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SPECIAL ARTICLE

IMPLICATIONS OF ICD-10 FOR SARCOPENIA CLINICAL PRACTICE AND CLINICAL TRIALS: REPORT BY THE INTERNATIONAL CONFERENCE ON FRAILTY AND SARCOPENIA RESEARCH TASK FORCE

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Abstract: Establishment of an ICD-10-CM code for sarcopenia in 2016 was an important step towards reaching international consensus on the need for a nosological framework of age-related skeletal muscle decline. The International Conference on Frailty and Sarcopenia Research Task Force met in April 2017 to discuss the meaning, significance, and barriers to the implementation of the new code as well as strategies to accelerate development of new therapies. Analyses by the Sarcopenia Definitions and Outcomes Consortium are underway to develop quantitative definitions of sarcopenia. A consensus conference is planned to evaluate this analysis. The Task Force also discussed lessons learned from sarcopenia trials that could be applied to future trials, as well as lessons from the osteoporosis field, a clinical condition with many constructs similar to sarcopenia and for which ad hoc treatments have been developed and approved by regulatory agencies.

Key words: Sarcopenia, frailty, obesity, disability, intervention studies, prevention.

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Introduction

The age-related loss of muscle mass and strength, known as sarcopenia, is a major cause of frailty and disability in older persons worldwide. Nevertheless, progress in developing treatments for sarcopenia has been hindered by a lack of consensus on how the condition is defined and diagnosed (1). A major step forward in correcting this deficiency was achieved on October 1, 2016, when a unique ICD10 code for sarcopenia was established (2). In April 2017, the International Conference on Frailty and Sarcopenia Research Task Force met in Barcelona, Spain to discuss the meaning and significance of the new ICD-10 code.

Background and History of ICD-10 for Sarcopenia

The International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) is the latest version of a system used by physicians, researchers, and health systems to classify diseases and other health conditions according to recognized diagnoses. Based on the ICD-10 system used by all World Health Organization (WHO) member countries, the ICD-10-CM Code Book is the US version, prepared by the ICD-10 Coordination and Maintenance (C&M) Committee (including representatives from the Centers for Medicare and Medicaid Services [CMS], the Centers for Disease Control and Prevention [CDC], and the National Center for Health Statistics [NCHS]). The ICD-10-CM diagnostic codes are mandated in

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the US for all health care providers as a means of removing barriers for diagnosis, standardizing recognition of disease conditions, and providing robust data for outcomes research.

The Aging in Motion (AIM) coalition (aginginmotion.org), established by the Alliance for Aging Research in 2011, submitted a proposal to the CDC in 2014 to create an ICD-10 code for sarcopenia. This code was considered crucial for recognizing this age-related condition and characterizing it among the many conditions affecting the older person. The proposal outlined the evolution of sarcopenia as a distinct diagnosis, the efforts to reach an international consensus definition (3, 4), the impact of sarcopenia on function, and the potential for development of drugs to treat the condition. The submission of the proposal was followed by a public meeting with the C&M committee where concerns were raised that sarcopenia could be conflated with muscle and neurological conditions. An extensive literature review allayed these concerns, and a revised version of the proposal addressing these issues was sent to the CDC. Finally, in April 2016, a new code for sarcopenia – M62.84 - was added, and went into effect in October 2016. The code specifies that if underlying conditions such as other muscle diseases are present, they should be coded first, followed by the code for sarcopenia. However, sarcopenia should be coded first if associated with conditions such as generalized weakness or accelerated physical disability. These refinements to the way sarcopenia should be coded are designed to ensure that data are captured accurately.

Implications of ICD-10 Codes for Sarcopenia

Establishing the ICD-10 code allows the recognition of sarcopenia as a separately reportable condition by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA). Indeed, sarcopenia was selected as one of eight conditions to be addressed by patient-focused drug development meetings conducted by the FDA in 2017. Establishment of the code also has the potential to incentivize funders and sponsors to allocate increased resources to address sarcopenia.

Task Force participants noted that establishing ICD10 codes is the first step, allowing for the collection of data demonstrating a change in various metrics of muscle weakness and disability across large population cohorts, which would allow those metrics to be used to support drug development. The FDA has requested qualitative research to validate assessment tools for the measurement of outcomes that are useful to patients. Functional assessments and Patient-reported outcome (PRO) are among the types of endpoints that hold appeal for regulatory agencies, who might accept a quantitative measure of benefit plus a PRO as co-primary endpoints in a confirmatory clinical trial.

Nonetheless, there remain barriers to the use of the ICD-10 among both general practitioners and specialists. Patients may complain of loss of physical function, such as not being able to lift a grandchild, however they do not understand "sarcopenia", which further hinders translation into clinical practice. Payers may also be slow to embrace the new code given the relatively high prevalence of sarcopenia, in contrast to low-prevalence disorders with clear endpoints that can be modified by the intervention. Task Force members cited the need to communicate with professional societies to raise awareness of the code and ensure clinical recognition and coverage of sarcopenia. On the international front, establishment of an ICD-10-CM code in the US may encourage creation of a unique code in the next version of the WHO code book, ICD-11.

In clinical practice, another challenge with moving ICD-10 forward is creating awareness that sarcopenia interventions can help prevent disability. Sarcopenia has a relevant impact on quality of life over the lifespan, but individuals may not yet be aware of the myriad of ways through which sarcopenia can lead to a loss of independence and increase risk of death. Moreover, individuals and physicians should be made aware that sarcopenia is a problem that can be addressed. With increased awareness, patients and clinicians may begin to see treatment of sarcopenia as a means to avoid disability, similarly to how they were educated to treat hypertension as a means of preventing stroke. To get to this point, however, Task Force members cited the need for more health economics data and the identification of surrogate endpoints (e.g., increased hospitalizations, institutionalizations, healthcare services consumption), which will be facilitated by the introduction of the ICD-10 code.

Improved screening tools for sarcopenia, including self-administered instruments, are also needed to maximize the potential benefits of the ICD-10 code. Given that heightened awareness of sarcopenia in the general public may lead to higher demand for physical therapists and/or dietitians, sarcopenia researchers should devise messages that align with the goals of these allied health practitioners. To increase the efficiency of clinical trials, new models are needed to engage potential participants, which can be particularly challenging in older populations. Clinics that focus on falls or other functional impairments that result from sarcopenia may be one useful approach.

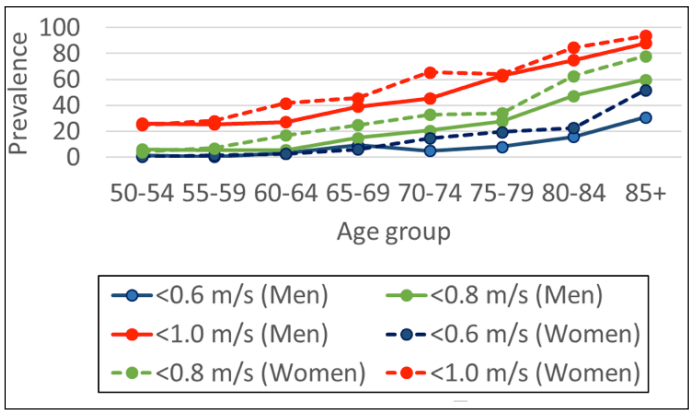
Establishing Evidence-Based Cut-points to Define Sarcopenia

Declining muscle strength is a universal feature of aging that people often dismiss as inevitable. Thus, there is a need to distinguish between normal aging of the skeletal muscle and sarcopenia, a clinical condition can and should be prevented and treated. The first phase of the FNIH Sarcopenia Project established a clinical paradigm for identifying subjects with sarcopenia in which poor physical function should immediately lead to the evaluation of possible weakness. If muscle weakness is excluded, other conditions should be considered, while quantification of muscle mass is recommended in the presence

of weakness. Sarcopenia is present when muscle weakness and low muscle mass coexist (4).

To implement this paradigm, assessment tools for weakness and low muscle mass are needed. The Sarcopenia Project used clinical data from over 26,000 individuals in nine studies to define normal and abnormal cut-points for different assessments. The derived cut-points were then used to estimate prevalence and predictive capacity for major clinical outcomes, such as mortality and falls. Establishing a cut-point for a disease that follows a continuum – such as hypertension -- always relies on some underlying arbitrary decisions. A cut-point that results in a low prevalence could result in too few individuals identified and treated (determining a high number of false negative results), while a cutpoint that overestimates the prevalence of the condition may result in over-treatment. The choice of a cut-point thus balances sensitivity and specificity (e.g., false negatives and false positives) according to the needs of the evaluation. As a screening tool, sensitivity might be particularly important in order to be more comprehensive in the identification of subjects at risk, whereas specificity may be preferred to filter individuals to be treated with a costly intervention. In establishing cut-points, one also needs to identify what outcome is most important – e.g. mobility (slowness), mortality, falls, or hospitalization. A barrier in sarcopenia research is that no single outcome serves as a gold standard against which potential definitions would be evaluated. Consensus on what outcomes are most important for sarcopenia would help solidify its definition.

Figure 1
Prevalence of Slow Gait in the General United States Population (NHANES)



How slow gait is defined substantially affects its prevalence. If it is defined as slower than 1 m/sec, the prevalence of slow gait is substantially greater than if it is defined as less than .6 m/sec. Adapted from Cummings, et al., JAMA 2014 (5).

Epidemiological data can help answer these questions. For example, using data from the National Health and Nutrition Examination Survey (NHANES), Cummings et al. demonstrated how applying different cut-points to define slow gait speed resulted in different prevalence estimates across age groups, with increasing prevalence of slow gait with increasing age (Figure 1) (5). Batsis et al. also showed that prevalence differs depending on the end-point used, for example, if prevalence is based on low lean mass versus weakness (6-8).

The Sarcopenia Definitions and Outcomes Consortium Project, an ongoing project funded by the US National Institute on Aging and the Foundation for the NIH, included in their analysis data from nine cohort studies, applying different statistical methods to determine the best way to compare strength, muscle mass, and physical performance in a heterogeneous population. Unfortunately, none of the studies included in the FNIH-Sarcopenia Project simultaneously included all three key measures: gait speed, weakness, and lean mass. In addition, other factors that need to be considered include race, ethnicity, and the cost of screening. Body size affects measures of sarcopenia, with obese individuals needing stronger muscles to carry their excess weight. Therefore, the analysis searched for and identified several candidate measures and cut-points that accurately categorized participants as either sarcopenic or non-sarcopenic, regardless of whether they were slim or overweight. These various measures were tested in the large dataset to determine which combination of factors provided the best discriminatory power. The ratio of appendicular lean mass to body mass index was chosen as the most reliable marker for capturing skeletal muscle loss, although other parameters were also possible and further evaluation of these data are underway.

Separate analyses for men and women revealed important differences. For example, while grip strength and slower walking speed appear to correlate with the risk of falls and death in both men and women, slow walking speed increases the risk of mortality more in men than in women, although the prevalence of slow walking speed is higher in women. Women are also much more likely to be disabled. Because of these sex differences the Sarcopenia Definitions and Outcomes Consortium created different cut-points for men and women, although they noted that sex-specific cut-points are not commonly used in other disease areas.

Task Force members raised several caveats about the analyses of the Sarcopenia Definitions and Outcomes Consortium project. Since the studies from which the cohorts were derived mostly required participants to be community dwelling and ambulatory, the analyses completed thus far included relatively few with mobility complaints, cognitive impairment, or other medical conditions that are associated with a high prevalence of sarcopenia. The influence of race and country of origin also needs to be explored, and concerns were expressed about using body mass index in the algorithm because of the high prevalence of obesity in the US (potentially biasing the application of the measure/cut-points in non-US populations). Indeed, sarcopenic obesity may be a different condition (9). The Sarcopenia Definitions and Outcomes Consortium analyses will be presented and discussed at consensus conference later in 2017 to reach agreement on definitions of sarcopenia.

It may be that additional data, including functional data, are needed before a consensus can be reached. Many clinical cohorts are available in Europe that focus on function. These cohorts could enable exploration of the predictive capacity of sarcopenia for disability or hospitalization. Efforts to acquire and combine these datasets could provide important insight into the prevalence of clinically meaningful aspects of sarcopenia. Indeed, refining cut-points for better capturing hard outcomes as well as outcomes valued by older people is essential if the field wants to move forward and effectively address unmet clinical needs.

Learning from Current Trials in Sarcopenia and Osteoporosis

The Task Force also reflected on lessons learned from ongoing trials on sarcopenia and osteoporosis (Table 1). A recent analysis of 123 sarcopenia intervention studies found that most were single-center randomized studies focused on nutrition and exercise. Few used recent consensus definitions of sarcopenia and an extreme variety of endpoints were considered. For example, muscle mass and strength were primary outcome variables in less than 30% of studies and physical performance was included in less than 20% (10). While some studies have demonstrated beneficial effects of resistance exercise training combined with protein supplementation in younger adults, a meta-analysis of 15 studies failed to show a similar effect in older healthy, frail, and sarcopenic adults (11). However, a very recent systematic overview showed that exercise and nutrition improved outcomes in well-defined populations using strict criteria for the diagnosis of sarcopenia and frailty as inclusion criteria (12).

Difficulty recruiting sarcopenic participants was cited as a major challenge in this field of research (e.g., in the trial conducted on the anti-myostatin drug REGN1033). Establishing clinical services specifically designed for sarcopenic patients might provide a solution to this problem. Diverse communication strategies (e.g., mass mailing, raising awareness in primary care) might be used to reach the community as demonstrated by the successful results of the LIFE study (13).

Trial design also presented recruitment challenges in the SPRINTT (Sarcopenia & Physical fRailty IN older people: multi-componenT Treatment strategies) trial. This study is designed to compare a multicomponent intervention (consisting of structure physical activity, personalized nutritional counseling/dietary intervention, and an informational/communication technology [ICT] intervention versus a healthy aging lifestyle education program) to prevent mobility disability in 1,500 individuals with physical frailty and sarcopenia (14). In addition to testing the effectiveness of the intervention, SPRINTT was designed to provide a clear operationalization of the theoretical concept of a condition (i.e., "physical frailty and sarcopenia", PF&S) (15) that can meet the methodological construct required by regulatory agencies; and included the definition of diagnostic and prognostic biomarkers. Thus, when designing the trial, the SPRINTT Consortium conferred with the European Medicines Agency (EMA), which provided its scientific advice and finally endorsed the trial design, statistical approach, and the proposed definition of PF&S. It is noteworthy that the EMA accepted for the first time to consider a condition focused on loss of function (i.e., the skeletal muscle-related loss of mobility) instead of the traditional paradigms of diseases. Specifically, the EMA Committee for Medicinal Products for Human Use (CHMP) agreed on the operational definition of sarcopenia based on the FNIH proposed criteria of low appendicular body mass normalised for body mass index or low appendicular body mass (4) and a low score at the Short Physical Performance Battery (SPPB, formal correspondence on file). The EMA CHMP is then awaiting final refinement of the applied selection/inclusion criteria based on the evaluation of the study final results. Overall, SPRINTT will generate data on the body composition (measured by DXA) and physical function (SPPB and 400 meter walk) from 1,500 frail sarcopenic older persons and their 2-year change. It is paramount to wait for these data becoming available to the scientific community as they could meaningfully impact the ongoing discussions on sarcopenia diagnosis by taking into account a representative European sample of older people at risk of mobility disability. The trial began in January 2016, and sixteen clinical sites are currently recruiting participants in eleven European countries and the recruitment is expected to the completed at the end of September 2017.

A meta-analysis of studies combining exercise and protein supplementation demonstrated additive effects on muscle mass and strength in both younger and older subjects (16), although as mentioned earlier, results in older adults are weaker (11). Some studies have shown benefits of nutritional supplementation. For example, a meta-analysis of high-protein oral nutritional supplements in patients following hospital discharge showed a reduction in complications and re-admissions as well as improvements in weight and grip strength (17). As described in Table 1, nutritional supplementation (alone or in combination with exercise) is a widely-studied treatment strategy (13, 14, 18-21). The variable results obtained from available studies raise many questions about the design of the intervention (e.g., adequacy of the dosing, appropriateness of the specific nutrients), the eligibility criteria (i.e., recruitment of the best candidates to benefit from the supplementation), and the adopted measures for measuring the risk condition and the endpoints. The aging process is responsible for declines in both bone (osteoporosis) and muscle (sarcopenia) health, contributing to frailty (22) and leading to increased risk of fracture, disability, loss of independence, decreased quality of life, and increased mortality. Yet, the development of treatments for osteoporosis has far outpaced those for sarcopenia. As mentioned earlier, one of the factors

that has enabled the development of osteoporosis treatments is the availability of ICD codes and a clear operational definition (based on dual x-ray absorptiometry, or DXA) for the condition. In this way, physicians have been able to diagnose the condition, researchers to collect data about its prevalence and pathophysiological mechanisms, and pharmaceutical companies to design ad hoc interventions. In the field of sarcopenia, things appear more complicated because, whereas osteoporosis (i.e., low bone mineral density, BMD) is naturally related to the fracture endpoint, a similarly strong relationship does not exist between the skeletal muscle and a clinically relevant and organ-specific outcome.

Endpoints that matter to patients, such as falls or hip fracture for osteoporosis, are also less clear for sarcopenia. For osteoporosis trials, the EMA requires demonstration of an effect on both spinal and non-spinal fractures. Possible hard clinical outcomes for sarcopenia clinical trials include mobility disability, activities of daily living (ADL) disability, fractures, recurrent falls, injurious falls, mortality, or hospitalization. A surrogate marker would be ideal. Validating a surrogate endpoint requires demonstrating that it correlates with medically relevant endpoints in the natural course of the disease and in treated subjects. In addition, regulators want to see a demonstration of the magnitude of the relationship between the surrogate and the hard endpoint in treated subjects. Surrogate endpoints that might be acceptable in sarcopenia clinical trials include grip strength, walking speed, or chair stand since they correlate with mortality and other clinical outcomes (23, 24). Regulators are also increasingly requiring as co-primary endpoints patient-reported outcomes (PROs). Various auto-evaluation questionnaires, like the Short Form Health Survey (SF-36), have been extensively tested in similar populations and validated in numerous languages. Recently, Beaudart and colleagues developed a sarcopenia-specific quality of life questionnaire (SarQoL) that has been shown to be valid, consistent and reliable (25, 26). The SarQoL (www.sarqol.org) can be used for both clinical and research purposes, but still needs to be validated regarding sensitivity to change. It has been translated into 11 languages with another 19 translations in development. SarQol and SF-36 are currently being measured head-to-head in the SARA observational clinical study, a project currently recruiting patients with sarcopenia or sarcopenic obesity (according the FNIH DXA criteria and very low SPPB score) both in Europe and in the US. The osteoporosis field also benefits from the availability of the International Osteoporosis Foundation's Fracture Risk Assessment tool, the IOFFRAX®, which has been scientifically validated and translated for global use. This simple questionnaire enables the identification of persons at elevated risk for fracture who may be appropriate subjects for clinical trials. A one-minute osteoporosis risk test is also available as a screening tool. In the sarcopenia and frailty fields, similar screening tools have been developed, including the Gérontopôle Frailty Screening Test (GFST) (27), the SARC-F (28), and FRAIL (29). We are confident the ongoing initiatives could generate objective data to contribute identifying better methodologies for studying and characterizing age-related sarcopenia in the more concerned population, older persons at increased risk of losing physical function, of hospitalization and other sarcopenia related major outcomes.

Designing Preventive Trials for Sarcopenia

The establishment of ICD-10 codes and related efforts described above to define sarcopenia and establish evidence-based cut-points to be used diagnostically should enable more productive and efficient clinical trials of sarcopenia interventions. However, there are also efforts underway to prevent sarcopenia, both by targeting people at-risk for the disease (because of a sedentary lifestyle, inadequate energy intake, and other intrinsic factors) as well as individuals with specific conditions characterized by accelerated and/or accentuated aging (30-32). A key issue in geriatric medicine is whether to focus on treatment or prevention. In sarcopenia, public health interventions should follow a life-course approach in order to positively affect the earlier phases of the skeletal muscle decline (roughly starting after the age of 40 years). If lifestyle and behavioral interventions (e.g., nutrition, physical activity) might be foreseen on the large scale given their likely cost-effectiveness and public health interest, the development of drugs for sarcopenia might represent short-term and intense interventions reserved for individuals affected by specific sarcopenia conditions, or target a higher risk sub-population not responding to the life-style intervention and deserving long-term pharmacological treatment.

Designing a prevention trial requires targeting of a risk factor. For example, the University of Florida Institute on Aging is conducting a prevention trial called ENRGISE (ENabling Reduction of lowGrade Inflammation in Seniors) that targets age-related inflammation as a risk factor for mobility loss, frailty, and sarcopenia (33). After conducting a systematic review of anti-inflammatory interventions, they selected an approach that combines an angiotensin receptor blocker (i.e., losartan) with omega-3 fatty acids, two widely available and low-cost interventions. If proven efficacious, this combined intervention could be relatively easy to deliver to older adults at high risk of mobility disability. At the time of the Task Force meeting, the trial was nearing its recruitment goal for a pilot study that will include the assessment of novel inflammatory biomarkers and could provide preliminary data to design a definitive clinical trial.

Conclusions

Sarcopenia is a highly prevalent condition of older age, and a major contributor to frailty and disability. It thus presents a considerable social and economic burden. Establishing an

Table 1
Selected Sarcopenia Intervention Studies

	Intervention	Inclusion criteria	Study Design	Primary Outcome Measures	Secondary Outcome Measures	Major Findings
LIFE (13)	Physical activity vs. health education	Age 70-89 yrs Sedentary SPPB≤9 Able to walk 400m in ≤15 min No major cognitive impairment	Multi-center, single-blind, parallel randomized	400 m walk		Physical activity over 2.6 years significantly reduced major mobility disability among older adults.
REGN	Anti-myostatin REGN 1033 with and without exercise	IWGS consensus criteria for sarcopenia	12 week randomized controlled 2X2 Factorial (dose finding)	Total lean mass and ALM (DXA)	Body composition (by MRI) Strength and function: 6MWT Chair stand Chest press Leg press Hand grip SPPB Stair climb	REGN1033 increased total lean mass and ALM, and decreased regional fat mass at week 12. Strength and function trended in positive direction.
SPRINTT (14)	Long-term structured physical activity + Personalized nutritional counseling + ICT intervention vs. healthy aging lifestyle education	≥ 70 years Able to walk 400m in ≤15 min SPPB 3-9 Low muscle mass by DXA Sedentary	Multi-center randomized controlled trial	Incident inability to complete the 400m walk test	Persistent mobility disability; Physical performance and muscle strength modifications; Body composition changes; Mortality; Hospitalization; Institutionalization	1002 participants randomized as of June 2, 2017
Tieland studies (20,21)	Protein supplementation Resistance exercise + protein supplementation	≥65 years Pre-frail or Frail (Fried criteria [22])	Randomized, controlled	Lean body mass (DXA)	Muscle fiber cross sectional area Maximum strength (1-RM, handgrip) SPPB Plasma glucose, insulin, renal function markers	Protein supplementation improved physical performance but did not increase muscle mass. Resistance exercise improved strength and physical performance. Protein supplementation required during resistance exercise to increase muscle mass
Provide (18)	Vitamin D and leucine-rich protein supplementation	≥65 years SPPB 4-9 Low skeletal mass BMI 20-30 kg/m2 MMSE ≥25	13-week, multicenter, randomized, controlled, double-blind, parallel study	Handgrip strength SPPB	Appendicular muscle mass (DXA) Self-report questionnaires on physical activity, ADL, and health related QOL	Vitamin D and leucine-enriched whey protein supplementation improved muscle mass and lower extremity function in sarcopenic older adults but did not affect handgrip strength or SPPB
VIVE-1	Targeted exercise program + protein-carbohydrate experimental beverage	≥65 years SPPB 3-9 BMI <35 6CIT ≤ 14	24-week, randomized, controlled, single-blind, parallel study	SPPB	Plasma levels of IGF-1, IL-6, vitamin D.	Improved gait speed but no significant effect of supplementation. Supplementation resulted in reduced intramuscular fat infiltration.
ENERGISE (Prevention trial)	Angiotensin receptor blocker + Omega 3 fish oil	≥70 years Self-reported difficulty walking or climbing stairs IL-6 > 2.5 pg/ml and < 10 pg/ml	2x2 factorial randomized pilot	Plasma level of IL-6 Walking speed (400 m walk)	SPPB Frailty (Fried criteria) Grip strength Isokinetic knee extension strength Inability to walk 400m Biomarkers of inflammation	Nearing recruitment goals for pilot study.
Cramer et al (19)	Energy rich, high protein ONS vs similar ONS enriched in protein, vitamin D and CaHMB	≥65 years with sarcopenia (EWGSOP definition) and malnutrition	24-week, randomized, controlled, double-blind, parallel study	Leg extension strength (maximal voluntary isokinetic peak torque)	Grip strength Gait speed Muscle mass (DXA) Muscle quality (strength related to LMM)	Both ONS groups improved strength, gait speed and muscle quality. In non-severe sarcopenia strength improved faster with experimental ONS

ADL: Activities of Daily Living, ALM: Appendicular Lean Mass, BMI – Body Mass Index, CaHMB: calcium 3-hydroxy-3-methyl butyrate, DXA – Dual-energy X-ray Absorptiometry, EWGSOP: European Working Group on Sarcopenia in Older People, ICT: Information and Communications Technology. IGF-1: Insulin-like Growth Factor 1, IL-6: Interleukin 6, LMM: leg muscle mass, MMSE: Mini-Mental State Examination, ONS: Oral Nutritional Supplement, QOL: Quality of Life, SPPB: Short Physical Performance Battery, 1-RM: 1 Repetition Maximum, 6MWT: 6 Minute Walk Test, 6CIT: 6-item Cognitive Impairment Test,

ICD-10 code for sarcopenia is an important first step towards developing effective treatments, but there are significant gaps in knowledge and tools related to risk assessment, and regulatory guidelines are needed. Large clinical trials (SPRINTT, ENRGIZE, etc.) are currently ongoing in age-related sarcopenia and age-related inflammation that will generate meaningful data to better characterize this therapeutic area and feed regulatory appraisal. It will be important to integrate PROs in next coming initiatives, in order to link objective measurement of physical function to what is meaningful for the older person.

Moreover, ICFSR Task Force participants suggested building a risk model similar to FRAX for osteoporosis and/or investigating the value of indexing threshold values for sarcopenia measures and outcomes using a risk-based analysis for one of the strong clinical endpoints. They also mentioned the need to reach consensus on a core outcome set to bring standardization and comparability to research and improve the evidence base (34).

Finally, the Task Force discussed specific characteristics that every trial on sarcopenia should include in its design. Factors that may contribute to the failure of studies to demonstrate benefit include insufficient exposure due to short duration trials and heterogeneity among participants. In addition, there is a clear need to identify endpoints that are clinically meaningful and that are associated with improved clinical outcomes such as reduced disability and mortality. Some workshop participants advocated an increased focus on conducting sarcopenia trials in primary care centers. Certainly, this will require increased attention to issues such as 1) training and providing the necessary tools for general practitioners to conduct grip strength and other evaluations, 2) facilities improvements to handle large numbers of older people coming to the clinics, 3) relief for the increased administrative burden, and 4) strategies to address the transportation needs of trial participants. Other strategies suggested to improve intervention trials for sarcopenia, included conducting trial in well-defined populations with sarcopenia and identifying subpopulations where medical need is addressed, identifying confounding factors, combining treatment modalities in trials, establishing and implementing clear requirements for study sites, and optimizing/standardizing regulations for IRB/ethics approvals.

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References

1. Cesari M, Fielding R, Benichou O, et al. Pharmacological Interventions in Frailty and Sarcopenia: Report by the International Conference on Frailty and Sarcopenia Research Task Force. J Frailty Aging. 2015;4(3):114-20.
2. Anker SD, Morley JE, von Haehling S. Welcome to the ICD-10 code for sarcopenia. J Cachexia Sarcopenia Muscle. 2016;7(5):512-4.
3. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010;39(4):412-23.
4. Studenski SA, Peters KW, Alley DE, Cawthon PM, et al. The FNIH sarcopenia project: rationale, study description, conference recommendations, and final estimates. J Gerontol A Biol Sci Med Sci. 2014;69(5):547-58.
5. Cummings SR, Studenski S, Ferrucci L. A diagnosis of dismobility--giving mobility clinical visibility: a Mobility Working Group recommendation. JAMA. 2014;311(20):2061-2.
6. Masanes F, Rojano I. Luque X, et al. Cut-off points for muscle mass -- not grip strength or gait speed -- determine variations in sarcopenia prevalence. J Nutr Health Aging. 2016.
7. Batsis JA, Mackenzie TA, Jones JD, Lopez-Jimenez F, Bartels SJ. Sarcopenia, sarcopenic obesity and inflammation: Results from the 1999-2004 National Health and Nutrition Examination Survey. Clin Nutr. 2016.
8. Batsis JA, Mackenzie TA, Lopez-Jimenez F, Bartels SJ. Sarcopenia, sarcopenic obesity, and functional impairments in older adults: National Health and Nutrition Examination Surveys 19992004. Nutr Res. 2015;35(12):1031-9.
9. Wannamethee SG, Atkins JL. Muscle loss and obesity: the health implications of sarcopenia and sarcopenic obesity. Proc Nutr Soc. 2015;74(4):405-12.
10. Pena Ordonez GG, Bustamante Montes LP, Ramirez Duran N, Sanchez Castellano C, Cruz-Jentoft AJ. Populations and outcome measures used in ongoing research in sarcopenia. Aging Clin Exp Res. 2016.
11. Thomas DK, Quinn MA, Saunders DH, Greig CA. Protein Supplementation Does Not Significantly Augment the Effects of Resistance Exercise Training in Older Adults: A Systematic Review. J Am Med Dir Assoc. 2016;17(10):959 e1-9.
12. Lozano-Montoya I, Correa-Perez A, Abraha I, et al. Nonpharmacological interventions to treat physical frailty and sarcopenia in older patients: a systematic overview - the SENATOR Project ONTOP Series. Clin Interv Aging. 2017;12:721-40.
13. Pahor M, Guralnik JM, Ambrosius WT, et al. Effect of structured physical activity on prevention of major mobility disability in older adults: the LIFE study randomized clinical trial. JAMA. 2014;311(23):2387-96.
14. Landi F, Cesari M, Calvani R, et al. The «Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies» (SPRINTT) randomized controlled trial: design and methods. Aging Clin Exp Res. 2017;29(1):89-100.
15. Cesari M, Landi F, Calvani R, et al. Rationale for a preliminary operational definition of physical frailty and sarcopenia in the SPRINTT trial. Aging Clin Exp Res. 2017;29(1):81-8.
16. Cermak NM, Res PT, de Groot LC, Saris WH, van Loon LJ. Protein supplementation augments the adaptive response of skeletal muscle to resistance-type exercise training: a meta-analysis. Am J Clin Nutr. 2012;96(6):1454-64.
17. Cawood AL, Elia M, Stratton RJ. Systematic review and meta-analysis of the effects of high protein oral nutritional supplements. Ageing Res Rev. 2012;11(2):278-96.
18. Bauer JM, Verlaan S, Bautmans I, et al. Effects of a vitamin D and leucine-enriched whey protein nutritional supplement on measures of sarcopenia in older adults, the PROVIDE study: a randomized, double-blind, placebo-controlled trial. J Am Med Dir Assoc. 2015;16(9):740-7.
19. Cramer JT, Cruz-Jentoft AJ, Landi F, et al. Impacts of HighProtein Oral

Nutritional Supplements Among Malnourished Men and Women with Sarcopenia: A Multicenter, Randomized, Double-Blinded, Controlled Trial. J Am Med Dir Assoc. 2016;17(11):1044-55.
20. Tieland M, Dirks ML, van der Zwaluw N, et al. Protein supplementation increases muscle mass gain during prolonged resistance-type exercise training in frail elderly people: a randomized, double-blind, placebo-controlled trial. J Am Med Dir Assoc. 2012;13(8):713-9.
21. Tieland M, van de Rest O, Dirks ML, et al. Protein supplementation improves physical performance in frail elderly people: a randomized, doubleblind, placebo-controlled trial. J Am Med Dir Assoc. 2012;13(8):720-6.
22. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3):M146-56.
23. Cooper R, Kuh D, Cooper C, et al. Objective measures of physical capability and subsequent health: a systematic review. Age Ageing. 2011;40(1):14-23.
24. Simmonds SJ, Syddall HE, Westbury LD, Dodds RM, Cooper C, Aihie Sayer A. Grip strength among community-dwelling older people predicts hospital admission during the following decade. Age Ageing. 2015;44(6):954-9.
25. Beaudart C, Biver E, Reginster JY, et al. Validation of the SarQoL(R), a specific health-related quality of life questionnaire for Sarcopenia. J Cachexia Sarcopenia Muscle. 2017;8(2):238-44.
26. Beaudart C, Biver E, Reginster JY, et al. Development of a selfadministrated quality of life questionnaire for sarcopenia in elderly subjects: the SarQoL. Age Ageing. 2015;44(6):960-6.
27. Vellas B, Balardy L, Gillette-Guyonnet S, et al. Looking for frailty in community-dwelling older persons: the Gerontopole Frailty Screening Tool (GFST). J Nutr Health Aging. 2013;17(7):629-31.
28. Malmstrom TK, Miller DK, Simonsick EM, Ferrucci L, Morley JE. SARC-F: a symptom score to predict persons with sarcopenia at risk for poor functional outcomes. J Cachexia Sarcopenia Muscle. 2016;7(1):28-36.
29. Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. J Nutr Health Aging. 2012;16(7):601-8.
30. Janssen I, Heymsfield SB, Wang ZM, Ross R. Skeletal muscle mass and distribution in 468 men and women aged 18-88 yr. J Appl Physiol (1985). 2000;89(1):81-8.
31. Saini A, Faulkner S, Al-Shanti N, Stewart C. Powerful signals for weak muscles. Ageing Res Rev. 2009;8(4):251-67.
32. Vellas B, Fielding R, Bhasin S, et al. Sarcopenia Trials in Specific Diseases: Report by the International Conference on Frailty and Sarcopenia Research Task Force. J Frailty Aging. 2016;5(4):194-200.
33. Fougere B, Boulanger E, Nourhashemi F, Guyonnet S, Cesari M. Chronic Inflammation: Accelerator of Biological Aging. J Gerontol A Biol Sci Med Sci. 2016.
34. Reginster JY, Cooper C, Rizzoli R, et al. Recommendations for the conduct of clinical trials for drugs to treat or prevent sarcopenia. Aging Clin Exp Res. 2016;28(1):47-58.