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INTERNATIONAL CLINICAL PRACTICE GUIDELINES FOR SARCOPENIA (ICFSR): SCREENING, DIAGNOSIS AND MANAGEMENT

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Abstract: *Objectives:* Sarcopenia, defined as an age-associated loss of skeletal muscle function and muscle mass, occurs in approximately 6 - 22 % of older adults. This paper presents evidence-based clinical practice guidelines for screening, diagnosis and management of sarcopenia from the task force of the International Conference on Sarcopenia and Frailty Research (ICSFR). *Methods:* To develop the guidelines, we drew upon the best available evidence from two systematic reviews paired with consensus statements by international working groups on sarcopenia. Eight topics were selected for the recommendations: (i) defining sarcopenia; (ii) screening and diagnosis; (iii) physical activity prescription; (iv) protein supplementation; (v) vitamin D supplementation; (vi) anabolic hormone prescription; (vii) medications under development; and (viii) research. The ICSFR task force evaluated the evidence behind each topic including the quality of evidence, the benefit-harm balance of treatment, patient preferences/values, and cost-effectiveness. Recommendations were graded as either strong or conditional (weak) as per the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach. Consensus was achieved via one face-to-face workshop and a modified Delphi process. *Recommendations:* We make a conditional recommendation for the use of an internationally accepted measurement tool for the diagnosis of sarcopenia including the EWGSOP and FNIH definitions, and advocate for rapid screening using gait speed or the SARC-F. To treat sarcopenia, we strongly recommend the prescription of resistance-based physical activity, and conditionally recommend protein supplementation/a protein-rich diet. No recommendation is given for Vitamin D supplementation or for anabolic hormone prescription. There is a lack of robust evidence to assess the strength of other treatment options.

Key words: Sarcopenia/diagnosis, sarcopenia/therapy, muscle strength, aged, 80 and over, practice guideline.

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Introduction

Since 2016, the World Health Organization (WHO)'s International Statistical Classification of Diseases and Related Health Problems (ICD) has recognised sarcopenia as a disease; code ICD-10-CM (M62.84) (1). Sarcopenia is defined as an age-associated loss of skeletal muscle function and muscle mass, and is common in older adults (2-6). The overall prevalence of sarcopenia is estimated to be approximately 6 - 22 % in adults aged 65 years and over, with a variation in prevalence across healthcare settings (7-11). Prevalence also increases with age (12-17). The number of older adults with sarcopenia will continue to grow alongside the rapid increase in the number and proportion of older adults globally (18).

Recognition of sarcopenia as a disease has led to major research efforts into the best practices for its screening, diagnosis and management. Through the translation of current, comprehensive evidence into clinical practice, it may be possible to reduce the risk for falls, fractures, functional decline, hospitalisation and mortality associated with the condition (4, 19-21). The purpose of this paper is to present evidence-based clinical practice guidelines (CPGs) for the most effective practices to screen for, diagnose and manage sarcopenia in older adults. The target audience for the guidelines includes all clinicians and allied health professionals. The guidelines are not intended to replace clinical judgement, but rather, should be used by practitioners to guide care in line with patient preferences and priorities. The guidelines may also be used for the formulation of regulatory policies (22).

Methods

Guideline Development and Review Process

The guidelines were developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (23). This approach involved a structured evaluation of the current literature base, followed by a formulation of recommendations (23). Three panels were formed to develop the guidelines:

- an international, multidisciplinary guideline development task force from the International Conference on Sarcopenia and Frailty Research (ICSFR), representing Europe, Asia, North America, and Oceania. This task force comprised relevant experts across multiple professional associations, including geriatricians, gerontologists, musculoskeletal physiologists, allied health professionals and methodology experts;
- a steering committee; and
- an independent, external reviewing group comprising general practitioners (GPs) (n=7), nurse practitioners (n=3), community dwelling older adults (n=12), a pharmacist, physiotherapists (n=3), personal trainers running an exercise program for older adults (n=2), occupational therapists (n=4), a health economist, a nutritionist, and a dietician.

The GRADE Evidence to Decision (EtD) framework was used by the guideline development group to construct each recommendation (24). Concepts of the AGREE II evaluation framework were also incorporated into our development protocol, methodology, and reporting (22).

The first step in guideline development was a full day international ICSFR task force workshop, held in Miami, USA (March 2018). At this workshop, clinical questions relating to the clinical diagnosis and management of sarcopenia were presented by task force members and discussed in detail, including: how to diagnose sarcopenia; which interventions and follow-up should be implemented after the diagnosis of sarcopenia; potential nutritional and physical activity interventions and their underlying evidence-base; medical interventions; and which outcome measurements to consider when grading the quality of clinical trials. As part of the workshop, task force members also received a short training session on guideline development, incorporating how to grade the strength and quality of evidence according to GRADE (23) criteria.

Searching the Evidence

For each recommendation, the Population, Intervention, Comparator, and Outcome (PICO) literature search query was as follows:

- For older adults with sarcopenia (P), what are the relative benefits and harms of different treatment/management strategies reported in randomised clinical trials (I) compared with usual care (C) on strength, physical performance, the ability to perform activities of daily living (ADLs), muscle mass, falls, and patient values and preferences (O)?

To develop the guidelines, we drew upon the best available evidence from recent systematic reviews (4, 11), their included randomised clinical trials (RCTs), and consensus statements by international workgroups on sarcopenia. These sarcopenia working groups included: the European Working Group on Sarcopenia in Older People (EWGSOP) (25); the Asian Working Group for Sarcopenia (AWGS) (3); the US Foundation for the National Institutes of Health (FNIH) (26); the International Sarcopenia Initiative (ISI) (11) and the International Working Group on Sarcopenia (IWGS) (5). To identify additional relevant publications, we utilised two main strategies: (i) the aggregate publication libraries of task force members, many of whom were a member of one or more international working groups on sarcopenia; and (ii) PubMed and Scopus database searches with combinations of the search terms "sarcopenia/diagnosis*", "sarcopenia/therapy*", "aged", "intervention" and "treatment" as per the recent systematic review of Yoshimura and colleagues (4). To identify publications from Low-Middle Income Countries (LMICs), we utilised the expertise of task force members conducting research in these countries.

The guidelines are tailored for the screening, diagnosis and

management of sarcopenia in adults aged 65 years and older. To promote generalisability of our outcomes across medical specialties, we focused our evidence-base on interventions involving community-dwelling older adults.

Grading the Evidence: Strength and Certainty of Evidence

Based on the supporting evidence-base, the task force graded the strength and quality of each recommendation for the treatment of sarcopenia. The strength of a recommendation refers to the benefit-harm balance, cost-effectiveness, patient preferences and values, as well as the quality of the supporting evidence (27, 28). When grading the recommendation's strength, the task force specifically focused on both the importance of the outcome to patients, and the number of patients who would benefit from the treatment, in line with the GRADE EtD framework (24). A strong recommendation indicated that the desirable clinical benefits effects of the intervention strongly outweighed the risk of undesirable outcomes (27, 28). A conditional (weak) recommendation indicated that the treatment had considerable undesirable outcomes (such as patient burden, unwanted side effects, and risk of adverse clinical outcomes) which undermined the health benefits of the treatment – that is, whilst many health practitioners would choose this treatment modality, many would not (27, 28). For example, if there was substantial variability in patient preferences and values regarding outcomes, or if patient values were unknown, then a recommendation was graded as conditional (24). When insufficient evidence existed to support any recommendation, then a statement of "no recommendation" was reported.

The certainty (quality) of each recommendation referred to the overall certainty of the evidence for the effect (23, 24). To grade the certainty of evidence, the task force considered imprecision, risk of bias, inconsistency, publication bias and indirectness (24). The four rankings of evidence certainty (23, 27, 28) were as follows:

- High: Further research is very unlikely to change confidence in the estimate of effect;
- Moderate: Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate;
- Low: Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate;
- Very Low: Any estimate of effect is very uncertain

Decision tables were used to record the task force's judgements according to the GRADE criteria, and in turn, how these judgements influenced the development of each guideline (29). Where there were gaps in the evidence-base, a consensus between ICFSR task force members was used to form best-practice recommendations

Patient Values and Preferences

It was emphasised by the task force that the evidence base behind each guideline should incorporate factors important to the older adults themselves, including autonomy in their processes of care, and ease of accessibility to healthcare needed. Patient views and preferences were sought through consultation with patients themselves. A patient information guide was also drafted by the ICSFR task force, based on information the patients themselves thought was important to know.

Practical Issues

To ensure that the guidelines were applicable across LMICs, the task force accounted for the resource and financial challenges that many LMICs face. Organisational barriers potentially impeding the application of the guidelines were also taken into consideration.

Guideline Scope

Determining the most appropriate diagnostic tool for sarcopenia is currently under considerable debate (30, 31). In view of this controversy, the nuances as to which specific sarcopenia diagnostic tool is best (EWGSOP (25), AWGS (3), FNIH (26), IWGS (5), ISI (11), and the screening tool SARC-F (32)) is beyond the scope of this manuscript.

Recommendations

Table 1 displays the ICSFR recommendations for the recognition and management of sarcopenia.

Recommendation 1: Screening

Older adults aged 65 years and older should be screened for sarcopenia annually, or after the occurrence of major health events (Grade: conditional recommendation, low certainty of evidence)

The task force conditionally recommends that older adults aged 65 years and older should be screened annually for sarcopenia, or after the occurrence of major health events such as falls resulting in hospitalisation. This screening should be opportunistic, for instance at annual health check-up or flu vaccination appointments. The task force agreed upon regular screening for sarcopenia for several reasons. First, all older adults are at risk of developing sarcopenia, particularly those with low physical activity levels (33, 34). Second, sarcopenia is common across all populations of older people (11, 34-39), and may be transient in its early stages (11, 40-43). Third, sarcopenia places a heavy burden on the individual, their care-giver, and the healthcare system (11). Fourth, screening for sarcopenia is effective (44-50); and fifth, the majority of older adults, allied health professionals and GPs from our external guidelines review group were in agreement with annual screening.

The level of certainty for sarcopenia screening was graded

Table 1
Clinical Practice Guidelines for Older People with Sarcopenia

	Guideline	Strength of Evidence†	Certainty of Evidence††
1.Screening	1A. Older adults aged 65 years and older should be screened for sarcopenia annually, or after the occurrence of major health events	Conditional	++
	1B. Screening for sarcopenia can be performed using gait speed, or with the SARC-F questionnaire	Conditional	++
	1C. Individuals screened as positive for sarcopenia should be referred for further assessment to confirm the presence of the disease	Conditional	++
2. Diagnosis	2A. It is recommended that health practitioners use an objective measurement tool for the diagnosis of Sarcopenia, utilising any of the published consensus definitions	Conditional	+++
	2B. DXA should be used to determine low lean mass when diagnosing sarcopenia	Conditional	++
	2C. Walking speed or grip strength should be used to determine low levels of muscle strength and physical performance respectively when diagnosing sarcopenia	Strong	+++
3. Physical Activity	3A. In patients with sarcopenia, prescription of resistance-based training may be effective to improve lean mass, strength and physical function	Strong	+++
4. Protein	4A. We recommend clinicians consider protein supplementation/a protein-rich diet for older adults with sarcopenia	Conditional	++
	4B. Clinicians may also consider discussing with patients the importance of adequate calorie and protein intake	Conditional	+
	4C. Nutritional (protein) intervention should be combined with a physical activity intervention	Conditional	++
5. Vitamin D	5A. Insufficient evidence exists to determine whether a Vitamin D supplementation regime by itself is effective in older adults with sarcopenia	Insufficient evidence	+
6. Anabolic Hormones	6A. The current evidence is insufficient to recommend anabolic hormones for the management of sarcopenia	Insufficient evidence	+
7. Pharmacologic Interventions	7A. Pharmacological interventions are not recommended as first-line therapy for the management of sarcopenia	Insufficient evidence	+
8. Research	8A.. Future international collaboration and large-scale RCTs focusing specifically on older people with sarcopenia are recommended	n/a	n/a

DXA = dual-energy x-ray absorptiometry; †† Strength of Evidence (categories) (23):

The strength of evidence considers the benefit-harm balance, patient preferences/values, cost-effectiveness, as well as the certainty of evidence. Strong means that benefits clearly outweigh any risks; Conditional means that clinicians would only refer the intervention under specific conditions because there is a fine balance between risks and burdens; Insufficient evidence (No recommendation) – there is insufficient evidence to determine net benefits or risks; † Certainty of Evidence (categories): ++++ High: Further research is very unlikely to change confidence in the estimate of effect; +++ Moderate: Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate; ++ Low: Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate; + Very Low: Any estimate of effect is very uncertain

as low, noting that issues such as cost-effectiveness, resources and patient accessibility to screening services have not been investigated well in the literature. Indeed, external feedback from a health economic review of our guidelines stressed that an organised, formal screening program for sarcopenia may not be cost-effective, although opportunistic screening may be. Understandably, pragmatic cost-effectiveness modelling studies are needed to evaluate the benefits of incorporating routine screening. The task force also highlighted that there is currently no direct evidence in support of a specific frequency for sarcopenia screening, and it is likely that new research evidence would impact on the certainty of this recommendation.

Screening for sarcopenia can be performed using gait speed, or with the SARC-F questionnaire (Grade: conditional recommendation, low certainty of evidence)

Screening tests for sarcopenia need to be rapid and easy to use. The ICFSR preferred screening techniques for sarcopenia include gait speed (51-54) and the SARC-F questionnaire (30, 32, 55, 56); gait speed is well recognised as a screening tool for sarcopenia (6), and SARC-F has been found to have moderate-high specificity in accurately identifying sarcopenia, although with only moderate sensitivity (50, 57, 58). The recommendation for screening using gait speed or the SARC-F was supported by all primary care members in our external reviewing group.

Of importance, the task force did consider grip strength as a screening tool for sarcopenia, but this was voted out in the consensus process for two main reasons: (i) the new EWGSOP guidelines for sarcopenia [EWGSOP-2 (59)] recommend that grip strength is a diagnostic assessment rather than a screening test; and (ii) the specific feedback we received from the primary care members of our external reviewing group, most of whom stated that they would prefer not to perform grip strength measurement in their primary care clinics.

Table 2
Diagnosis of Sarcopenia according to International Working Groups

International Working Group	Year	Recommendation for diagnosing Sarcopenia	Notes
European Working Group on Sarcopenia in Older People (EWGSOP) (25)	2010	"Both low muscle mass and low muscle function (strength or performance)", assessed in clinical practice using: (i) DXA, BIA, or anthropometrics; (ii) grip strength; and (iii) gait speed, SPPB, or TGUG respectively.	The EWGSOP is currently working towards a revised sarcopenia diagnosis (EWGSOP-2) which will place muscle strength in the centre of the diagnostic process, as opposed to muscle mass (60). The revised EWGSOP definition of sarcopenia (expected publication 2019)(60) states that: (i) probable sarcopenia is identified by low muscle strength; sarcopenia diagnosis is supported by additional documentation of low muscle quantity and/or quality; and severe sarcopenia is diagnosed when physical performance ability (measured by SPPB, TUG or a 400m walking test) is also low.
Asian Working Group for Sarcopenia (AWGS) (3)	2014	"Low muscle mass plus low muscle strength and/or low physical performance"	Similar to the EWGSOP working definition, although using cut-off points specific to older adults from/ descendent from South-East Asia
Foundation for the National Institutes of Health (FNIH) (26, 62)	2014	As per the EWGSOP definition, using DXA, gait speed and grip strength for measurement of LBM, muscle strength and physical performance respectively.	Based on a detailed evaluation of clinically relevant cut-off points for weakness and low LBM.
International Working Group on Sarcopenia (IWGS) (5)	2011	"Low whole-body or appendicular fat-free mass (measured using DXA) in combination with poor physical functioning (defined as gait speed <1m/s)".	Patients who are bedridden, cannot perform a chair rise, or with gait speed <1m/s should undergo DXA measurement, and sarcopenia diagnosed using validated definitions.
European Society of Clinical Nutrition and Metabolism (ESPEN) (63)	2017	Endorsement of the EWGSOP diagnosis	Highlights that diagnostic criteria for sarcopenia have not yet been fully established
International Sarcopenia Initiative (ISI) (11)	2014	As per IWGS and EWGSOP definitions	Formed by international experts from the EWGSOP and IWGS

TUG = Timed Up and Go test; SPPB = Short Physical Performance Battery; BIA = Bioelectrical Impedance Analysis; DXA = Dual-energy X-Ray Absorptiometry; LBM = Lean Body Mass

Individuals screened as positive for sarcopenia should be referred for further assessment to confirm the presence of the disease (Grade: conditional recommendation, low certainty of evidence).

The task force recommends that individuals screened as positive for sarcopenia should be referred for further assessment to confirm the presence of the disease. There are two main reasons for this recommendation: first, unmanaged sarcopenia can quickly increase risk for mortality and functional decline (34, 41); and second, detection of sarcopenia in its early stages may significantly contribute to less morbidity and mortality related to the condition (4, 11). We note that although there is a paucity of research into care pathways for sarcopenia screening and assessment, all international consensus statements agree with the importance of an assessment referral after a positive screening (3, 5, 11, 25, 26).

Recommendation 2: Diagnosis

It is recommended that health practitioners use an objective measurement tool for the diagnosis of Sarcopenia, utilising any of the published consensus definitions (Grade: conditional recommendation; moderate certainty of evidence)

Clinicians should ensure that they are accurately measuring sarcopenia before beginning sarcopenia treatment. The task force emphasized the importance of using an objective measurement tool for the diagnosis of sarcopenia, using any of the validated, international operational tools, such as those developed by either the EWGSOP (25), FNIH (26), IWGS (5), and AWGS (3) - the latter with specific cut-off points for older adults from/descendent from South-East Asia. Table 2 outlines the diagnostic recommendations for the various international working groups on Sarcopenia. The most commonly used diagnostic tool is that of the EWGSOP, which has good sensitivity and specificity (> 80%) for diagnosing sarcopenia, and is supported by moderate-quality evidence (30, 60). A revised version of the EWGSOP diagnosis tool has very recently been developed, and is also described in Table 2.

DXA imaging should be used to determine low levels of lean body mass (LBM) when diagnosing sarcopenia (Grade: conditional recommendation; low certainty of evidence)

Dual-energy X-ray absorptiometry (DXA) imaging can be used to identify low lean body mass (LBM), and its use has been approved as part of the sarcopenia ICD-10 diagnosis code. DXA use is also endorsed by the EWGSOP (25), FNIH (26), IWGS (5), and AWGS (3). A major challenge for the task force was to determine to what extent DXA scans could be used for all older aged adults across all settings, including those in LMICs where accessibility to resources was low. After much debate, it was decided that DXA imaging should be conditionally recommended as a method to determine low LBM

when diagnosing sarcopenia. Whilst there are many advantages to using DXA, older adults with sarcopenia who externally reviewed our ICFSR guidelines stated that they did not want expensive scans or testing to determine muscle loss (noting unnecessary costs and time), preferring instead to rely on their primary care provider's clinical judgement for a diagnosis of sarcopenia. Similarly, our external health economics reviewer stated that the added value of DXA for diagnosis may not justify additional costs.

The certainty of evidence for DXA imaging was ranked low by the task force due to: (i) the distinct lack of DXA studies in LMICs; (ii) the limitations of DXA imaging, for instance, it measures LBM rather than muscle mass per se, and can misclassify body composition in individuals with high levels of water and fibrous tissue; and (iii) there may be no additional benefit to incorporating DXA measurement of LBM regarding prediction of falls, fractures, or lowered physical performance and mobility (63, 64).

Magnetic Resonance Imaging (MRI) or Computed Tomography (CT) scanning can also be used to determine levels of LBM, and are currently deemed gold standards for body composition measurement, however, they are costly and have higher radiation exposure than DXA (65). If DXA, CT and MRI are not available, it is suggested that the health practitioner use his or her own clinical judgement to assess muscle mass. Indeed, most GP and nurse practitioner members of our external reviewing committee indicated that they would prefer to use their clinical judgement in making the diagnosis in primary care, rather than using DXA, MRI or CT scanning; some indicated that they would use calf circumference measurement to gauge muscle mass levels, and most would likely refer to a physiotherapist for further evaluation. Other methods to assess LBM are diagnostic ultrasound morphometry (66), radio labelled creatine (64, 67), and bioelectrical impedance analysis (BIA) (65, 68, 69). However, current evidence is insufficient to support these alternative means for sarcopenia diagnosis in older adults. Regarding BIA, although it is relatively easy to use and is endorsed by both the EWGSOP (25) and AWGS (3), it is well known to be less accurate than DXA (68, 69).

Gait speed and grip strength should be used to determine low levels of muscle strength and physical performance when diagnosing sarcopenia (Grade: strong recommendation; moderate certainty of evidence)

Gait speed and grip strength were strongly recommended by the task force as feasible and valid measurements of muscle function (strength and physical performance) in clinical practice, based on the evidence from the two background meta-analyses (4, 11), and endorsement by international working groups on sarcopenia (3, 25). Cut-off values should be tailored to the specific characteristics of the population (70).

Recommendation 3: Physical Activity (Resistance-Based Training)

In patients with sarcopenia, prescription of resistance-based training can be effective to improve muscle strength, skeletal muscle mass and physical function. (Grade: strong recommendation, moderate certainty of evidence)

Physical activity, with a focus on progressive resistance-based (strength) training, was endorsed by the task force as a first-line therapy to manage sarcopenia. The majority of the evidence behind this recommendation comes from the two background meta-analyses (4, 11), with support from all international workgroup statements regarding interventions for sarcopenia (3, 5, 11, 25, 26), as well as all task force members. Resistance-based training refers to any physical activity which produces skeletal muscle contraction/s by using external resistance such as dumbbells, free weights, elastic therapy bands and body weight itself. The health benefits of resistance-based training for older adults include muscle hypertrophy, strength gain, and improved physical performance (34, 71-75).

Most of the evidence for physical activity prescription comes from studies of non-sarcopenic older adults, or those with mild-moderate sarcopenia. Table 2 displays a summary of findings for resistance training intervention for older adults with sarcopenia. Our review found very low certaintly of evidence for the beneficial effects of resistance-based training in adults with sarcopenia. For instance, a close examination of the studies included in the background meta-analyses (4, 11) revealed only two small-scale RCTs (all n < 200) (76, 77); that is, if we exclude generic studies of older adults, those investigating sarcopenic obesity, and the studies of older adults with frailty. Whilst these two RCTs (76, 77) showed positive effects of resistance training on muscle strength, muscle mass, and physical performance, it was noted that they used BIA to measure muscle mass. Notwithstanding this, sarcopenia is a major component of the geriatric condition of frailty (54, 78-80), and if we look at resistance-based training in community-dwelling adults with frailty, there appears to be a positive, dose-response effect on muscle strength and muscle mass, at least in the single, small-scaled study included in our background meta-analyses (81). Because of its dose-response effect and large anecdotal effect observed by clinician members of our task force, the task force voted to raise the level of certainty of evidence of physical activity, specifically resistance-based training, to moderate.

No trials of physical activity in older adults, to our knowledge, included patient reported outcome measurements (PROMs) [such as the SAR-QOL (82)], to gauge the effectiveness of the program. Notwithstanding this, it was judged important by the task force clinicians to prescribe physical activity in line with patient goals and preferences, which in turn, may increase adherence to the program; older adults are known to have low adherence to physical activity programs (83). Physical activity prescription for older adults

Table 3

A summary of findings table showing the effectiveness of physical activity intervention for adults with sarcopenia

Certainty assessment							Mean Difference (95% CI)	Certainty	Outcome Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Grip Strength (kg) at 3 months									
3	randomised trials	serious	serious	not serious	serious	none	0.42 (-2.46 – 3.30)	Very Low	CRITICAL
Knee Extension Strength (N) at 3 months									
2	randomised trials	serious	serious	not serious	serious	none	0.26 (0.14 - 0.38)	Very Low	CRITICAL
Normal Gait Speed at 3 months									
3	randomised trials	serious	serious	not serious	not serious	none	0.11 (0.04 - 0.19) 0.04)	Very Low	CRITICAL
Appendicular skeletal muscle mass (kg) at 3 months									
3	randomised trials	serious	not serious	not serious	serious	none	-0.38 (0.01 – 0.74 0.10)	Very Low	IMPORTANT

CI: Confidence interval; OR: Odds ratio; † This Summary of Findings table was formulated from 'Forest plots for nutritional intervention' from the background systematic review of sarcopenia treatments by Yoshimura and colleagues (4)

with sarcopenia should also be functional-outcome based, and incorporate best-practice principles regarding intensity, volume and progression (33).

Clinicians may also consider patient referral to a Physiotherapist (PT) or Exercise Physiologist (EP) for an individually tailored resistance-training program. We note that most patients consulted during our external review process reported that they would agree to a PT/EP-based physical activity program if they were having functional difficulties, although they were less likely to agree to such a program as a preventative measure. Barriers cited to participation were cost, transportation and lack of support. Additionally, our external health economist review identified that an individually-tailored physical activity program may not be as cost-effective as group physical activity classes, although there is currently no cost-benefit research to support this claim.

Worth mentioning is that most benefits of resistance training apply to all older adults (84), regardless of whether or not they have sarcopenia. Thus, in LMICs where resources are scarce, physical activity participation is the most widely available option for sarcopenia management. For that reason, local, state and national health departments should be encouraged to prioritize physical activity for all older adults. We note that reducing sedentary time in older adults with sarcopenia may also be advantageous (85, 86).

Recommendation 4: Protein Supplementation

We recommend that clinicians consider protein supplementation/a protein-rich diet for older adults with sarcopenia (Grade: conditional recommendation; low certainty of evidence)

All experts unanimously agreed on the importance of adequate protein intake for older adults with sarcopenia, noting that non-pharmacological interventions for the management of sarcopenia should be included as first-line therapy. Our evidence-based summary of findings for protein supplementation [based on a background systematic review (19)] is shown in Table 3. The certainty of the evidence was ranked as low by the task force for five main reasons. First, most of the evidence came from only a handful of small scale RCTs of older adults with sarcopenia (all n < 200) (4, 11). Second, there were high selection and attrition biases in the included RCTs; the major concerns were non-random allocation to intervention/control groups, and a lack of allocation concealment (4, 19). Third, none of the relevant nutritional trials used established diagnostic criteria to identify sarcopenia, choosing instead to define sarcopenia using loss of skeletal muscle mass only (4, 19). Fourth, no trials investigated patient-centered outcomes or cost effectiveness. Fifth, we identified ambiguity around the absolute risk reduction; that is, it was unclear based on evidence whether protein supplementation actually improved muscle mass (appendicular skeletal muscle volume, appendicular skeletal muscle index, LBM), strength (grip strength, knee extension strength) or gait speed.

A subsequent endeavor for the task force was to determine the transferability of these RCT results to all individuals with sarcopenia, particularly those with co-morbidities. However, the current evidence-base was insufficient to complete this task. Of additional note is that the task force did consider the benefits of supplementation with leucine and its metabolic derivative hydroxy methylbutyrate (HMB). However, the evidence-base is very limited for older adults with sarcopenia (87-89) and any estimate of effect is uncertain.

Clinicians may also consider discussing with patients the importance of adequate calorie and protein intake (Grade: conditional recommendation; very low certainty of evidence).

It was conditionally recommended by the task force that clinicians may also consider an evaluation of protein

Table 4
A summary of findings table showing the effectiveness of nutritional intervention for adults with sarcopenia

Certainty assessment							Mean Difference (95% CI)	Certainty	Outcome Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Grip Strength (kg)									
3	randomised trials	serious	not serious	not serious	serious	none	0.36 (-1.40 - 0.67)	Very Low	CRITICAL
Knee Extension Strength (Nm) at 3 months									
2	randomised trials	serious	not serious	not serious	serious	none	-1.61 (-5.43 - 2.20)	Very Low	CRITICAL
Knee Extension Strength (Nm/kg) at 3 months									
1	randomised trials	serious	n/a	not serious	serious	none	0.11 (0.03 - 0.20)	Very Low	CRITICAL
Knee Extension Strength (N) at 3 months									
1	randomised trials	serious	n/a	not serious	serious	none	2.07 (-18.8 - 22.9)	Very Low	CRITICAL
Normal Gait Speed									
3	randomised trials	serious	not serious	not serious	serious	none	- 0.01 (-0.06 - 0.04)	Very Low	CRITICAL
Appendicular skeletal muscle mass (kg) at 3 months									
3	randomised trials	serious	serious	not serious	serious	none	-0.34 (-0.78 - 0.10)	Very Low	IMPORTANT
Appendicular skeletal muscle index (ASMI) (kg/m2) at 4 months									
1	randomised trials	serious	n/a	not serious	serious	none	0.15 (-0.66 - 0.96)	Very Low	IMPORTANT
Lean Body Mass (LBM) (kg/m2)									
1	randomised trials	serious	n/a	not serious	serious	none	3.30 (-0.56 - 7.16)	Very Low	IMPORTANT

CI: Confidence interval; OR: Odds ratio; † This Summary of Findings table was formulated from 'Forest plots for nutritional intervention' from the background systematic review of sarcopenia treatments by Yoshimura and colleagues (4)

and protein-energy intake, as well as discussing with their patients the importance of adequate calorie and protein intake. Although there is a distinct lack of research evidence behind this recommendation, our external nutritionist and patient consulting group both emphasised the importance of education to improve protein intake in the older adult with sarcopenia. The nutritionist review also highlighted that in addition to protein intake, full dietary patterns should be addressed. That is, healthy fat/Omega-3 and hydration should be addressed, as well as the quality of calories ingested (processed vs non-processed foods) and the impact of medications on nutritional intake.

Nutritional (protein) intervention should be combined with a physical activity intervention (Grade: conditional, low certainty of evidence)

The task force conditionally recommends that nutritional supplementation should be combined with a physical activity intervention for older adults with sarcopenia. To form this recommendation, the task force drew upon relevant systematic reviews (4, 11, 19) and consensus statements from international organisations on sarcopenia (25, 90). There is evidence that a combined nutritional-physical activity intervention can improve gait speed and knee extension strength when compared to individual physical activity or nutritional intervention, respectively (4, 19, 76, 77, 91, 92). However, based on the most relevant background systematic review (4), the task force judged that there was a very low level of certainty regarding the effectiveness of combining protein supplementation with a physical activity intervention. The certainty was ranked as very low due to the imprecision of results, the low number of trials, the small size of the included studies, and the high likelihood of selection, detection and attrition biases (4).

Recommendation 5: Vitamin D

Insufficient evidence exists to determine whether a Vitamin D supplementation regime by itself is effective in older adults with sarcopenia (Grade: no recommendation; very low certainty of evidence)

The task force agreed that there is insufficient evidence to recommend a Vitamin D supplementation regime for older adults with sarcopenia. Available evidence provides only a very low certainty that a specific Vitamin D supplementation regime is effective for older adults with sarcopenia. There was considerable deliberation amongst the task force before this grading was allocated, given that Vitamin D deficiency is commonly associated with sarcopenia, low grip strength, and atrophy of skeletal muscle mass (93, 94), and that a recent, large-scale (n = 380) trial found that Vitamin-D combined with a leucine oral supplement improved muscle mass and lower extremity function in individuals with sarcopenia, even without physical activity (87). However, this health-benefit could not to be attributed to Vitamin D alone. Overall, with the ambiguity of results and low sample size of the majority of clinical trials on sarcopenia, there is a significant probability that health-benefits

may not outweigh potential undesirable outcomes. If a patient with sarcopenia presents with low Vitamin D (< 20 ng/mL measured by a 25-hydroxyvitamin D test), it is suggested that the clinician use his or her judgement regarding the prescription of a Vitamin D supplement, keeping in mind other conditions which may benefit from supplementation. It is also important to recognize that normal values of 25(OH) Vitamin D vary according to ethnicity (95-97).

Recommendation 6: Anabolic Hormones

The current evidence is insufficient to recommend anabolic hormones for the management of sarcopenia (Grade: no recommendation; very low certainty of evidence)

The evidence to date offers only a very low level of certainty, and does not provide reassurance that a testosterone-supplementation regime is effective in older adults with sarcopenia. Although low testosterone levels are associated with higher levels of sarcopenia (96, 98), the background systematic review used for our guidelines paper (4) only identified one quality RCT which investigated a selective androgen receptor modulator (SARM) supplementation in older adults with sarcopenia (4). This RCT by Papanicolaou et al. (99) was relatively small (n = 172), and found that twice-daily supplementation with 50 mg of MK-0773 (a SARM), in sarcopenic older female participants improved lean body mass (LBM) without having any improvement on strength or function over six months (99).

Seeking further evidence on the effect of anabolic hormones, the task force also considered the results from RCTs of older adults without sarcopenia. For instance, meta-analysis in persons with low testosterone have shown an improvement in lean tissue mass and strength with testosterone treatment (100). In addition, Snyder et al (101) showed a small, but statistically significant, increase in walking distance with testosterone in older men with limited mobility. SARMs improved lean body mass (LBM) and stair climb in healthy older people (102, 103). Similar but less impressive results were seen in persons with cancer cachexia (104). There was also insufficient evidence regarding the cost-effectiveness, and patient preferences regarding anabolic hormone therapy.

Thus, overall, the task force judged that there was insufficient evidence to recommend anabolic hormone supplementation for older adults with sarcopenia.

Recommendation 7: Pharmacologic interventions

Pharmacologic interventions are not recommended as first-line therapy for the management of sarcopenia (Grade: no recommendation, very low certainty of evidence)

Other Drugs Under Development

Growth hormone increased muscle mass associated with nitrogen retention, but did not increase strength (105-107). The ghrelin agonist (Anamorelin) increased growth hormone and increased muscle mass but not strength (108). A number of studies have shown that antibodies to myostatin or activin II receptors result in a marked increase in muscle mass and a small increase in strength and 6 minute walking distance (109-112). There is some evidence to suggest that perindopril (Angiotension Converting Enzyme Inhibitor) and espindolol (a non-specific β-1 and β-2 adrenergic receptor antagonist) may improve muscle function (113). Overall there is inadequate data in persons with sarcopenia to recommend the use of any of these drugs at present for the management of sarcopenia.

There was a strong consensus by the task force that pharmacologic interventions should not be first therapy for the management of sarcopenia. The safety and efficiency of new medications is currently unknown, and there is an absence of phase III and IV clinical trials for the treatment of sarcopenia. International working groups on sarcopenia also highlight the lack of successful pharmacological interventions for sarcopenia (90). Given this lack of clear evidence on pharmacological interventions, clinicians are advised to base second-line therapy for sarcopenia on addressing their patient's health issues, co-morbidities and any associated medications.

Recommendation 8: Research

The task force identified a number of methodological factors integral to moving research into sarcopenia forwards (see Box 1). A major concern is the lack of robust, large-scale clinical trials with long-term follow-up for older adults with sarcopenia. Indeed, the recent LIFE (114, 115) and SPRINTT (116) projects have both emphasised the importance of using large-scale clinical trials to inform treatment options for the management of sarcopenia. Areas for future research are also listed in Box 1.

Combined Treatment Plans

Combined treatment plans for the management of sarcopenia are recommended by the task force - a recommendation which was endorsed by both the allied health and GP members of our external review group. Furthermore, a specific suggestion for combined sarcopenia management was provided by our GP external review group, of which the task force supported. That is, when an older adult with sarcopenia presents to a healthcare provider, they should receive:

- Referral to a Physiotherapist/Exercise Physiologist for further evaluation and community-based group exercise classes which focus on resistance-based training;
- Protein supplementation; and
- Education on the importance of physical activity to improve strength and function, and adequate calorie and protein intake.

Patients in our external review all agreed that improved education and encouragement by health care professionals

Box 1
Methodology considerations, and areas for future research

Methodology Considerations for Future Research Studies

1. Established diagnostic criteria for sarcopenia should be used when conducting clinical trials.
2. Clinical outcomes relevant to healthcare policy makers should be incorporated. Such outcomes include falls, injurious fractures, admissions to aged care facilities and mortality. Using these outcomes may increase the likelihood of funding for clinical trials.
3. Outcomes important for the older adult with sarcopenia should be included. For instance, PROMs (such as SAR-QOL, or achieving personal goals such as walking to the letter-box, or cooking dinner independently).
4. The intervention needs to be feasible, valid and acceptable to relevant stakeholders (including local, state and national healthcare policy makers, clinicians and patients).
5. Mixed-methods studies combining quantitative and qualitative research are needed. Qualitative research involves patient interview and focus groups, and can unlock issues of adherence and acceptability of interventions, including the importance of social environment.
6. More efforts should be made to improve the transparency of reporting in clinical trials.
7. Clinical trials need to be designed so that randomisation errors and selection biases are eliminated.
8. Nutritional trials need to ensure that both the control and intervention group are receiving adequate and equal calorie intakes. Trials also need to account for the amount of protein consumed as part of the diets of participants. If diets are already adequate, it may dampen the effect of any supplements.

Areas for Future Research

1. There needs to be more clarity around which biomarkers should be used as outcome measurements.
2. The ultimate target population are older adults with sarcopenia and those with co-morbidities. Thus, we need to include these populations in clinical trials.
3. There needs to be more theoretical underpinning of where and when treatment would come in.
4. The combination of pharmaceutical interventions combined with nutritional supplementation needs to be investigated.
5. Cost-effectiveness evaluations in clinical trials are needed to determine the extent to which the intervention impacts on decreasing health inequalities
6. Robust, large-scale clinical trials involving participants from different countries are needed. It is not easy to show large changes in clinical trials of sarcopenia, and large-scale studies are urgently needed.
7. Nutritional research needs to expand outside of protein and Vitamin D research. For instance, nutrients with anti-inflammatory properties (Omega-3, phytochemicals, and some vitamins and minerals) deserve research attention, as do specific food groups (including fruit and vegetables), and dietary patterns (such as the Mediterranean diet). Studies on nitrogen balance (related to energy and protein intake) should also be considered.
8. We need studies on the differences between the functional trajectories of primary and secondary sarcopenia. Primary sarcopenia may develop slowly, so long-term intervention studies are likely needed. Secondary sarcopenia (which develops from another co-morbidity) may develop rapidly, so trials with both short/longer-term data collection periods are warranted.
9. Trials in specific settings and populations are needed. For example: primary care, cardiology, oncology, rheumatology, endocrinology, orthopaedics, and long-term care. Ideally, we need to separate out clinical trials for hospital, post-hospital and the community.
10. The impact of averting sedentariness on sarcopenia development and progression needs researching.
11. Research studies on what outcomes are considered relevant by patients with sarcopenia are needed.
12. We need to determine whether pharmacological interventions to avert chronic low-grade inflammation impact on sarcopenia outcomes

on cause and reversal of condition might provide motivation regarding participation in physical activity and/or improving dietary patterns.

The task force also highlights that management of sarcopenia requires an inter-professional healthcare team approach to develop an individualised plan for treatment, with this suggestion coming from allied health members of our external review group. An individualised plan is a good opportunity for healthcare providers to promote person-centred care and shared decision making.

Patient-Specific Information

Shown in Appendix 1 is patient-specific information on sarcopenia, based on specific feedback from our external consultant patient group. Important for patients was the knowledge that treatment for sarcopenia did not involve taking prescription medications, but rather, involved resistance-based

training and ensuring adequate protein intake. In addition, because sarcopenia has a diagnosis code, patients highlighted that it was important to know that physicians are permitted to bill for its diagnosis and treatment.

Discussion

These guidelines have been designed from a person-centred perspective to support health practitioners manage older adults with sarcopenia in their daily practice. To develop the guidelines, the ICSFR task force systematically examined the evidence-base for sarcopenia, covering screening, diagnosis and management of the condition. There were sometimes large gaps in the evidence-base, and where this occurred, the task force filled these gaps with consensus-based best practice recommendations.

The guidelines are not designed for use in isolation. Rather, we advocate for healthcare practitioners to use their clinical judgement when guiding patient management, keeping into account patient co-morbidities, medications, and goals, preferences and values of care. Healthcare practitioners should also discuss the harms and benefits of appropriate management options for sarcopenia with the patient and their care-giver. Notably, the guidelines were developed in consultation with patients themselves, and it is suggested that future consensus statements and clinical guidelines for sarcopenia continue to involve patients in decisions about best practice.

Limitations

The guidelines may not be applicable to all patients or contexts. For instance, an older adult with secondary sarcopenia resulting from a chronic condition (such as chronic renal failure), may require different management strategies from an older adult with primary sarcopenia or pre-sarcopenia. In addition, these guidelines focused on sarcopenia management for community-dwelling older adults. It is likely that older adults in different settings (for instance, in aged care facilities) may require different screening and management options.

The focus of these guidelines is on an individual patient, rather than a public health perspective. Recommendations specific for public health may differ when using the same evidence-base, namely due to the lack of cost-effectiveness studies of sarcopenia screening or intervention. At the public health level, healthcare policy makers need to carefully consider the availability of resources, cost-effectiveness, and the additional workforce needed to implement screening, diagnosis and management strategies for sarcopenia in older adults.

Guideline update

Updates of these guidelines will need to keep pace with advances in medical treatments, technologies, and any future modifications in diagnostic criteria for sarcopenia. For that reason, the guideline development group will regularly monitor the current validity of each recommendation. It is expected that the guidelines may need updating by the task force, either fully or partially, between 2021 – 2023. Guidelines specific to specialties (endocrinology; surgery; cardiology; respiratory; pharmacy; oncology; internal medicine, amongst others) and distinctive settings (acute care; rehabilitation settings; aged care facilities; primary and community care settings) are advocated for.

Conclusion

We present the ICSFR task force clinical practice guidelines for sarcopenia. There exists considerable room for improvement of the methodological quality of clinical trials for sarcopenia. The quality of supporting evidence for the management of sarcopenia was low. Future international collaboration and large-scale clinical trials focusing specifically on older people with sarcopenia are needed. Clinical trials also need to focus on outcomes relevant to stakeholders, clinicians and patients. Such outcomes include cost-effectiveness, and the rate of falls, fractures, and admission to residential aged care facilities.

Industry Relationship: In the interests of transparency, all members of the guideline development team, the steering committee and the external review committee were required to disclose current COIs. Industry participants were present during the ICFSR task force meeting, although given their conflict of interest (COI), they did not write or vote on the recommendations contained within this manuscript. Similarly, task force members with COIs were not permitted to write or vote on sections in which they had a current COI.

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