the relative efficacy of the two interventions through a fair comparison.

Once results from a specific intervention are obtained, special care needs to be taken before generalizing them to different settings and populations. In particular, numerous endogenous and exogenous factors may influence the participants' response to Phase II trials evaluating sarcopenia interventions (Table 2; see also(10)).

Among the endogenous factors, age is obviously the main contributor to the muscle decline. The sarcopenia process is a *continuum* over time since adulthood. Therefore, the selection of younger participants is likely to lead to the evaluation of greater and more functional muscles(36). Gender also determines relevant differences in skeletal muscle. In fact, independently of age, men always tend to have higher amount of lean mass than women(37). Moreover, the decline of muscle mass with aging does not follow a similar pattern in men and women(38). Finally, it is noteworthy that the quality of the muscle itself may differ between men and women as shown by the different ratio existing between muscle mass and strength across genders(5).

Race is another endogenous factor to carefully consider when recruiting participants for studies on sarcopenia. Body composition is significantly different across races and ethnicities, with African Americans characterized by higher amount of muscle mass than Caucasians, Hispanics, or Asians(39, 40). Race differences also exist for adipose tissue(41), consequently adding a further confounder to evaluate when measuring the skeletal muscle quality(8, 42).

Among the biological conditions potentially affecting the skeletal muscle, inflammation is for sure one of the most studied. Pro-inflammatory cytokines (in particular, tumor necrosis factor- α and interleukin-6) are able to directly influence the skeletal muscle quality and quantity(15), as shown by numerous studies performed in animal(43, 44) as well as human(45) models. Moreover, inflammation may also exert indirect negative effects by inducing anorexia, determining anemia, and/or altering hormonal profiles(46, 47). Age-related hormonal changes (in particular, testosterone and growth hormone) may also concur in enhancing the rate of muscle decline. Several studies have demonstrated that testosterone, a potent anabolic stimulus(48), is strongly associated with appendicular lean mass(49). Similarly, growth hormone has a relevant lipolytic action which declines with aging, leading to higher adipose tissue and increased insulin resistance(50) (consequently, feeding the vicious cycle of the disabling process which involves both sarcopenia and inflammation(51)).

Theoretically, any clinical condition departing from the physiological aging process may affect the study of sarcopenia. Unfortunately, in older persons it is often difficult distinguishing "normality" (or "aging") from "disease". In the design of a clinical study on sarcopenia, every attempt should be made to avoid that the presence of a disease may lead to

biased results (or at least, every departure from normality should be adequately taken into account). First of all, body composition-related conditions (such as obesity or metabolic syndrome) should be carefully considered as directly influencing the skeletal muscle. In this context, diabetes may be included as well because it is a disease with specific body composition modifications(52) and a strong inflammatory basis(53). Congestive heart failure is not only characterized by liquid retention (potentially altering the body composition assessment), but also by cachexia and skeletal muscle wasting(54). The body wasting determined by serious illnesses (also including cancer, chronic renal failure, chronic obstructive respiratory disease, AIDS, rheumatoid arthritis) is a major confounder to be evaluated when planning a sarcopenia study. As discussed above, the inflammatory stimulus in these conditions is so evident they may serve as models of accelerated aging. Neurological disorders (in particular, stroke and Parkinson's disease) should also be taken into account in the recruitment phase because significantly affecting the muscle (in both its quality and quantity).

Among the behavioral (exogenous) factors, physical activity, smoking, alcohol consumption, and nutrition represent the most important to consider when evaluating participants for sarcopenia trials. Moreover, several medications are able to significantly influence the skeletal muscle (e.g., testosterone, growth hormone replacement therapy, anti-cytokine treatments)(10). Finally, among the exogenous factors to evaluate, the lack of social support should not be ignored. Besides of potentially decreasing the compliance/adherence to the study, this factor (extremely frequent at old age) may relevantly limit subject's activities causing sedentariness (due to lower mood or dependence for physical function). Last but not least, willingness/ability to adhere to the study protocol as well as to provide informed consent are obvious additional participant-related factors determining the successful recruitment and conduction of the study.

CONCLUSIONS

The increasing evidence showing the importance of the age-related muscle decline (in both its quantitative and qualitative forms) as potential causal factor for major health-related outcomes has led to an increased demand of testing interventions aimed at preventing and/or delaying sarcopenia. Phase II trials on sarcopenia are now needed to determine which are the most promising interventions to be verified in subsequent Phase III trials. The road is surely still long and difficult before a safe and effective intervention will be able to modify the history of the age-related muscle decline. In the meanwhile, several theoretical and methodological issues on sarcopenia should be clarified. In particular, the definition of common basis on which build up and conduct future studies addressing this characteristic age-related phenomenon are strongly needed.

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Figure 1.
Number of articles in PubMed on "sarcopenia" according to publication year.

Table 1

Possible model populations of accelerated aging (with related weaknesses and strengths) on which targeting sarcopenia interventions.

Population	Weaknesses	Strengths
Healthy volunteers restrained from physical activities	<ul style="list-style-type: none"> - Ethical concerns, especially for longer term studies - Difficult recruitment of older persons 	<ul style="list-style-type: none"> - Possible easy recruitment - Few clinical and biological confounders potentially affecting the study findings
Progeroid patients	<ul style="list-style-type: none"> - Ethical concerns - Limited number of patients - Not exactly mimicking normal aging 	<ul style="list-style-type: none"> - Multisystemic accelerated aging
Bed-ridden subjects due to acute illness (e.g., influenza, hip fractures, elective surgery)	<ul style="list-style-type: none"> - Possible interference of the acute condition on the skeletal muscle decline - Possible influence of treatment-related factors 	<ul style="list-style-type: none"> - Possible easy recruitment - Possible evaluation of specific (primary condition-based) stimuli on the determination of the muscle loss
Patients with specific conditions characterized by chronic elevation of inflammatory status (e.g., acquired immune deficiency syndrome [AIDS], rheumatoid arthritis)	<ul style="list-style-type: none"> - Limited number of (older) patients for some specific diseases - Possible interference of the primary condition on the skeletal muscle decline - Specifically focused on inflammation as determinant of muscle decline 	<ul style="list-style-type: none"> - Multisystemic accelerated aging
Older subjects with initial muscle impairment	<ul style="list-style-type: none"> - Disabling process already started (thus, limited use for real preventive studies) - Presence of (age-related) comorbidities 	<ul style="list-style-type: none"> - Easy recruitment - Specifically focused on older persons

Table 2

Main endogenous and exogenous factors to be considered as inclusion/exclusion criteria for Phase II trials on sarcopenia.

Endogenous	Exogenous
Age	Physical activity level
Gender	Smoking status
Race/Ethnicity	Nutritional status
Inflammation	Alcohol consumption
Hormonal modifications	Medications use
Baseline body composition	Social support *
Clinical conditions (e.g., AIDS, anemia, arthritis, cancer, chronic obstructive pulmonary disease, cognitive impairment *, congestive heart failure, depression diabetes, kidney disease, metabolic syndrome, neurological diseases [stroke, spinal compression], Parkinson's disease)	

* These factors do not directly influence the study outcomes (i.e., muscle decline), but may significantly affect the conduction of the study