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Perspective

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Development of treatments for sarcopenia: new challenges, opportunities and perspectives

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Abstract

Sarcopenia is characterized by loss of muscle mass, strength and function, and is associated with decline in physical function, falls, fractures and premature mortality. Despite increasing recognition of its clinical and societal burden, progress in translating advances in sarcopenia research into approved pharmacological therapies has remained limited. Potential barriers include heterogeneity in trial design regarding eligibility criteria, follow-up duration and outcomes, as well as limited regulatory harmonization. Given advances in sarcopenia research, the continued absence of approved treatments and the need to integrate perspectives that have emerged since the 2020 ESCEO recommendations for the conduct of sarcopenia clinical trials, this Perspective provides up-to-date expert perspectives on the development of treatments for sarcopenia, informed by discussions held by a working group convened by the World Health Organization Collaborating Centre for Epidemiology of Musculoskeletal Conditions and Ageing. Developments in the definition of sarcopenia, the regulatory landscape and therapeutic approaches are presented, together with considerations for the design of pharmacological trials, including target populations, the selection and assessment of trial outcomes (including digital health measures and patient-reported outcome measures), trial duration, use of biomarkers and patient expectations of treatments.

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Introduction

Sarcopenia is defined as a progressive and generalized skeletal muscle disorder characterized by loss of muscle mass and muscle strength and function and is associated with increased risk of adverse outcomes including decline in physical function, physical disability, falls, fractures and premature mortality[1–4]. Patients often describe the condition in terms of its consequences, including falls, fatigue, difficulty performing everyday tasks and increasing dependence on others. Sarcopenia markedly affects functional ability, reduces independence and quality of life, and contributes to increased healthcare costs through long-term care needs[5]. Despite its high prevalence (with estimates of 9.9% to 40.4% among community-dwelling older adults, depending on the definition used[6]) and substantial clinical consequences, sarcopenia remains under-recognized in both clinical practice and regulatory frameworks[7]. In fact, it was not listed as a disease in the World Health Organization (WHO) International Classification of Diseases, Tenth Revision (ICD-10)[8], although in 2016 was assigned the specific code M62.84 in the American-led ICD-10 Clinical Modification (ICD-10-CM)[9,10]. In the WHO's Eleventh Revision (ICD-11)[11], which came into effect in January 2022, sarcopenia still does not have a dedicated diagnostic code but can be classified under FB32.Y ('other specified disorders of muscles')[12]. Under-recognition of sarcopenia extends beyond healthcare professionals and includes low awareness among patients themselves[7]. Improving public awareness, education and community-based identification strategies could therefore be important alongside efforts to enhance clinical recognition. Despite increasing recognition of sarcopenia as a major determinant of disability, translation into approved pharmacological therapies has remained limited. Potential barriers include heterogeneity in trial design regarding eligibility criteria, duration of follow-up, operational definitions and endpoints, uncertainty regarding clinically meaningful outcomes, and limited regulatory harmonization across regions such as differences between regulatory agencies in their requirements for the approval of new therapies[13,14].

In 2016, an expert panel convened by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) published consensus recommendations for the conduct of clinical trials for drugs to prevent and to treat sarcopenia[15]. Between 2016 and 2020, understanding of risk factors for sarcopenia progressed, along with new definitions of sarcopenia, while the number of pharmacological agents under investigation increased. In response to these conceptual and methodological advances, ESCEO convened a second multidisciplinary working group in 2020, which provided updated recommendations for phase II and III trials, including minimum duration, inclusion criteria and outcome selection, with the aim of improving methodological rigour and comparability between trials[13].

Given subsequent advances in sarcopenia research, the continued absence of effective pharmacological treatments, and the need to better integrate perspectives developed since the 2020 ESCEO recommendations, The World Health Organization (WHO) Collaborating Centre for Epidemiology of Musculoskeletal Conditions and Ageing evaluated contemporary challenges and opportunities in sarcopenia therapeutic development. A multidisciplinary expert working group was convened in February 2026. The working group comprised more than 40 participants, including clinicians, researchers, representatives of regulatory agencies, and a patient advocate, who brought expertise from a range of disciplines relevant to ageing and musculoskeletal health, including geriatric medicine, rheumatology, endocrinology, osteoporosis and sarcopenia, clinical pharmacology, epidemiology, health economics and outcomes research, and regulatory science.

This Perspective aims to present these current perspectives and show how they compare with the 2020 ESCEO recommendations. Developments in the definition of sarcopenia, the regulatory landscape and therapeutic approaches are discussed, together with considerations for the design of pharmacological trials, including target populations, the selection and assessment of trial outcomes (including digital health measures and patient-reported outcome measures (PROMs)), trial duration, the use of biomarkers and patients' expectations. This article provides expert perspectives rather than a formal consensus statement and should not be interpreted as providing updated recommendations. An exhaustive review of previous sarcopenia trials or biomarkers is beyond the scope of this article.

The changing landscape of sarcopenia drug development

Evolution of the definition of sarcopenia

In 2019 and 2020, various definitions of sarcopenia were proposed by different expert working groups: the revised European Working Group on Sarcopenia in Older People (EWGSOP2)[2], the 2019 Asian Working Group for Sarcopenia (AWGS)[16] and the Sarcopenia Definition and Outcomes Consortium (SDOC)[17,18]. EWGSOP2 defined confirmed sarcopenia as the presence of low muscle strength and low muscle quantity or quality, whereas AWGS 2019 defined sarcopenia as low muscle mass, with low muscle strength or poor physical performance[19]. By contrast, SDOC recommended that sarcopenia should be defined as the combination of low grip strength and low gait speed as these characteristics were strongly related to incident adverse health outcomes, in contrast to lean mass derived from dual-energy X-ray absorptiometry (DXA)[17,20]. Despite these efforts, no internationally agreed operational definition for sarcopenia has emerged. This lack of harmonization has important implications for therapeutic development because differences in measures used and diagnostic thresholds will probably influence participant eligibility, event rates, responsiveness to intervention, and cross-trial comparability. To address the lack of harmonization regarding definitional approaches to sarcopenia, the Global Leadership Initiative in Sarcopenia (GLIS), which includes members of the other sarcopenia working groups outlined previously, conducted a two-phase international Delphi process in 2022–2023 to establish a global conceptual definition of sarcopenia and is in the process of developing a global operational definition. In the conceptual framework proposed by GLIS in 2024, muscle mass, muscle strength and muscle-specific strength are core components of sarcopenia, whereas physical performance is conceptualized primarily as an outcome of the condition[4] (Fig. 1). Similarly, an updated 2025 consensus of AWGS simplified their diagnostic algorithm to require only concurrent low muscle mass and muscle strength, with physical performance included as an outcome measure rather than a diagnostic criterion[21]. This conceptual framework has important implications for clinical trial design, particularly for distinguishing inclusion criteria from outcome measures. This framing of sarcopenia with a focus on muscle health and with physical performance as an outcome could create challenges for pharmacological development, which generally requires a defined disease and target population. Early stages of muscle decline might be best addressed through exercise, nutrition and lifestyle interventions, whereas drug development might be more appropriately focused on individuals with established sarcopenia or at high risk of adverse outcomes. In addition,

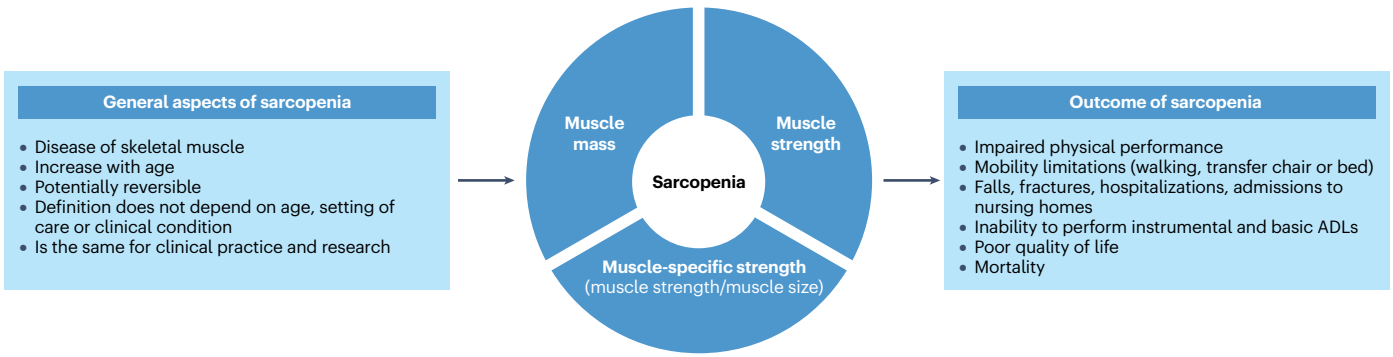

Fig. 1 | Graphical representation of the conceptual definition of sarcopenia according to the GLIS. The Global Leadership Initiative in Sarcopenia (GLIS) regards muscle mass, muscle strength and muscle-specific strength (defined as muscle strength divided by muscle size) as components of sarcopenia, whereas impaired physical performance is regarded as an outcome (rather than a component) of sarcopenia. ADLs, activities of daily living. Figure reproduced with permission from ref. 4, Oxford University Press.

by using a definition of sarcopenia that does not require impaired physical performance, contemporary frameworks could identify individuals with early-stage sarcopenia, before functional limitations are evident. Doing so could broaden the population eligible for treatment but also make it more difficult to demonstrate improvement in function-based endpoints, as trials might be evaluating the prevention of functional decline rather than recovery from existing functional impairment. The components used to define sarcopenia according to various sarcopenia working groups are presented in Table 1.

Evolution of the regulatory landscape

The current regulatory landscape for sarcopenia treatment is characterized by a lack of both globally accepted regulatory guidelines and approved pharmacological therapies[22]. A 2024 workshop hosted by the Society on Sarcopenia, Cachexia and Wasting Disorders highlighted advances in sarcopenia research, including emerging assessment methods, validated physical performance measures for clinical trials, and potential new therapies. Ongoing challenges were also identified, including inconsistencies in diagnostic criteria, difficulties establishing clinically meaningful trial endpoints, and regulatory barriers to treatment approval[23]. Discussions emphasized that regulatory approval will require clinically meaningful improvements in patient-reported outcomes, physical function and/or morbidity and mortality[23]. The European Medicines Agency recognizes that older adults, particularly those with frailty, should be adequately represented in clinical trials because their benefit–risk profiles can differ from those of younger populations, and recommends routine baseline assessment of physical frailty in adults ≥65 years of age using validated instruments to improve understanding of treatment efficacy and safety in this population[24]. The SPRINTT (Sarcopenia and Physical Frailty in Older People: Multi-component Treatment Strategies) randomized controlled trial, which investigated whether an intervention based on physical activity with technological support and nutritional counselling can prevent mobility disability in older adults with sarcopenia and physical frailty, demonstrates the effective involvement of regulators in the design of interventional clinical trials[25]. For example, the SPRINTT investigators engaged in regulatory dialogues with the European Medicines Agency to reach a consensus on the definition of the target population and study methodology, and had quarterly teleconferences to discuss progress of the trial, safety aspects and emerging challenges[25].

Evolution of therapeutic approaches

Despite the expanding landscape of pharmacological therapies under investigation for sarcopenia[26], therapeutic development in sarcopenia has been complicated by the multifactorial biology of muscle ageing and the imperfect relationship between gains in muscle mass and improvements in clinically meaningful function. For example, several interventions have demonstrated anabolic effects without consistent benefits for strength, mobility or quality of life. Previous therapeutic strategies for sarcopenia included anabolic agents (growth hormone[27,28], testosterone[29] and selective androgen receptor modulators[30]), but evidence that they consistently improve muscle strength and/or function among individuals with sarcopenia is limited[31].

The angiotensin-converting enzyme inhibitor perindopril improved 6-min walk distance and health-related quality of life (HRQoL) (as measured by the EuroQol-5D (EQ-5D)[32] questionnaire) in a trial of older adults with functional impairment[33]. Moreover, BIO101 (20-hydroxyecdysone), an investigational drug thought to activate the Mas receptor, thereby potentially restoring balance in the renin–angiotensin system, improved gait speed in a phase II trial involving participants with sarcopenia ≥65 years old[34]. However, no effect of BIO101 on lean mass was observed, and it is now unclear whether the effect on these endpoints was mediated by direct effects on the muscle.

In mouse studies, approaches targeting cellular senescence have shown promise for the treatment of skeletal muscle deficits: metformin treatment increased muscle strength in a mouse model of Duchenne muscular dystrophy[35], and RJx-01, a combination of metformin and galantamine, attenuated loss of lean mass and improved muscle strength and physical performance in *Opa1*$^{-/-}$ mice and improved muscle strength and exercise endurance in naturally aged mice[36].

Other avenues include microbiome-derived therapies, such as urolithin A, an activator of mitophagy, which increased muscle strength and physical performance in a trial of middle-aged adults with low endurance[37].

The close biological interrelationship between muscle and bone suggests potential utility for therapies targeting both tissues simultaneously[38]. However, in a 2025 trial involving individuals with osteoporosis, treatment with denosumab did not significantly improve DXA-derived appendicular lean mass (ALM) index (calculated as ALM divided by height squared), lower extremity lean mass, grip strength,

Table 1 | Components used to define sarcopenia according to various sarcopenia working groups

Working group	Components used to define sarcopenia	Ref.
Revised European Working Group on Sarcopenia in Older People (EWGSOP2) (2019)	Probable sarcopenia: low muscle strength Confirmed sarcopenia: low muscle strength plus low muscle quantity or quality Severe sarcopenia: low muscle strength plus low muscle quantity or quality plus poor physical performance	2
2019 Asian Working Group for Sarcopenia (AWGS)	Low muscle mass plus low muscle strength and/or low physical performance	16
Sarcopenia Definition and Outcomes Consortium (SDOC) (2020)	Low grip strength plus low gait speed	17
Global Leadership Initiative in Sarcopenia (GLIS) (2024)	Muscle mass, muscle strength and muscle-specific strength are core components of a conceptual definition of sarcopenia[a,b]	4
2025 Asian Working Group for Sarcopenia (AWGS)	Low muscle mass plus low muscle strength[a]	21

[a]Physical performance is regarded as an outcome of sarcopenia. [b]Work to finalize an operational definition of sarcopenia is ongoing.

chair stand test performance, gait speed or short physical performance battery (SPPB) score[39].

Bimagrumab, an investigational monoclonal antibody that promotes muscle growth and fat loss by inhibiting activin type II receptors, was shown to accelerate the recovery of thigh muscle volume and reversal of accumulated intermuscular adipose tissue following 2 weeks in a joint-immobilizing cast[40]. In a proof-of-concept phase II study in community-dwelling older adults with mobility limitations and low ALM index, bimagrumab significantly increased thigh muscle volume, ALM and total body lean mass without having a significant effect on grip strength or gait speed at week 24, although bimagrumab improved gait speed and 6-min walk distance among participants with poorer baseline performance on these respective measures[41]. The antibody LY2495655, which neutralizes myostatin (an inhibitor of muscle growth), significantly increased ALM in a phase II trial of older individuals with a history of falls within the past year; however, its effects on strength and physical performance were inconsistent[42].

Overall, these studies reflect the core challenge of inconsistent effects across muscle size, strength and function, requiring deeper levels of underlying mechanistic understanding. One potential explanation is that muscle strength is influenced not only by muscle mass, but also by neural factors, including motor-unit recruitment, firing rates and neuromuscular junction function[43]. Furthermore, muscle quality, including intramuscular and intermuscular fat infiltration (myosteatosis), can influence force production independently of muscle quantity, potentially explaining why increases in muscle mass do not always translate into improvements in strength or physical performance[44]. In clinical trials, improvements arising from exercise and nutritional interventions provided to both treatment and control groups might also reduce the additional benefits observed from therapeutic interventions.

The studies discussed in this section highlight both the promise and the challenges of developing effective pharmacological treatments for sarcopenia and the difficulty of translating gains in muscle mass into meaningful improvements in physical performance. Importantly, these discrepancies suggest that functional endpoints could be prioritized over surrogate measures when evaluating therapeutic efficacy in sarcopenia. Work to develop a core outcome set for pharmacological trials in sarcopenia is currently underway[45,46] and could help improve consensus in this area.

In the past 5 years, the rapid increase in the use of incretin-based weight loss medications, such as glucagon-like peptide-1 (GLP-1) receptor agonists[47], could have substantial implications for sarcopenia as the use of these drugs can cause reductions in lean mass[48,49]. The impact of GLP-1 receptor agonist-associated reductions in lean mass remains incompletely understood, particularly in older populations at high risk of sarcopenia. This evolving therapeutic landscape might increase the importance of interventions that preserve muscle quantity, quality and function during pharmacologically induced weight loss, particularly in older adults with obesity and multimorbidity. For example, in a 2026 systematic review that evaluated body composition changes associated with use of incretin therapies in adults with obesity, reductions in muscle-related indices exceeded prespecified benchmarks for two-thirds of incretin-based interventions and half of non-pharmacologic interventions that resulted in weight loss[50]. Despite the associated loss of lean soft tissue, the marked reduction in adipose tissue and improved metabolic health with use of incretin-based therapies could improve physical performance, thus potentially obscuring relationships across muscle mass, strength and performance that might be observed in classical sarcopenia. If such patients were included in trials, measures of body composition and muscle quantity or quality could be particularly important because the aim might be to preserve muscle before functional impairment occurs. Further work is needed to determine whether the development of pharmacological interventions for sarcopenia in patients receiving incretin-based therapies should be considered a separate regulatory context of use.

Target population for pharmacological trials in sarcopenia

Throughout the following sections, distinctions between phase II and phase III trials reflect their different objectives: dose-finding and proof-of-concept (phase II) versus confirmation of clinical efficacy and safety and real-world applicability (phase III). For clinical trials of investigational medicinal products in sarcopenia, the preferred design is a randomized, double-blind, placebo-controlled parallel-arm study. Table 2 summarizes the 2020 ESCEO recommendations and the new perspectives that emerged during the 2026 Working Group meeting regarding the development of interventions for the treatment of sarcopenia.

In our view, participants with the following types of sarcopenia should be eligible for phase II and III trials: primary (age-associated), secondary (attributable to factors such as comorbidities, malnutrition and inactivity), acute (rapid decline due to a health event) and chronic (gradual decline attributable to ageing or disease or lifestyle). However, this broad inclusion strategy introduces biological and clinical heterogeneity, which could dilute treatment effects and should be addressed through prespecified subgroup analyses. Stratification

by sex is important to account for sex differences in lean mass, strength and function, and acute and chronic sarcopenia could be considered separately as differences in their underlying causes, rates of progression and potential for recovery might influence responses to treatment. However, a consequence of stratification by sarcopenia type (acute versus chronic) or comorbidity (severity or type) is that the statistical power of the trial would be reduced. Patient priorities, which can vary according to disease stage, clinical context and individual circumstances, should also be considered in the selection of endpoints.

As the trial comparator should be a placebo along with the usual standard of care, which would include physical activity (depending on the population) and nutrition[13], both trial arms should receive physical activity and nutrition interventions, if appropriate.

For both phase II and III studies, the inclusion criteria in the 2020 ESCEO recommendations[13] required participants to have both low muscle strength and low physical performance according to the tests and thresholds proposed in EWGSOP2[2]. A score of ≤8 on the SPPB, comprising standing balance, gait speed and chair stand tests, as proposed as a sarcopenia cutoff point in EWGSOP2, could be added to the inclusion criteria for both phase II and III trials. These new perspectives on the inclusion and exclusion criteria for phase II and phase III trials, summarized in Table 2, were informed by the principle that the use of narrower inclusion criteria in phase II trials minimizes risk to participants and increases sensitivity for detecting a treatment effect, whereas in phase III trials, broader inclusion criteria will better reflect the diverse populations for which the treatment is intended. These perspectives also reflect that it is unrealistic to expect older participants

Table 2 | Summary of 2020 ESCEO recommendations and new perspectives regarding the development of interventions for the treatment of sarcopenia

Aspect of trial	Phase II trials		Phase III trials	
	2020 ESCEO recommendations[13]	New perspectives	2020 ESCEO recommendations	New perspectives
Inclusion criteria	Age ≥70 years Able to walk Low muscle strength and poor physical performance	Age ≥70 years Community-dwelling EWGSOP2 criteria with SPPB score ≤8	Age ≥70 years Able to walk Low muscle strength and poor physical performance	Age ≥65 years (no upper age limit; lower age limit should be justified) From any setting (community-dwelling or nursing home) EWGSOP2 criteria with SPPB score ≤8
Exclusion criteria	Severe malnutrition Acute immobility Specific advanced pathologies Physical limitation attributable to a specific disease other than sarcopenia	Severe or unstable disease (for a condition other than sarcopenia) Current treatment with anabolic or catabolic drugs	Severe malnutrition Acute immobility Specific advanced pathologies Physical limitation attributable to a specific disease other than sarcopenia	Severe or unstable disease (for a condition other than sarcopenia) Current treatment with anabolic or catabolic drugs
Primary outcome(s)	Primary and/or secondary outcomes could include the following, depending on the mechanism of action of the investigational drug: Improvement of physical performance (SPPB, gait speed, 400-m walk, TUG test, chair stand test) Improvement of muscle strength (handgrip, knee extensor) Increase of muscle mass (CT, MRI, DXA, urinary D_3-creatine dilution method) Improvement of muscle quality (CT, MRI, MRS, muscle biopsy) Muscle metabolism or muscle–bone interaction biomarker	No new perspectives compared with the 2020 ESCEO recommendations	Incidence of inability to perform 400-m walk test plus PROM	Co-primary endpoints including a physical performance measure along with a disease-specific PROM (SarQoL) No core outcome set currently proposed, but development is underway[a] Flexibility allowed for choice of outcomes, but decision requires justification by applicant
Secondary outcome(s)		Can include muscle mass ascertained using the D_3-creatine dilution method as a potential secondary outcome	Muscle strength (Jamar dynamometer) Muscle mass (DXA)	Include the following as potential outcomes: Muscle strength Muscle mass (including D_3-creatine dilution-derived) Muscle function Muscle morphology Generic health-related quality of life/ functional limitations PROM
Duration of treatment window and/or follow-up	6 months of treatment and follow-up	Typical duration 3–6 months, but depends on the treatment mechanism(s) of action and trial outcomes	12 months of treatment and follow-up	Typical duration ≥12 months, but depends on the treatment mechanism(s) of action and trial outcomes
Timepoint assessment	Every 3 months	No specific timepoint specified as dependent on the treatment mechanism(s) of action	Every 3 months; minimum of at least every 6 months	No specific timepoint specified as dependent on the treatment mechanism(s) of action

The new perspectives presented should not be interpreted as formal guidelines or concrete recommendations. CT, computed tomography; DXA, dual-energy X-ray absorptiometry; ESCEO, European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases; EWGSOP2, 2019 Revised European Working Group on Sarcopenia in Older People; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; PROM, patient-reported outcome measure; SarQoL, sarcopenia quality of life questionnaire; SPPB, short physical performance battery; TUG, timed up-and-go. [a]Research to establish a core outcome set for sarcopenia intervention studies is underway[45,46].

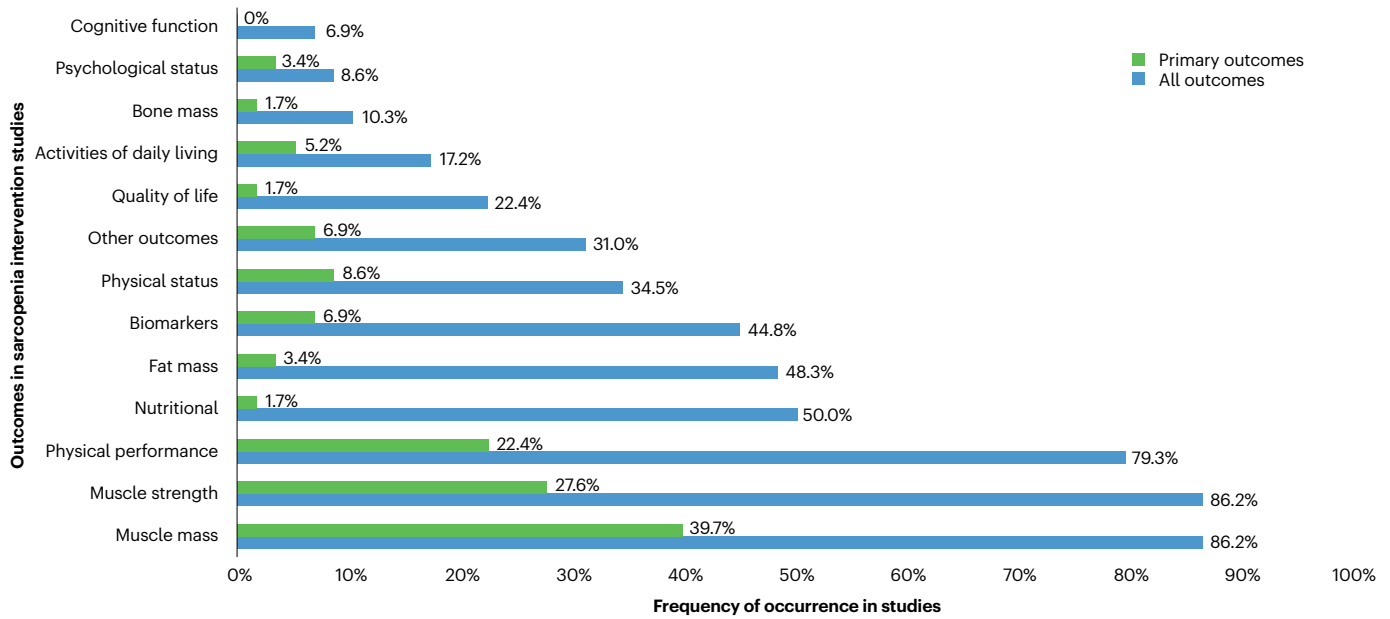

Fig. 2 | Frequency of outcomes reported in sarcopenia intervention studies. According to a 2024 scoping review[45] of sarcopenia intervention studies, the outcomes most frequently reported in randomized controlled trials (RCTs) are muscle mass (present in 86.2% of studies), muscle strength (86.2%) and physical performance (79.3%). The review included 58 RCTs of patients with sarcopenia diagnosed according to a consensus definition. Figure reproduced from ref. 45, Springer Nature.

with sarcopenia to not have other comorbidities, but also that those with severe or rapidly progressive comorbid conditions should be excluded from sarcopenia trials.

It is important to note that measures of strength and physical performance are influenced by factors beyond skeletal muscle, including neurological, cardiovascular and other age-related conditions. Therefore, identifying those with low muscle strength or physical performance might not adequately identify individuals in whom skeletal muscle pathology is the principal cause of impairment or who are therefore most likely to benefit from a muscle-targeted pharmacological intervention. Furthermore, the underlying cause and clinical context could also be considered when selecting pharmacological interventions and trial outcomes. For example, acute muscle loss associated with hospitalization or bed rest can differ from muscle loss occurring in the context of chronic inflammation. Consequently, the most appropriate therapeutic approach, treatment duration and clinical endpoints could differ between these settings.

Evaluating outcomes in pharmacological trials in sarcopenia

Choice of primary and secondary outcomes

The selection of trial outcomes remains one of the principal challenges in sarcopenia research, reflecting the multidimensional nature of the condition. A 2024 scoping review to identify the most frequently reported outcomes in 58 randomized controlled trials of sarcopenia treatments found that muscle mass (50 studies), muscle strength (50 studies) and physical performance (46 studies) were most often reported[45] (Fig. 2). This review also highlighted the extensive heterogeneity of reported outcomes within these broad categories, along with the urgent need to develop a core outcome set for sarcopenia intervention studies[45]. Although having a core outcome set has benefits, flexibility is also required in the selection of outcomes, depending on the patient population considered, the type of drug and the mechanism of action. For example, the suitability of outcomes might depend on whether the target population has acute or chronic sarcopenia and on the duration of the intervention. The conceptual definition of sarcopenia according to GLIS[4] suggests that outcomes such as muscle strength, physical performance and ability to perform activities of daily living might be the most appropriate to assess the results of treatment in clinical practice. Physical performance outcomes are also important in both phase II and III trials, given their close link with disability and patients' HRQoL. A 2019 position paper endorsed by ESCEO recommended the use of grip strength to measure muscle strength and the use of gait speed over 4 m or SPPB score to measure physical performance in daily practice[51]. Some sarcopenia trials have used multiple physical performance outcomes. For example, the BIO101 trial discussed previously used gait speed as the primary outcome and included the SPPB, stair-climb power and knee extension as secondary outcomes[34]. Minimal clinically important differences have been proposed for several outcomes relevant to sarcopenia, including measures of physical performance and quality of life[5]; however, their application to trials of novel therapeutics for sarcopenia requires caution, as available estimates have often been derived from different populations.

The inclusion of secondary outcomes ascertained using digital devices could also be suitable for sarcopenia trials, as illustrated later in this Perspective. Furthermore, a 2025 report from an International Conference on Frailty and Sarcopenia Research task force recognized the benefits of including PROMs as outcomes in sarcopenia trials, especially those pertaining to HRQoL, as they capture patients' subjective experiences[52]. Importantly, a hierarchy of outcomes should be defined a priori, distinguishing between mechanistic, intermediate,

and patient-relevant endpoints. These perspectives on the selection of primary and secondary outcomes are summarized in Table 2.

Use of digital health measures for the assessment of trial outcomes

At present, digital health-derived outcomes should be considered exploratory or supportive endpoints rather than primary endpoints in pivotal sarcopenia trials. As in all outcomes for clinical trials, those in sarcopenia trials ascertained using digital health should be clinically relevant, vary in response to treatments and be methodologically robust. Regulatory acceptance will depend on demonstration of analytical validity, clinical validity and sensitivity to change. Examples of digital devices and techniques for the assessment of outcomes include body-worn sensors that acquire data by accelerometers and gyroscopes and that provide digital mobility outcomes. Digital mobility outcomes have already been validated for several diseases (including hip fracture, Parkinson's disease, chronic obstructive pulmonary disease and multiple sclerosis) by the European Union-funded Mobilise-D project[53], but not yet for sarcopenia. Other digital health technologies used to assess outcomes include wearables such as smart insoles[54] and wireless earbuds[55]; artificial intelligence-powered motion tracking for analysis of gait[56] and sit-to-stand performance[57]; and AI-powered medical imaging to assess muscle mass and/or quality using magnetic resonance imaging[58], computed tomography[59], radiography[60] and ultrasonography[61]. Another example is a novel proprietary technology that uses abdominal computed tomography images to segment and quantify muscle and fat distribution as well as muscle quality[62]. However, previous studies have typically only examined correlations between these digitally derived outcomes and established sarcopenia parameters such as lean mass, strength and physical performance. For example, during the meeting, representatives of regulators expressed an interest in considering digital health measures as outcomes in sarcopenia trials, but advice regarding the validation of these outcomes should be sought from the appropriate regulatory authority.

Many digital products are focused on health interventions rather than outcome measurement. For example, trials of digital health interventions in the past few years have included the use of an exercise game that improved muscle mass, strength and functional performance among older adults at a rural long-term care facility[63], and a wearable device-assisted walking programme that increased muscle mass and handgrip strength among healthy adults 65 years of age and above[64]. Thus, digital health interventions are sometimes developed as digital therapeutics, that is, as software-driven medical interventions designed to treat a condition. Therefore, more collaboration between clinicians and the designers of these digital health interventions could be required to ensure that they accurately measure clinically relevant outcomes. When digital therapeutics are developed, whether standalone or alongside pharmaceutical interventions, early interaction with regulators is highly recommended in order to achieve alignment on the optimal regulatory pathway and evidence requirements. Although their use is currently limited, digital health outcome measures could become increasingly common in sarcopenia trials over the coming years.

Appropriate patient-reported outcome measures

PROMs are important outcomes in phase III sarcopenia trials as they capture patients' subjective experiences and perspectives, unlike objective measurements[52]. There are many types of PROMs, including function-focused (SF-36[65]), disease-specific HRQoL (SarQoL[66]) and generic HRQoL (EQ-5D[32]) PROMs. Previous sarcopenia intervention studies have utilized PROMs to assess a wide variety of domains including quality of life, depressive symptoms, loneliness and/or social isolation, daytime sleepiness, the effects of insomnia, and sleep quality and/or disturbance[67]. SarQoL, a self-administered questionnaire published in 2015, remains the only validated sarcopenia-specific PROM for HRQoL[68,69]. It includes seven HRQoL domains: physical and mental health; locomotion; body composition; functionality; activities of daily living; leisure activities; and fears[66]. Total and domain-specific scores can be calculated. It has been translated into 35 languages, with 19 validated in sarcopenic populations[70,71]. A 2025 systematic review and meta-analysis of the psychometric properties of SarQoL demonstrated high performance regarding reliability, validity and responsiveness[72]. SarQoL could also have advantages over generic quality-of-life measures, such as the EQ-5D and SF-36, because it was specifically developed to assess the impact of sarcopenia across multiple HRQoL domains. This disease-specific focus could make SarQoL more sensitive to changes resulting from pharmacological interventions for sarcopenia and better able to capture patient-reported outcomes that are particularly relevant to the condition. For example, in a longitudinal study, SarQoL demonstrated significantly greater responsiveness than the SF-36 Physical Component Summary, the EQ-5D Utility Index and the Euroqol visual analogue scale[73]. Overall, SarQoL demonstrates good psychometric properties, suggesting it is an appropriate tool for assessing patient-reported QoL in sarcopenia trials.

The suitability of a PROM to capture the patient-relevant outcome for the intervention being considered could be used to determine the choice of PROM as a phase III trial outcome. However, it is recognized that each instrument only captures part of the patient experience. Therefore, phase III primary trial outcomes should include an objective end point such as measured physical function, complemented by both a disease-specific HRQoL PROM (such as SarQoL) and potentially a generic tool such as EQ-5D for comparability and economic evaluation. However, PROMs can be influenced by cultural, cognitive and contextual factors, which should be considered in multinational trials.

Duration of observation for pharmacological trials in sarcopenia

As mentioned above, the purpose of phase II trials is to obtain 'proof of concept' for a new molecule or chemical entity and to assess the effective dose-range to determine the optimum dose to use in phase III trials. By contrast, phase III trials aim to demonstrate functional improvement and the durability of a new entity's effect, such that it is safe and effective for use in the management of sarcopenia. Adequate duration of observation is essential to ensure that clinically meaningful effects can be detected and sustained. Trial duration must also balance the need for robust efficacy data with minimizing the burden on trial participants and exposure to investigational products. Typical durations of 3–6 months for phase II trials and ≥12 months for phase III trials could be suitable as pragmatic starting positions. However, the trial duration should be aligned with the type of drug, its mechanism of action and the trial outcomes, and it is important to engage with regulators early and provide effective justification for the proposed duration of observation, and to provide valid reasons for departing from these principles. These principles are important for the interpretability of the trial results, and for balancing the benefits and risks to participants. For example, whether the outcome measure is muscle mass, muscle strength, physical performance or a PROM could influence the time required to observe an effect, with physical performance measures

and PROMs probably requiring more time to change in response to treatment. Similarly, different durations of observation for anabolic agents (3–6 months for phase II; ≥12 months for phase III), myostatin inhibitors (≥6 months for phase II; ≥12 months for phase III); and anti-inflammatory agents (≥6–9 months for phase II; ≥12–18 months for phase III) could be suitable as pragmatic starting positions, due to differences in their mechanisms of action. These perspectives regarding treatment durations in sarcopenia trials are presented in Table 2.

Use of biomarkers in sarcopenia trials

Biomarker selection in sarcopenia trials remains an evolving area with substantial methodological and regulatory uncertainty. This lack of clarity regarding appropriate biomarkers persisted after the 2020 ESCEO recommendations for the conduct of sarcopenia clinical trials[13] were published. Therefore, a separate ESCEO working group proposed a framework for selecting biochemical markers for use in phase II and III sarcopenia trials and published a consensus article in 2023[74]. This paper proposed classifying biochemical markers as those evaluating musculoskeletal status (myostatin-follistatin, brain-derived neurotrophic factor, N-terminal type III procollagen and serum creatinine to serum cystatin C ratio in phase II–III trials) and those evaluating non-muscle-specific pathophysiological mechanisms (insulin-like growth factor-1 (IGF-I), dehydroepiandrosterone sulfate, cortisol, C-reactive protein (CRP), IL-6 and TNF in phase II trials, and IGF-I and CRP in phase III trials), and also proposed optional biochemical markers that might provide insights into the mode of action of pharmacological therapies. Analytical advancements since the publication of this article include the increasing adoption of liquid chromatography–tandem mass spectrometry (LC–MS/MS) over traditional enzyme-linked immunosorbent assay (ELISA) methods[75,76], greater accessibility of emerging technologies, such as high-throughput proteomics platforms[77], and the rise of metabolomics and lipidomics[78], enabling the exploration of complex biochemical pathways. However, limitations regarding the use of biochemical markers remain and include limited knowledge of typical biological variability and, thus, responsiveness to biological variation over time, high variation in laboratory processes and a lack of standardization of methods[79]. These considerations therefore mean that, currently, such biomarkers should be viewed in the context of research insight rather than contributing to regulatory approval. Thus, so far, no biomarkers have yet been established as appropriate surrogate outcomes in sarcopenia trials, and development of a qualification roadmap for biomarkers for sarcopenia trials tied to context of use remains a priority.

Ascertainment of muscle mass in sarcopenia trials

An important consideration is the distinction between lean mass and skeletal muscle size or volume. DXA-derived lean mass is a common surrogate measure of muscle mass and has been widely used in sarcopenia trials. However, the use of this measure has limitations. For example, DXA-derived lean mass also includes internal organs, water and other non-fat and non-bone soft tissue. Furthermore, the relatively weak relationship between DXA-derived lean mass and muscle strength and physical function should not necessarily be interpreted as evidence that skeletal muscle quantity is unimportant, as DXA-derived lean mass is an imperfect surrogate for skeletal muscle. Research has demonstrated that low muscle mass ascertained using the D_3-creatine (D_3Cr) dilution method is associated with adverse health outcomes including falls, disability, hip fracture and mortality[80]. This technique, which estimates skeletal muscle mass by determining the total body creatine pool, has been successfully implemented in numerous studies involving populations of different ages and settings[81–85]. Therefore, D_3Cr-derived muscle mass could be considered a secondary outcome in phase II and III trials for sarcopenia drugs, as shown in Table 2. Although D_3Cr-derived muscle mass has not yet been demonstrated to be responsive to pharmacological anabolic interventions, preliminary evidence from a small randomized trial involving 21 older adults suggests that it might be responsive to non-pharmacological interventions, with increases in D_3Cr-derived muscle mass observed following 15 weeks of high-intensity strength training[86]. An ongoing investigation involving postmenopausal women from the Women's Health Initiative aims to create age-standardized muscle mass percentile curves to characterize the distribution of D_3Cr-derived muscle mass in cancer survivors and non-cancer controls, and to generate risk-prediction algorithms to detect low muscle mass[87]. A 2024 consensus exercise identified 14 potential biomarkers of ageing that can be used as outcome measures in intervention studies, including muscle mass[88]; however, there is no consensus on what constitutes a 'gold standard' for skeletal muscle mass measurement, and optimum approaches and guidelines for quantifying muscle mass and composition in vivo are required[89].

Patient expectations of sarcopenia treatments

As reflected by principles of the Professional Society for Health Economics and Outcomes Research (ISPOR) and Innovative Medicines Initiative Patient Preferences in Benefit–Risk Assessments during the Drug Life Cycle (IMI PREFER), early and continuous patient engagement in sarcopenia trials, with patient representatives involved throughout all stages of drug development, is important, and patient preferences should ideally inform end point selection, trial design and regulatory dialogue[90–92]. Regarding future treatments for sarcopenia, key priorities for patients include maintaining independence, improving or preserving function, and reducing the risk of adverse health outcomes such as falls, fractures and hospital admission[93,94]. Patients also value a 'whole-person approach' to treatment, involving an integrated, personalized and feasible care plan. Furthermore, patient perspectives indicate that meaningful treatment benefit extends beyond modest improvements in surrogate measures and should include sustained gains in independence, daily functioning, social participation and the ability to maintain valued roles and activities.

Meaningful patient engagement should encompass involvement in study design, end point selection, recruitment strategies, interpretation of findings and dissemination of results. Appropriate support and accessibility measures are essential to enable effective participation by individuals living with sarcopenia. Incorporating these preferences into trial design could enhance both recruitment and the clinical relevance of study findings.

Conclusions

The WHO Collaborating Centre identified key priorities and methodological considerations for advancing the development of pharmacological interventions for sarcopenia. Development of treatments for sarcopenia is entirely congruent with the WHO's priorities on maintaining healthy ageing and functional ability[95]. The UN Decade of Healthy Ageing (2021–2030) represents a global commitment to improving the lives of older people by creating age-friendly environments and delivering integrated and long-term care[96]. The UN Decade of Healthy Ageing (2021–2030) thus provides an opportunity to improve musculoskeletal health globally. However, improving musculoskeletal health globally requires tools and interventions that are feasible in

low-resource settings and valid across diverse populations and cultural contexts.

For investigators, regulators and pharmaceutical companies, these up-to-date perspectives provide a practical basis for decisions about the design of sarcopenia intervention studies, including participant eligibility, selection of endpoints and treatment duration. They also highlight the importance of tailoring these design features to the mechanism of action and expected temporal response of an intervention. By clarifying areas in which current evidence supports particular approaches, while identifying those requiring further methodological development, this Perspective will help inform the design of future pharmacological interventions for sarcopenia. Although the flexibility embedded within these perspectives might facilitate their application in low-resource settings, we acknowledge that several of the suggested tools would be challenging to implement in such settings and that the membership of this working group was predominantly European. Given ethnic and/or regional differences in body composition, diagnostic thresholds might not be directly transferable between populations. Therefore, multiregional trials might need to prespecify the diagnostic criteria and population-specific thresholds to be applied, where validated, and whether geographical region will be used as a stratification factor.

Other than the possibility of novel interventions emerging, there is substantial innovation in the area of biomarkers and novel outcomes, together with new digital tools and the establishment of SarQoL as the principal PROM for sarcopenia intervention studies. Early and continuous engagement with regulators and patient representatives when planning and conducting sarcopenia trials is important to ensure that their perspectives and priorities are reflected throughout all stages of drug development. Progress in this field will require harmonization of definitions, robust and clinically meaningful endpoints, including identification of a core outcome set, and continued collaboration between academia, industry, regulators and patients.

References

1. Cruz-Jentoft, A. Sarcopenia, the last organ insufficiency. *Eur. Geriatr. Med.* **7**, 195–196 (2016).
2. Cruz-Jentoft, A. J. et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing* **48**, 16–31 (2019).
3. Sayer, A. A. et al. Sarcopenia. *Nat. Rev. Dis. Primers* **10**, 68 (2024).
4. Kirk, B. et al. The conceptual definition of sarcopenia: Delphi Consensus from the Global Leadership Initiative in Sarcopenia (GLIS). *Age Ageing* **53**, afae052 (2024).
5. Beaudart, C. et al. Health outcomes of sarcopenia: a consensus report by the outcome working group of the Global Leadership Initiative in Sarcopenia (GLIS). *Aging Clin. Exp. Res.* **37**, 100 (2025).
6. Mayhew, A. et al. The prevalence of sarcopenia in community-dwelling older adults, an exploration of differences between studies and within definitions: a systematic review and meta-analyses. *Age Ageing* **48**, 48–56 (2019).
7. Lewis, E. G., Hurst, C., Errington, L. & Sayer, A. A. Perceptions of sarcopenia in patients, health and care professionals, and the public: a scoping review of studies from different countries. *Eur. Geriatr. Med.* **16**, 99–113 (2025).
8. World Health Organization. *International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10), version 2019* https://icd.who.int/browse10/2019/en (2019).
9. National Center for Health Statistics. *International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM)* https://www.cdc.gov/nchs/icd/icd-10-cm/ (Centers for Disease Control and Prevention, 2026).
10. Anker, S. D., Morley, J. E. & von Haehling, S. Welcome to the ICD-10 code for sarcopenia. *J. Cachexia Sarcopenia Muscle* **7**, 512–514 (2016).
11. World Health Organization. *ICD-11 for Mortality and Morbidity Statistics, January 2026 release* https://icd.who.int/browse/2026-01/mms/en (2026).
12. World Health Organization. *Package of Interventions for Rehabilitation: Module 2: Musculoskeletal Conditions* https://www.who.int/publications/i/item/9789240071100 (2023).
13. Reginster, J.-Y. et al. Update on the ESCEO recommendation for the conduct of clinical trials for drugs aiming at the treatment of sarcopenia in older adults. *Aging Clin. Exp. Res.* **33**, 3–17 (2021).
14. Cesari, M. et al. Challenges in the development of drugs for sarcopenia and frailty – report from the International Conference on Frailty and Sarcopenia Research (ICFSR) task force. *J. Frailty Aging* **11**, 135–142 (2022).
15. Reginster, J. Y. et al. Recommendations for the conduct of clinical trials for drugs to treat or prevent sarcopenia. *Aging Clin. Exp. Res.* **28**, 47–58 (2016).
16. Chen, L.-K. et al. Asian Working Group for Sarcopenia: 2019 consensus update on sarcopenia diagnosis and treatment. *J. Am. Med. Dir. Assoc.* **21**, 300–307 (2020).
17. Bhasin, S. et al. Sarcopenia definition: the position statements of the sarcopenia definition and outcomes consortium. *J. Am. Geriatr. Soc.* **68**, 1410–1418 (2020).
18. Sayer, A. A. & Cruz-Jentoft, A. Sarcopenia definition, diagnosis and treatment: consensus is growing. *Age Ageing* **51**, afac220 (2022).
19. Voulgaridou, G. et al. Diagnostic criteria and measurement techniques of sarcopenia: a critical evaluation of the up-to-date evidence. *Nutrients* **16**, 436 (2024).
20. Cawthon, P. M. et al. Putative cut-points in sarcopenia components and incident adverse health outcomes: an SDOC analysis. *J. Am. Geriatr. Soc.* **68**, 1429–1437 (2020).
21. Chen, L.-K. et al. A focus shift from sarcopenia to muscle health in the Asian Working Group for Sarcopenia 2025 consensus update. *Nat. Aging* **5**, 2164–2175 (2025).
22. Evans, W. J. et al. Sarcopenia: no consensus, no diagnostic criteria, and no approved indication—how did we get here? *Geroscience* **46**, 183–190 (2024).
23. von Haehling, S., Langer, H. T., Heymsfield, S. B., Evans, W. J. & Anker, S. D. Sarcopenia in ageing and chronic illness: trial endpoints and regulatory issues. *J. Cachexia Sarcopenia Muscle* **16**, e13841 (2025).
24. European Medicines Agency. *Reflection Paper on Physical Frailty: Instruments for Baseline Characterisation of Older Populations in Clinical Trials* https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-physical-frailty-instruments-baseline-characterisation-older-populations-clinical-trials-first-version_en.pdf (2018).
25. Bernabei, R. et al. Multicomponent intervention to prevent mobility disability in frail older adults: randomised controlled trial (SPRINTT project). *BMJ* **377**, e068788 (2022).
26. Bahat, G. & Ozkok, S. The current landscape of pharmacotherapies for sarcopenia. *Drugs Aging* **41**, 83–112 (2024).
27. Rudman, D. et al. Effects of human growth hormone in men over 60 years old. *N. Engl. J. Med.* **323**, 1–6 (1990).
28. Papadakis, M. A. et al. Growth hormone replacement in healthy older men improves body composition but not functional ability. *Ann. Intern. Med.* **124**, 708–716 (1996).
29. Buratto, J., Kirk, B., Phu, S., Vogrin, S. & Duque, G. Safety and efficacy of testosterone therapy on musculoskeletal health and clinical outcomes in men: a systematic review and meta-analysis of randomized placebo-controlled trials. *Endocr. Pract.* **29**, 727–734 (2023).
30. Mohideen, H., Hussain, H., Dahiya, D. S. & Wehbe, H. Selective androgen receptor modulators: an emerging liver toxin. *J. Clin. Transl. Hepatol.* **11**, 188–196 (2022).
31. Cacciatore, S. et al. Emerging targets and treatments for sarcopenia: a narrative review. *Nutrients* **16**, 3271 (2024).
32. Balestroni, G. & Bertolotti, G. EuroQol-5D (EQ-5D): an instrument for measuring quality of life. *Monaldi Arch. Chest Dis.* **78**, 155–159 (2012).
33. Sumukadas, D., Witham, M. D., Struthers, A. D. & McMurdo, M. E. Effect of perindopril on physical function in elderly people with functional impairment: a randomized controlled trial. *CMAJ* **177**, 867–874 (2007).
34. Fielding, R. A. et al. BIO101 in sarcopenic seniors at risk of mobility disability: results of a double-blind randomised interventional phase 2b trial. *J. Cachexia Sarcopenia Muscle* **16**, e13750 (2025).
35. Dong, X. et al. Metformin increases sarcolemma integrity and ameliorates neuromuscular deficits in a murine model of duchenne muscular dystrophy. *Front. Physiol.* **12**, 642908 (2021).
36. Tezze, C. et al. A combination of metformin and galantamine exhibits synergistic benefits in the treatment of sarcopenia. *JCI Insight* **8**, e168787 (2023).
37. Singh, A. et al. Urolithin A improves muscle strength, exercise performance, and biomarkers of mitochondrial health in a randomized trial in middle-aged adults. *Cell Rep. Med.* **3**, 100633 (2022).
38. Tarantino, U. et al. Sarcopenia and bone health: new acquisitions for a firm liaison. *Ther. Adv. Musculoskelet. Dis.* **14**, 1759720X221138354 (2022).
39. Haeri, N. S., Perera, S. & Greenspan, S. L. Impact of denosumab on muscle health in older adults in long-term care. *Bone* **198**, 117552 (2025).
40. Rooks, D. S. et al. Effect of bimagrumab on thigh muscle volume and composition in men with casting-induced atrophy. *J. Cachexia Sarcopenia Muscle* **8**, 727–734 (2017).
41. Rooks, D. et al. Treatment of sarcopenia with bimagrumab: results from a phase II, randomized, controlled, proof-of-concept study. *J. Am. Geriatr. Soc.* **65**, 1988–1995 (2017).
42. Becker, C. et al. Myostatin antibody (LY2495655) in older weak fallers: a proof-of-concept, randomised, phase 2 trial. *Lancet Diabetes Endocrinol.* **3**, 948–957 (2015).
43. Clark, B. C. Neural mechanisms of age-related loss of muscle performance and physical function. *J. Gerontol. A* **78** (Suppl. 1), 8–13 (2023).
44. Dondero, K., Friedman, B., Rekant, J., Landers-Ramos, R. & Addison, O. The effects of myosteatosis on skeletal muscle function in older adults. *Physiol. Rep.* **12**, e16042 (2024).

45. Van Heden, S. et al. Towards a core outcome set for sarcopenia intervention studies: a scoping review identifying the most frequently reported outcomes across randomized controlled trials in sarcopenia. *Eur. Geriatr. Med.* **16**, 2033–2045 (2025).
46. COMET Initiative Database. *Towards Developing a Core Outcome Set (COS) for Sarcopenia Intervention Studies* https://www.cometinitiative.org/Studies/Details/2991 (2026).
47. Jackson, S. E., Brown, J., Llewellyn, C., Mytton, O. & Shahab, L. Prevalence of use and interest in using glucagon-like peptide-1 receptor agonists for weight loss: a population study in Great Britain. *BMC Med.* **24**, 1 (2026).
48. Scheen, A. J. GLP-1-derived therapies and sarcopenia: plea for a specific focus on at risk special populations. *Diabetes Metab.* **52**, 101708 (2025).
49. Pantazopoulos, D., Gouveri, E., Papazoglou, D. & Papanas, N. GLP-1 receptor agonists and sarcopenia: weight loss at a cost? A brief narrative review. *Diabetes Res. Clin. Pract.* **229**, 112924 (2025).
50. Batsis, J. A. et al. Effect of incretin-based and nonpharmacologic weight loss on body composition: a systematic review. *Ann. Intern. Med.* **179**, 996–1013 (2026).
51. Beaudart, C. et al. Assessment of muscle function and physical performance in daily clinical practice : a position paper endorsed by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO). *Calcif. Tissue Int.* **105**, 1–14 (2019).
52. Beaudart, C. et al. Patient-reported outcomes in sarcopenia: an ICFSR task force report. *J. Frailty Aging* **14**, 100010 (2025).
53. Becker, C. et al. Digital mobility outcomes to describe real-world walking during recovery from a hip fracture: the Mobilise-D perspective. *Eur. Geriatr. Med.* **17**, 163–177 (2026).
54. Kim, S., Kim, S., Kim, H., Kim, H. & Yoo, J.-I. Cross-sectional study comparing smart insoles and manual methods for short physical performance battery in hip fracture patients. *Aging Clin. Exp. Res.* **37**, 61 (2025).
55. Shin, J., Kweon, H. J. & Choi, J. Assessment of gait parameters using wearable sensors and their association with muscle mass, strength, and physical performance in Korean older adults: cross-sectional study. *JMIR Form. Res.* **9**, e63928 (2025).
56. Kim, S. et al. Assessing physical abilities of sarcopenia patients using gait analysis and smart insole for development of digital biomarker. *Sci. Rep.* **13**, 10602 (2023).
57. Ruiz-Cárdenas, J. D., Montemurro, A., Martínez-García, M.dM. & Rodríguez-Juan, J. J. Sit-to-stand video analysis–based app for diagnosing sarcopenia and its relationship with health-related risk factors and frailty in community-dwelling older adults: diagnostic accuracy study. *J. Med. Internet Res.* **25**, e47873 (2023).
58. Smith, A. C. et al. Leg muscle volume, intramuscular fat and force generation: insights from a computer-vision model and fat-water MRI. *J. Cachexia Sarcopenia Muscle* **16**, e13735 (2025).
59. Lee, H. T., Hyun, J. K. & Kim, S. Y. Enhancing the diagnosis of sarcopenia through low-dose chest CT and artificial intelligence-based segmentation: optimizing resource utilization in healthcare. *J. Korean Soc. Radiol.* **86**, 501–511 (2025).
60. Park, H., Kim, H. & Yoo, J. AI-enhanced lower extremity X-ray segmentation: a promising tool for sarcopenia diagnosis. *Healthcare* **13**, 2488 (2025).
61. López-Gómez, J. J. et al. Artificial intelligence–assisted rectus femoris ultrasound vs. L3 computed tomography for sarcopenia assessment in oncology patients: establishing diagnostic cut-offs for muscle mass and quality. *Front. Nutr.* **12**, 1678989 (2025).
62. Kim, H.-K. & Kim, C.-H. Quality matters as much as quantity of skeletal muscle: clinical implications of myosteatosis in cardiometabolic health. *Endocrinol. Metab.* **36**, 1161–1174 (2021).
63. Tuan, S.-H. et al. Assessing the clinical effectiveness of an exergame-based exercise training program using ring fit adventure to prevent and postpone frailty and sarcopenia among older adults in rural long-term care facilities: randomized controlled trial. *J. Med. Internet Res.* **26**, e59468 (2024).
64. Wu, C.-E. & Manga, Y. B. Impact of wearable-assisted walking on sarcopenia and body composition in older adults. *BMC Geriatr.* **25**, 466 (2025).
65. Brazier, J. E. et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *BMJ* **305**, 160–164 (1992).
66. Beaudart, C. et al. Development of a self-administrated quality of life questionnaire for sarcopenia in elderly subjects: the SarQoL. *Age Ageing* **44**, 960–966 https://doi.org/10.1093/ageing/afv133 (2015).
67. Doza, G., Van Heden, S., Felix, F. O., Singh, V. & Beaudart, C. Impact of interventions on sarcopenia from the perspective of older persons: a systematic literature review. *J. Frailty Aging* **13**, 224–232 (2024).
68. Beaudart, C. et al. Validation of the SarQoL®, a specific health-related quality of life questionnaire for sarcopenia. *J. Cachexia Sarcopenia Muscle* **8**, 238–244 (2017).
69. Demonceau, C., Voz, B., Bruyère, O., Reginster, J. & Beaudart, C. Content validity of SarQoL, a quality of life questionnaire specific to sarcopenia. *Aging Clin. Exp. Res.* **36**, 101 (2024).
70. Beaudart, C. et al. Quality of life in sarcopenia measured with the SarQoL questionnaire: a meta-analysis of individual patient data. *Maturitas* **180**, 107902 (2024).
71. Beaudart, C. et al. Measuring health-related quality of life in sarcopenia: summary of the SarQoL psychometric properties. *Aging Clin. Exp. Res.* **35**, 1581–1593 (2023).
72. Demonceau, C. et al. Psychometric properties of the sarqol questionnaire: a systematic review and meta-analysis. *J. Cachexia Sarcopenia Muscle* **16**, e70122 (2025).
73. Geerinck, A., Bruyère, O., Locquet, M., Reginster, J.-Y. & Beaudart, C. Evaluation of the responsiveness of the SarQoL® questionnaire, a patient-reported outcome measure specific to sarcopenia. *Adv. Ther.* **35**, 1842–1858 (2018).
74. Ladang, A. et al. Biochemical markers of musculoskeletal health and aging to be assessed in clinical trials of drugs aiming at the treatment of sarcopenia: consensus paper from an expert group meeting organized by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) and the Centre Académique de Recherche et d'Expérimentation en Santé (CARES SPRL), under the auspices of the World Health Organization Collaborating Center for the Epidemiology of Musculoskeletal Conditions and Aging. *Calcif. Tissue Int.* **112**, 197–217 (2023).
75. Alanazi, S. Recent advances in liquid chromatography–mass spectrometry (LC–MS) applications in biological and applied sciences. *Anal. Sci. Adv.* **6**, e70024 (2025).
76. Demeuse, J. et al. Development and validation of an LC–MS/MS method for the simultaneous quantitation of angiotensin (1–7),(1–8),(1–9) and (1–10) in human plasma. *J. Chromatogr. B* **1232**, 123943 (2024).
77. Wang, H. et al. Methods and clinical biomarker discovery for targeted proteomics using Olink technology. *Proteom. Clin. Appl.* **18**, e2300233 (2024).
78. Anh, N. K., Thu, N. Q., Tien, N. T. N., Long, N. P. & Nguyen, H. T. Advancements in mass spectrometry-based targeted metabolomics and lipidomics: implications for clinical research. *Molecules* **29**, 5934 (2024).
79. Cao, H. et al. Advancing clinical biochemistry: addressing gaps and driving future innovations. *Front. Med.* **12**, 1521126 (2025).
80. Evans, W. J. & Cawthon, P. M. D3Creatine dilution as a direct, non-invasive and accurate measurement of muscle mass for aging research. *Calcif. Tissue Int.* **114**, 3–8 (2024).
81. Cataldi, D. et al. Association of body composition measures to muscle strength using DXA, D3Cr, and BIA in collegiate athletes. *Sci. Rep.* **15**, 5839 (2025).
82. Shankaran, M. et al. Skeletal muscle mass measured noninvasively by D_3-creatine dilution in children and term infants. *J. Pediatr. Clin. Pract.* **17**, 200158 (2025).
83. Cheng, E. et al. D3-creatine dilution, computed tomography and dual-energy X-ray absorptiometry for assessing myopenia and physical function in colon cancer: a cross-sectional study. *J. Cachexia Sarcopenia Muscle* **14**, 2768–2778 (2023).
84. Tan, D. Y. Z. et al. Novel algorithm to estimate fat-free muscle volumes in women using the urinary deuterated-creatine dilution method. *J. Cachexia Sarcopenia Muscle* **16**, e13872 (2025).
85. Evans, W. J. et al. Reductions in functional muscle mass and ability to ambulate in Duchenne muscular dystrophy from ages 4 to 24 years. *J. Physiol.* **602**, 4929–4939 (2024).
86. Balachandran, A. T. et al. Comparing D_3-creatine dilution and dual-energy X-ray absorptiometry muscle mass responses to strength training in low-functioning older adults. *J. Gerontol. A* **78**, 1591–1596 (2023).
87. Banack, H. R. et al. A protocol for remote collection of skeletal muscle mass via D_3-creatine dilution in community-dwelling postmenopausal women from the Women's Health Initiative. *PLoS ONE* **19**, e0300140 (2024).
88. Perri, G. et al. An expert consensus statement on biomarkers of aging for use in intervention studies. *J. Gerontol. A* **80**, glae297 (2025).
89. Heymsfield, S. B. et al. Reference methods for measuring skeletal muscle mass: a critical perspective. *J. Cachexia Sarcopenia Muscle* **17**, e70184 (2026).
90. de Bekker-Grob, E. W. et al. Giving patients' preferences a voice in medical treatment life cycle: the PREFER public–private project. *Patient* **10**, 263–266 (2017).
91. Bridges, J. F. et al. A roadmap for increasing the usefulness and impact of patient-preference studies in decision making in health: a good practices report of an ISPOR task force. *Value Health* **26**, 153–162 (2023).
92. Janssens, R. et al. How can patient preferences be used and communicated in the regulatory evaluation of medicinal products? Findings and recommendations from IMI PREFER and call to action. *Front. Pharmacol.* **14**, 1192770 (2023).
93. Hiligsmann, M. et al. Outcome priorities for older persons with sarcopenia. *J. Am. Med. Dir. Assoc.* **21**, 267–271 (2020).
94. US Food and Drug Administration. *The Voice of the Patient: Sarcopenia. Patient-Focused Drug Development (PFDD) Report* https://www.fda.gov/media/108220/download (2018).
95. World Health Organization. *WHO Clinical Consortium on Healthy Ageing 2023: Meeting Report, Geneva, Switzerland* https://www.who.int/publications/i/item/9789240093546 (2023).
96. World Health Organization. *United Nation's Decade of Healthy Ageing (2021–2030)* https://cdn.who.int/media/docs/default-source/decade-of-healthy-ageing/decade-proposal-final-apr2020-en.pdf (2020).

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Author contributions

All authors contributed substantially to discussion of the content and reviewed and/or edited the manuscript before submission. L.W., E.M.C. and N.C.H. wrote the first draft of the article.

Competing interests

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