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DESIGNING PHARMACEUTICAL TRIALS FOR SARCOPENIA IN FRAIL OLDER ADULTS: EU/US TASK FORCE RECOMMENDATIONS

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Abstract: An international task force of academic and industry leaders in sarcopenia research met on December 5, 2012 in Orlando, Florida to develop guidelines for designing and executing randomized clinical trials of sarcopenia treatments. The Task Force reviewed results from previous trials in related disease areas to extract lessons relevant to future sarcopenia trials, including practical issues regarding the design and conduct of trials in elderly populations, the definition of appropriate target populations, and the selection of screening tools, outcome measures, and biomarkers. They discussed regulatory issues, the challenges posed by trials of different types of interventions, and the need for standardization and harmonization. The Task Force concluded with recommendations for advancing the field toward better clinical trials.

Key words: Sarcopenia, clinical trial, skeletal muscle, frailty, intervention.

Introduction

Sarcopenia, the age-related loss of skeletal muscle mass and strength is a major component of frailty, with important consequences for further disability and mortality (1). Prevalence estimates range from 5-13% among 60-70 years old, and as high as 11-50% in those over age 80 (2). Yet despite its significant contribution to morbidity and mortality, many questions remain about the pathophysiology and optimal management of the syndrome. With this in mind, a task force of academic and industry leaders from both the United States and the European Union met in Orlando, Florida on December 5, 2012, prior to the International Conference on Sarcopenia Research (ICSR), to develop guidelines that would facilitate the design and execution of successful, informative, randomized controlled trials. The task force reviewed results from previous trials in related disease areas to extract lessons relevant to future sarcopenia trials, including practical issues regarding the design and conduct of trials in elderly populations, the definition of appropriate target populations, and the selection of screening tools, outcome measures, and biomarkers.

At least four operative definitions of sarcopenia have been published (3-6), and while they are all fundamentally similar, citing low muscle mass and problems with physical function, the lack of consensus on an accepted definition has stifled progress toward advancing understanding of the condition, developing new treatments, and conducting clinical trials (7). Sarcopenia is a major component of the geriatric syndrome of frailty (8); thus elderly individuals with sarcopenia are at increased risk of being frail. Moreover, there are many shared pathways between sarcopenia and frailty, including physical inactivity, hormonal changes, loss of motor units, hypo-nutrition, inflammation, and chronic diseases. Thus, targeting sarcopenia may represent a means of preventing frailty and dependency.

Sarcopenia , however, is frequently overlooked in clinical practice and geriatric medicine has not yet fully embraced sarcopenia as a condition to target with interventions. In addition, many adults with sarcopenia are not seen by geriatricians but by general practitioners, primary care providers, or some other type of specialist, e.g. cardiologist, oncologist; and these specialists as well as general practitioners may not be trained to assess muscle loss, weakness, and functional loss. Furthermore, many people, including health professionals, believe that poor functional capacity, weakness, and loss of skeletal muscle mass are unavoidable in old age. Despite these impediments, many initiatives driven by governments, academic centers, or medical societies are presently implementing assessment of sarcopenia into clinical practice (9).

Lessons from previous trials

Many studies have documented a decline in muscle strength and muscle mass as people age. Even older, competitive weight lifters experience declines in strength that follow a similar trajectory as is seen in more sedentary adults (10, 11) yet since they start at a higher level they may not lose a sufficient amount of lean mass to reach the threshold for sarcopenia. Exercise training has been tested in many trials for its ability to slow the decline of muscle function in older adults (12-15). Most of these use the American College of Sports Medicine (ACSM) recommendation of moderate velocity resistance training at 70-80% of maximum strength at least two to three

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times per week; and most assess knee extension strength as an outcome measure. These studies taken together indicate that resistance training can stabilize or increase muscle mass and delay the development of sarcopenia. Resistance training has also been shown to lower mortality and nursing home placement following hip fracture (16). A suggested alternative to resistance training incorporates blood flow restriction (BFR) into a low-intensity training regimen, and this results in muscle hypertrophy and increased strength (17). Recent data suggest that the underlying mechanism for this is the proliferation of myogenic stem cells resulting in muscle hypertrophy (18).

Whether strength training increases physical function is a more complex question, since multiple factors affect function, including pain, weakness, balance, endurance, coordination, and fear. Multiple randomized controlled trials have demonstrated a significant beneficial effect from resistance training in older people (19). One reason for the inconsistency is that many of the studies have examined older people who are already highly functional. The data are very consistent with regard to weak or frail older people; a substantial increase in strength, gait speed, stair climbing power, and spontaneous activity. However, in order to demonstrate a reduced incidence of sarcopenia, multi-year follow-up studies are needed. The LIFE-Pilot study randomized participants to either a Physical Activity (PA) intervention, which involved a combination of twice weekly supervised aerobic and resistance exercise as well as home-based exercises over one year, or to a successful aging (SA) intervention, which involved weekly educational workshops. Primary outcome measures were walking speed and performance on the Short Physical Performance Battery (SPPB). After 12 months of treatment (20) and for two years after that (21), individuals in the PA group performed significantly better than those in the SA group ($p<0.001$ at 12 months, $p<0.15$ at 36 months), suggesting that it may be feasible to intervene and change the trajectory of the functional decline. Moreover, these results suggest that treatment trials of only one year using surrogate outcomes of physical disability such as walking speed and SPPB may detect a treatment effect.

Obesity in elders further complicates the evaluation of sarcopenia, since individuals who are obese typically have greater muscle mass than their thin peers (22, 23) and weight loss causes loss of muscle. In the LIFE-Pilot study, positive benefits from the PA intervention were attenuated in obese individuals (24). Other clinical trials randomized obese older adults into four groups: weight management alone, exercise training alone, a combination of weight management and exercise training, or a control group; these trials showed that while diet alone increased physical performance, the combination of diet and exercise produced even greater improvements (25, 26).

Trial design issues

Trial design must take into consideration the nature of the intervention, i.e., lifestyle modification, such as weight loss or increased protein intake, or a pharmacological treatment. If the latter, the trial must be focused on the pharmacology of the drug. In either case, endpoints should be specific to the type of study. In a proof of concept study, for example, appropriate endpoints might be change in strength and muscle mass; while in a phase 3 or registration study, functional improvement along with some patient-reported-outcome would be necessary.

Target population – Screening to identify a potential sarcopenia target population for a clinical trial ideally would utilize simple tests that do not require time consuming, complex, or highly specialized methodologies. Such an approach has also been taken, for example, in identifying frailty using the International Academy of Nutrition and Aging (IANA) five-question FRAIL scale, which has been validated by Morley et al (27). A screening tool based on simple questions rather than actual measurements have also been developed for assessing risk of osteoporotic fractures (28). A screening tool for sarcopenia, the SARC-F (Strength, based on difficulty lifting or carrying 10 lbs, Assistance with walking, Rise from a chair, Climb stairs, Falls) has been proposed by Morley and colleagues. Over a 9-yr period, this tool has shown to be an excellent predictor of changes in activities of daily living (ADLs) and instrumental activities of daily living (IADLs), as well as hospitalization, slow gait speed, and mortality (unpublished). However, the real question is how the SARC-F score relates to sarcopenia as diagnosed by one of the more accepted definitions rather than whether they predict adverse outcomes. Sarcopenia includes both low muscle mass and poor function; thus the presence of poor function alone is not necessarily sarcopenia, but may be related to any number of co-morbid problems not related to muscle. More work will thus be required to assess the relationship of SARC-F score to measured sarcopenia.

Another approach would be to identify frail older adults in general practice settings as done at Gérontopôle of Toulouse, placing emphasis on the subjective impression from the general practitioner. Using this subjective approach in this setting, it was found that 94% of those referred were frail (53%) or pre frail (41%) according to Fried's criteria (9).

Once a potential target population has been identified (i.e. a frail elderly population), sarcopenia should be objectively identified before enrolling the participants in a trial. Based on the sarcopenia definition, strength (mainly grip strength) and/or physical performance (4 meter walk or the 400 meter walk), and muscle mass need to be assessed. Based on the availability of imaging techniques, strength and performance could be assessed in a first step to further narrow the target population which could finally be assessed for body composition parameters (29). Appropriate subjects to screen for sarcopenia can be found in outpatient clinics, although this approach may limit access to those who develop sarcopenia as a consequence of hospitalization for an acute illness. Other target populations include chronically ill frail older adults and patients with acute sarcopenia, for example as a result of confinement to a hospital bed for many days. Studies show that within ten days, healthy

elderly patients lose about a kilogram of muscle mass along with significant loss of function (30). It may also be helpful to screen potential subjects for nutritional status using one of several nutrition screening tools (31). Exclusion criteria may include malnutrition or severe functional impairments. Subjects with other co-morbid conditions may be included but the comorbidities should be included in the analysis (32).

Outcomes - Sarcopenia is a disabling condition; thus outcome measures must be related to meaningful changes in physical function. Strength itself may be a useful clinical outcome, but only as it relates to a change in physical function. Studies need to include physical function or other parameters associated with disability in order to provide informative determinants of strength and function. In addition, physical function is affected by many factors beyond strength, such as executive function, motivation, depression, and pulmonary function.

In a drug trial for sarcopenia, a composite outcome of increase in muscle mass and increase in performance or strength may be needed. Strength could, however, play a surrogate role to assess future functional change (33). Both moderate and high intensity exercise increases fitness and function, improve walking distance and stair climbing power. In addition, there is a self-efficacy component that contributes to functional gain in exercise trials of strength, since when people feel stronger and are able to push more weight, their performance improves even further.

To improve the value of strength as an outcome in sarcopenia trials, minimally important differences related to physical function need to be established as well as the association of changes in skeletal muscle mass with strength and physical function in a sarcopenic population. For non-exercise trials of anabolic therapy, it will also be important to identify responsiveness of strength measures to changes in skeletal muscle mass. Outcome measures must be reliable and valid and should also be related to the underlying disease process. Further, consideration must also be given to practical issues specific to the target populations, including issues of cost and space for equipment, and whether assessments will need to be done in the home with portable equipment.

Grip strength is a commonly used measure of strength in elderly populations and is useful across multiple study sites. Grip strength is thought to be useful if there is a systemic effect of intervention, although it does not change as quickly as muscles targeted by exercise in most intervention trials. Thus it may be better used for screening and patient stratification (after also stratifying on gender and nutritional status) rather than as an outcome measure. Since loss of function in people with sarcopenia typically manifests as poor mobility, a test of lower extremity strength, such as the one-repetition maximum (1RM) leg press test (34), is often used as a proxy outcome measure. The leg press test has high test-retest reliability even when administered by novices, requires little motor learning by patients and has a low risk of injury. However, in longitudinal epidemiology studies, lower extremity strength was no better than grip strength in predicting impaired physical function.

Mobility performance measures such as gait speed, SPPB, stair climbing time, the 400 meter walk, and six minute walk distance (6MWD) are commonly used functional measures, although much of the evidence supporting their use comes from studies of healthy, community-dwelling populations, while part of the target population in sarcopenia trials is more physically impaired and sicker. However, in a pooled analysis of nine cohort studies, gait speed was shown to be associated with survival in older adults (35); and in the Women's Health and Aging Study, a study of disabled older women, the SPPB was shown to be reliable and sensitive to change (36). Secondary analysis of data from community-dwelling elders and subacute stroke survivors also showed that gait speed, 6MWD, and SPPB all yield potential thresholds for detecting clinically meaningful changes (37). Accelerometers may also be used to assess activity as a measure of mobility although these devices raise concerns about subject compliance and interpretation of the data when there is an exercise component to the trial.

Functional measures, such as the Activities of Daily Living (ADL) scale, have potential as outcome measures in sarcopenia trials, although the current scale is not sensitive to changes over time.

Self-report measures are an alternative to performance measures, offer some advantages in terms of simplicity and cost savings, and have been shown to have comparable validity, sensitivity, and responsiveness to change in subjects followed after hip fracture (38). In the LIFE-Pilot study, several self-report measures confirmed that in this population as well, participants perceived change when performance changed (39). The optimal primary outcome may thus be one that measures function or mobility (objectively captured or simply self-reported by the patient.

Biomarkers and imaging

Three imaging technologies – Dual energy x-ray absorptiometry (DXA), computed tomography (CT), and magnetic resonance imaging (MRI) – are widely used to assess changes in muscle mass during clinical trials. Each of these has strengths and weaknesses. DXA measures precisely whole body and regional fat and lean mass using very small doses of radiation and is widely available in many countries, yet reproducibility across sites is limited by operational and methodological differences between different manufacturers and software developers and hydration status of the patient. CT provides a more direct and precise measure of muscle by measuring regional changes in skeletal muscle cross-sectional area (CSA), yet costs are high and CT is associated with significantly higher radiation exposure compared to DXA. MRI provides similar precision as CT with no radiation exposure, as well as additional capacity for multiple slice acquisition, yet costs are higher and there are additional technical complications. Ultrasound is another imaging modality that

Table 1
Outcome measures for sarcopenia trials

	Measure	Advantages	Limitations
Strength measures	Handgrip Strength	Simple and quick to administer Portable equipment Easy to train administrators Well-established marker of global muscle strength and health status	Not sensitive to changes or interventions Does not assess lower extremity strength Lack of dynamometers in every clinical setting Limitations in the currently available thresholds of risk
	Leg press test	Tests lower extremity strength High test-retest reliability Easy to train administrators	Space and equipment requirements Requires trained staff to assess the patient Mainly for research use Not a measure of functional capacity
	Knee extension strength	Possible assessment with portable device Correlated with lower extremity muscle functioning	Lack of dynamometers in every clinical setting Limitations in the currently available thresholds of risk
Lower extremity function measures	Gait speed	Simple, reliable, and sensitive to change Highly reproducible Easy to administer Requires little space Well-established marker of global muscle strength and health status Inexpensive	Mainly a screening instrument (global marker of wellbeing) Best performed with clock and switch mats
	SPPB	Reliable and sensitive to change	Its predictive value is qlmost equivalent to that of t he only gait speed test More time consuming than other mobility measures Ceiling effect.
	400 meter walk	Mimics key activity in daily life “Hard outcome” (marker of mobility disability) Optimal outcome measure for trials on physical disability (dichotomous variable)	Space requirement Mainly for research environment
	6 minute walk distance	Mimics key activity in daily life Measure of cardiorespiratory function Reliable and sensitive to change Existence of established thresholds of risk Potential conversion of results into physiological parameters Acceptable by regulators for other conditions such as heart failure, COPD, muscular dystrophy.	More time consuming than other physical performance measures Space requirement Stresses the physiological reserves to exhaustion (caution is required in frail older persons)
	Timed Up and Go test	Reliable and sensitive to change	Its predictive value is almost equivalent to that of t he only gait speed test More time consuming than other mobility measures
Disability measures	ADL scale	Simple, reliable method of identifying core self-care activities Measure of physical disability	All items not related to muscle strength
	Self reported measures	Simple Inexpensive Possibly sensitive and responsive to change	Subjective evaluations potentially affected by third factors Reliability May or may not be sensitive to changes in muscle mass or function
Muscle mass measures	DXA	Widely available Precision 1-4% Evaluation of adipose, muscular, and bone compartments Assessment of the organism as a whole as well as of specific sections of it	Radiation exposure (low dose) Excessive variability across instruments and sites. Does not directly measure muscle. Complicated by changes in body water Methodology related confounders
	CT	Precision 1-3% Measures direct physical property of muscle	Radiation exposure High cost Does not provide a measure of total muscle mass
	MRI	Precision 1-3% Agreement with CT No radiation exposure Capacity for multiple slice acquisition	Technically complex High cost Availability is geographically dependent
	Ultrasound	Inexpensive Widely available equipment Useful for bed-ridden or mobility impaired individuals	Limited experience in sarcopenia studies.Does not measure muscle mass Operator-dependent
Metabolomics profiling	Mass spectrometry	Possible identification of novel biomarkers Low patient burden	Expensive Still in an early exploratory phase of development

provides information similar to that obtained using MRI, and it is much cheaper and easier to acquire data of specific body regions, although it has not been traditionally used in the area of body composition change in the elderly.

In an interventional study testing the ability of protein supplementation to improve exercise-induced increases in muscle mass and strength, these various measures provided variable responses (40). For example, at baseline, muscle CSA by MRI was highly correlated with left leg muscle mass by CT, yet the change in response to treatment showed much weaker correlations, despite the fact that training load was consistent.

New measures under investigation

A method has been developed that uses mass spectrometry to determine total-body creatine pool size as a direct measure of skeletal muscle mass (41). This approach uses a single, orally-administered dose of creatine-(methyl-d3) followed by measurement of urinary D3 creatinine. In rats, the creatine pool size determined using this method has been shown to correlate with lean body mass and corresponded with predicted total muscle mass, thus providing a measure of changes in skeletal muscle mass.

Interventions: exercise, multidomain treatment

While many studies have supported the use of exercise as a treatment for sarcopenia, there are currently no clear guidelines from the research community that provide guidance to clinicians on prescribing exercise for this specific condition, i.e., what types of exercise, frequency, duration, and dose. Moreover, while there is widespread belief that physical activity will improve health outcomes in older adults, the evidence supporting this and delineating the optimal amount of exercise and the duration is weak. However, design features from large randomized trials of exercise in "mobility limited" or at-risk older adults could applied in drug trials for sarcopenia.

The LIFE-Pilot study, discussed earlier, laid the groundwork for the LIFE study, the largest and longest duration study of its kind to assess the effectiveness of a moderate-intensity physical activity program, including strength training, compared to a successful aging health education program. The LIFE Study is not a study of sarcopenia, its participants may or may not have sarcopenia, and sarcopenia is not an outcome of the study. However, it provides some insight into recruitment and feasibility of interventions. Recruitment of 1,600 participants, age 70-89 with a sedentary lifestyle and at high risk for mobility disability (SPPB score of 9 or less) but able to walk 400 meters in less than 15 minutes, was completed last year. At least 45% of the subjects have SPPB scores less than 7 and at least 22.5% are minorities. In order to enroll 1,600 participants, many strategies were used. The recruitment process began with a phone screen of 14,000 people, followed by screening with the SPPB and Community Healthy Activities Model Program for Seniors (CHAMPS) questionnaire, and then the 400 meter walk. The total cost of recruitment was $1.3 million, or $840 per randomized participant. After two years, fewer than 4% of randomized participants have been lost to follow up. Subjects will be followed for two to four years to test whether the lifestyle modification persists.

Drugs are also under investigation for the treatment of sarcopenia. For example, testosterone has been tested and shown to be effective in reversing sarcopenia in humans and mice through the regulation of myostatin and the activation of signaling pathways that lead to satellite cell proliferation and differentiation (42). In addition, several selective androgen receptor modulators (SARMs) and anti-myostatin therapies are tested in early phase efficacy trials (43). Other pathogenic factors underlying the development of sarcopenia may also represent potential targets for future pharmacological interventions. For example, there may be a neurogenic form of sarcopenia involving destabilization of the neuromuscular junction (NMJ) by proteolytic cleavage of agrin, a protein involved in the development of the NMJ (44). While there have been no studies demonstrating an effect of agrin on muscle mass, studies do suggest that agrin may be a marker for sarcopenia (45). Unfortunately, further studies are still needed before pharmacological interventions will be available for sarcopenia. In particular, safety issues and the relatively recent development of research in the field still limit the clinical adoption of available molecules.

Dietary interventions and nutritional supplements are also under investigation for the treatment of sarcopenia. For example, high dose essential amino acid (EAA) supplementation may help preserve function in physically inactive elderly people confined to bed (46). HMB (β-hydroxy β-methylbutyrate), a metabolite of leucine, is also being investigated in a bed-rest model as a means of preventing muscle loss in elderly people and those with chronic diseases (47).

Regulatory issues: FDA qualification

FDA approval requires 1) a clear indication, i.e., a disease or condition that is the target of drug treatment, prevention, or diagnosis; 2) context of use, i.e. a defined disease, target patient population, trial design features that are relevant to the outcome, labeling, or promotional claims; and 3) a clinical trial outcome assessment (COA), i.e., a drug development tool (DDT). Currently, sarcopenia is not recognized as a disease by the FDA and therefore may not be considered an indication that could lead to a drug approval. The FDA has signaled that it is open to functional outcomes in clinical trials, although muscle strength and other impairments would not be considered treatable indications.

The FDA published a draft guidance for industry regarding the qualification process for DDTs (48), which provides a framework for interactions between sponsors submitting DDTs

for approval and the FDA's Center for Drug Evaluation and Research (CDER). The qualification guidance outlines a two-stage process: the consultation and advice stage begins with a letter of intent, which is followed by submission of a briefing package, an initial meeting, and a period of investigation and further development of the DDT. In the second stage, a formal qualification package is submitted for review and discussion, and the CDER makes a recommendation regarding qualification. Once a DDT has been qualified, it can be used by drug developers for the qualified context in Investigational New Drug (IND), New Drug Application (NDA), or Therapeutic Biologic Applications (BLA) to the FDA.

The Alliance for Aging Research (www.agingresearch.org) has initiated a project called Aging in Motion (AIM) to promote research and innovation and raise awareness around health and quality of life issues resulting from sarcopenia and age-related functional decline. The Scientific Advisory Panel of AIM is planning to submit a letter of intent to the FDA, probably recommending the use of gait speed and SPPB as functional outcomes. However, there remains a question regarding which branch of the FDA would make decisions on a drug for sarcopenia, since there is no geriatrics section, nor one that deals specifically with functional decline. The lack of consensus on a clear definition for sarcopenia further impedes progress with the FDA.

Conclusions

The Task Force identified many important issues about sarcopenia clinical trials needing clearer definitions and guidelines for harmonization across centers, sites, and studies.

Critical next steps toward better clinical trials design include:

- The development of an evidence base of key measures and their behavior in diverse target populations over time (49).
- Acquisition of data linking body composition (e.g. muscle mass) to strength, mobility, and clinical events
- Correlations of physical performance measures to self-report information
- Promotion of studies about the pathophysiological trends of sarcopenia
- Promotion of studies about non-pharmacological interventions and early phase trials targeting sarcopenia
- Establishment of uniform inclusion/exclusion criteria for selecting target population in clinical trials on sarcopenia
- Development of studies aimed at identifying the minimum clinically relevant threshold of skeletal muscle mass modifications
- Evaluating the possibility of adding skeletal muscle mass assessment by CT or MRI in order to accurately study the quantitative dimension of sarcopenia (50).
- Identification of early biomarkers of muscle mass modifications
- Optimization of the objective assessment of lean muscle mass
- Development of better patient reported outcome (PRO) scales.

Finally, the Task Force stressed the need to engage families and physicians in efforts to address the problems of frailty (51) and sarcopenia in the rapidly aging population; and the need to identify novel funding mechanisms to support future trials.

References

1. Rolland Y, Czerwinski S, Abellan Van Kan G, Morley JE, Cesari M, Onder G, Woo J, Baumgartner R, Pillard F, Boirie Y, et al: Sarcopenia: its assessment, etiology, pathogenesis, consequences and future perspectives. J Nutr Health Aging 2008, 12:433-450.
2. von Haehling S, Morley JE, Anker SD: An overview of sarcopenia: facts and numbers on prevalence and clinical impact. J Cachexia Sarcopenia Muscle 2011, 1:129-133.
3. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, Martin FC, Michel JP, Rolland Y, Schneider SM, et al: Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing 2010, 39:412-423.
4. Fielding RA, Vellas B, Evans WJ, Bhasin S, Morley JE, Newman AB, Abellan van Kan G, Andrieu S, Bauer J, Breuille D, et al: Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International working group on sarcopenia. J Am Med Dir Assoc 2011, 12:249-256.
5. Morley JE, Abbatecola AM, Argiles JM, Baracos V, Bauer J, Bhasin S, Cederholm T, Coats AJ, Cummings SR, Evans WJ, et al: Sarcopenia with limited mobility: an international consensus. J Am Med Dir Assoc 2011, 12:403-409.
6. Muscaritoli M, Anker SD, Argiles J, Aversa Z, Bauer JM, Biolo G, Boirie Y, Bosaeus I, Cederholm T, Costelli P, et al: Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by Special Interest Groups (SIG) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics". Clin Nutr 2010, 29:154-159.
7. Roman D, Mahoney K, Mohamadi A: Sarcopenia: What's in a Name? J Am Med Dir Assoc 2012.
8. Evans WJ, Paolisso G, Abbatecola AM, Corsonello A, Bustacchini S, Strollo F, Lattanzio F: Frailty and muscle metabolism dysregulation in the elderly. Biogerontology 2010, 11:527-536.
9. Subra J, Gillette-Guyonnet S, Cesari M, Oustric S, Vellas B: The integration of frailty into clinical practice: preliminary results from the Gerontopole. J Nutr Health Aging 2012, 16:714-720.
10. Anton MM, Spirduso WW, Tanaka H: Age-related declines in anaerobic muscular performance: weightlifting and powerlifting. Med Sci Sports Exerc 2004, 36:143-147.
11. The DJ, Ploutz-Snyder L: Age, body mass, and gender as predictors of masters olympic weightlifting performance. Med Sci Sports Exerc 2003, 35:1216-1224.
12. Fiatarone MA, O'Neill EF, Ryan ND, Clements KM, Solares GR, Nelson ME, Roberts SB, Kehayias JJ, Lipsitz LA, Evans WJ: Exercise training and nutritional supplementation for physical frailty in very elderly people. N Engl J Med 1994, 330:1769-1775.
13. Kosek DJ, Kim JS, Petrella JK, Cross JM, Bamman MM: Efficacy of 3 days/wk resistance training on myofiber hypertrophy and myogenic mechanisms in young vs. older adults. J Appl Physiol 2006, 101:531-544.
14. Verdijk LB, Jonkers RA, Gleeson BG, Beelen M, Meijer K, Savelberg HH, Wodzig WK, Dendale P, van Loon LJ: Protein supplementation before and after exercise does not further augment skeletal muscle hypertrophy after resistance training in elderly men. Am J Clin Nutr 2009, 89:608-616.
15. Goodpaster BH, Chomentowski P, Ward BK, Rossi A, Glynn NW, Delmonico MJ, Kritchevsky SB, Pahor M, Newman AB: Effects of physical activity on strength and skeletal muscle fat infiltration in older adults: a randomized controlled trial. J Appl Physiol 2008, 105:1498-1503.
16. Singh NA, Quine S, Clemson LM, Williams EJ, Williamson DA, Stavrinos TM, Grady JN, Perry TJ, Lloyd BD, Smith EU, Singh MA: Effects of high-intensity progressive resistance training and targeted multidisciplinary treatment of frailty on mortality and nursing home admissions after hip fracture: a randomized controlled trial. J Am Med Dir Assoc 2012, 13:24-30.
17. Abe T, Kearns CF, Sato Y: Muscle size and strength are increased following walk training with restricted venous blood flow from the leg muscle, Kaatsu-walk training. J Appl Physiol 2006, 100:1460-1466.
18. Nielsen JL, Aagaard P, Bech RD, Nygaard T, Hvid LG, Wernbom M, Suetta C, Frandsen U: Proliferation of myogenic stem cells in human skeletal muscle in response to low-load resistance training with blood flow restriction. J Physiol 2012,

590:4351-4361.
19. Liu CJ, Latham N: Can progressive resistance strength training reduce physical disability in older adults? A meta-analysis study. Disabil Rehabil 2011, 33:87-97.
20. Pahor M, Blair SN, Espeland M, Fielding R, Gill TM, Guralnik JM, Hadley EC, King AC, Kritchevsky SB, Maraldi C, et al: Effects of a physical activity intervention on measures of physical performance: Results of the lifestyle interventions and independence for Elders Pilot (LIFE-P) study. J Gerontol A Biol Sci Med Sci 2006, 61:1157-1165.
21. Rejeski WJ, Marsh AP, Chmelo E, Prescott AJ, Dobrosielski M, Walkup MP, Espeland M, Miller ME, Kritchevsky S: The Lifestyle Interventions and Independence for Elders Pilot (LIFE-P): 2-year follow-up. J Gerontol A Biol Sci Med Sci 2009, 64:462-467.
22. Alley DE, Chang VW: The changing relationship of obesity and disability, 1988-2004. JAMA 2007, 298:2020-2027.
23. Hulens M, Vansant G, Lysens R, Claessens AL, Muls E, Brumagne S: Study of differences in peripheral muscle strength of lean versus obese women: an allometric approach. Int J Obes Relat Metab Disord 2001, 25:676-681.
24. Manini TM, Newman AB, Fielding R, Blair SN, Perri MG, Anton SD, Goodpaster BC, Katula JA, Rejeski WJ, Kritchevsky SB, et al: Effects of exercise on mobility in obese and nonobese older adults. Obesity (Silver Spring) 2010, 18:1168-1175.
25. Villareal DT, Chode S, Parimi N, Sinacore DR, Hilton T, Armamento-Villareal R, Napoli N, Qualls C, Shah K: Weight loss, exercise, or both and physical function in obese older adults. N Engl J Med 2011, 364:1218-1229.
26. Messier SP, Loeser RF, Miller GD, Morgan TM, Rejeski WJ, Sevick MA, Ettinger WH, Jr., Pahor M, Williamson JD: Exercise and dietary weight loss in overweight and obese older adults with knee osteoarthritis: the Arthritis, Diet, and Activity Promotion Trial. Arthritis Rheum 2004, 50:1501-1510.
27. Morley JE, Malmstrom TK, Miller DK: A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. J Nutr Health Aging 2012, 16:601-608.
28. Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E: FRAX and the assessment of fracture probability in men and women from the UK. Osteoporos Int 2008, 19:385-397.
29. Abellan van Kan G, Houles M, Vellas B: Identifying sarcopenia. Curr Opin Clin Nutr Metab Care 2012, 15:436-441.
30. Kortebein P, Ferrando A, Lombeida J, Wolfe R, Evans WJ: Effect of 10 days of bed rest on skeletal muscle in healthy older adults. JAMA 2007, 297:1772-1774.
31. Isenring EA, Banks M, Ferguson M, Bauer JD: Beyond malnutrition screening: appropriate methods to guide nutrition care for aged care residents. J Acad Nutr Diet 2012, 112:376-381.
32. Abellan van Kan G, Cameron Chumlea W, Gillette-Guyonet S, Houles M, Dupuy C, Rolland Y, Vellas B: Clinical trials on sarcopenia: methodological issues regarding phase 3 trials. Clin Geriatr Med 2011, 27:471-482.
33. Seynnes O, Fiatarone Singh MA, Hue O, Pras P, Legros P, Bernard PL: Physiological and functional responses to low-moderate versus high-intensity progressive resistance training in frail elders. J Gerontol A Biol Sci Med Sci 2004, 59:503-509.
34. Callahan D, Phillips E, Carabello R, Frontera WR, Fielding RA: Assessment of lower extremity muscle power in functionally-limited elders. Aging Clin Exp Res 2007, 19:194-199.
35. Studenski S, Perera S, Patel K, Rosano C, Faulkner K, Inzitari M, Brach J, Chandler J, Cawthon P, Connor EB, et al: Gait speed and survival in older adults. JAMA 2011, 305:50-58.
36. Ostir GV, Volpato S, Fried LP, Chaves P, Guralnik JM: Reliability and sensitivity to change assessed for a summary measure of lower body function: results from the Women's Health and Aging Study. J Clin Epidemiol 2002, 55:916-921.
37. Perera S, Mody SH, Woodman RC, Studenski SA: Meaningful change and responsiveness in common physical performance measures in older adults. J Am Geriatr Soc 2006, 54:743-749.
38. Latham NK, Mehta V, Nguyen AM, Jette AM, Olarsch S, Papanicolaou D, Chandler J: Performance-based or self-report measures of physical function: which should be used in clinical trials of hip fracture patients? Arch Phys Med Rehabil 2008, 89:2146-2155.
39. Kwon S, Perera S, Pahor M, Katula JA, King AC, Groessl EJ, Studenski SA: What is a meaningful change in physical performance? Findings from a clinical trial in older adults (the LIFE-P study). J Nutr Health Aging 2009, 13:538-544.
40. Chale A, Cloutier GJ, Hau C, Phillips EM, Dallal GE, Fielding RA: Efficacy of Whey Protein Supplementation on Resistance Exercise-Induced Changes in Lean Mass, Muscle Strength, and Physical Function in Mobility-Limited Older Adults. J Gerontol A Biol Sci Med Sci 2013;68:682-90.
41. Stimpson SA, Turner SM, Clifton LG, Poole JC, Mohammed HA, Shearer TW, Waitt GM, Hagerty LL, Remlinger KS, Hellerstein MK, Evans WJ: Total-body creatine pool size and skeletal muscle mass determination by creatine-(methyl-d3) dilution in rats. J Appl Physiol 2012, 112:1940-1948.
42. Kovacheva EL, Hikim AP, Shen R, Sinha I, Sinha-Hikim I: Testosterone supplementation reverses sarcopenia in aging through regulation of myostatin, c-Jun NH2-terminal kinase, Notch, and Akt signaling pathways. Endocrinology 2010, 151:628-638.
43. Cadilla R, Turnbull P: Selective androgen receptor modulators in drug discovery: medicinal chemistry and therapeutic potential. Curr Top Med Chem 2006, 6:245-270.
44. Butikofer L, Zurlinden A, Bolliger MF, Kunz B, Sonderegger P: Destabilization of the neuromuscular junction by proteolytic cleavage of agrin results in precocious sarcopenia. FASEB J 2011, 25:4378-4393.
45. Drey M, Sieber CC, Bauer JM, Uter W, Dahinden P, Fariello RG, Vrijbloed JW: C-terminal Agrin Fragment as a potential marker for sarcopenia caused by degeneration of the neuromuscular junction. Exp Gerontol 2012, 48:76-80.
46. Ferrando AA, Paddon-Jones D, Hays NP, Kortebein P, Ronsen O, Williams RH, McComb A, Symons TB, Wolfe RR, Evans W: EAA supplementation to increase nitrogen intake improves muscle function during bed rest in the elderly. Clin Nutr 2010, 29:18-23.
47. Deutz NE, Pereira SL, Hays NP, Oliver JS, Edens NK, Evans CM, Wolfe RR: Lean body mass is maintained by β-hydroxy-β-methylbutyrate (HMB) during 10 days of bed rest in older adults. . Clin Nutr 2013: in press.
48. Food and Drug Administration: Guidance for Industry: Qualification Process for Drug Development Tools, accessed 12/18/12 http://www.fda.gov/downloads/Drugs/GuidanceComplicanceRegulatoryInformationi/Guidances/UCM230597.pdf. 2010.
49. Chumlea WC, Cesari M, Evans WJ, Ferrucci L, Fielding RA, Pahor M, Studenski S, Vellas B: Sarcopenia: designing phase IIB trials. J Nutr Health Aging 2011, 15:450-455.
50. Lustgarten MS, Fielding RA: Assessment of analytical methods used to measure changes in body composition in the elderly and recommendations for their use in phase II clinical trials. J Nutr Health Aging 2011, 15:368-375.
51. Cesari M: Frailty and aging. J Frailty Aging 2012, 1:3-6.