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ORIGINAL ARTICLE

Populations and outcome measures used in ongoing research in sarcopenia

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Abstract
Background Sarcopenia research may be hampered by the heterogeneity of populations and outcome measures used in clinical studies.
Aim The aim of this study was to describe the inclusion/exclusion criteria and outcome measures used in ongoing research in sarcopenia.
Methods All active intervention studies registered in the World Health Organization with the keyword sarcopenia were included. Study design, type of intervention, inclusion/exclusion criteria and outcome measures were registered and classified.
Results In April 2014, 151 studies on sarcopenia were registered in the WHO database. One hundred twenty-three were intervention studies. Most trials (94.3 %) were single centre and randomized (93.5 %), 51.2 % were double blind. Nutritional interventions (36.6 %), physical exercise (12.2 %) or both (19.5 %) were the most common interventions tested. Only 54.4 % included subjects of both genders, and 46.3 % had an upper age limit. Definition of the target populations was heterogeneous, with 57.7 % including healthy subjects and none using recent definitions of sarcopenia. Lifestyle and the degree of physical activity of subjects were not described or considered in most cases (79.7 %). Subjects with cardiovascular, neuropsychiatric or metabolic disorders and those with physical disability were usually excluded. Muscle mass and muscle strength were the primary outcome variables in 28.5 and 29.5 % of studies and physical performance in 19.5 %, but only 4.1 % used the three variables used the three of them. An additional 26.8 % used biological outcome variables. Little information and agreement existed in the way muscle and physical performance parameters were measured.
Conclusions We found a large heterogeneity in trial design, definition of populations and outcome measures in present research.

Keywords Clinical trials · Sarcopenia · Inclusion/exclusion criteria · Outcomes

Introduction

Sarcopenia is defined as an age-related syndrome of progressive and generalized loss of skeletal muscle mass and function with a risk of adverse outcomes such as physical disability, poor quality of life and death [1, 2]. Sarcopenia is a common problem in geriatric care, with a prevalence as high as 29 % in community-dwelling populations and 33 % in long-term care populations [3, 4].

Current interventions to prevent or treat sarcopenia are mainly based on physical exercise and nutrition interventions, but evidence is only moderate quality due to variability in study populations, study designs, goal of the intervention (prevention or treatment), safety and outcome measures used (choice of primary and secondary outcomes, clinical significance, sensitivity to change, acceptability by regulatory agencies) [3, 5, 6]. These issues are also hampering research on new drugs to treat sarcopenia.

Choice of populations for clinical studies has also shown complex, as there are unsolved issues linked to the use of different definitions of sarcopenia (some based only on

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muscle mass, the newest ones on muscle mass and function), the choice of cut-off points (for different measures of muscle mass, muscle strength and physical performance), the setting (community, hospital, nursing homes) and interactions between sarcopenia and physical frailty [7–11].

Some expert groups are now trying to build consensus on how clinical trials for sarcopenia should be designed [12, 13], and a recent European Innovative Medicines Initiative (SPRINT-T) is trying to test some approaches to include sarcopenia and frailty in research in a large clinical trial, in cooperation with the European Medicines Agency (www.myspritntt.eu). However, while consensus is reached, little is known about how research is being performed at present in ongoing clinical trials. The aim of this study is to describe the inclusion/exclusion criteria and outcome measures used in ongoing research in sarcopenia.

Methods

Information regarding ongoing clinical trials on sarcopenia was obtained from the World Health Organization International Clinical Trials Registry Platform (WHOICTRP) on 16 April 2014 (http://apps.who.int/trialsearch/). This database is a collection of regular information about all trials registered in primary registries from countries around the world and is the most comprehensive global public repository of information on clinical trials.

Within this database, a search was performed for ongoing or completed clinical trials on sarcopenia. Trials in preclinical phases (animals), observational studies or those targeting populations below 50 years of age were excluded.

Variables recorded for each research protocol included the purpose of trial, number of centres involved, type of study, randomization, population setting and type of intervention. The main study variables were inclusion and exclusion criteria used to select the trial population, primary and secondary outcomes, and measurement instruments used for the three parameters most widely used to define sarcopenia (muscle mass, muscle strength and physical performance). Whenever there were links in the WHOICTRP to additional information on the trial, these were also searched for relevant variables.

The available information of each included trial was reviewed and classified based on the characteristics of the inclusion/exclusion criteria and the primary and secondary outcome variables. Other alternative sources referred by this platform were reviewed. The WHO database is the most comprehensive public collection of information about all the clinical trials registered around the world.

Descriptive data are presented as numbers, and percentages are used for categorical variables.

Results

As of 16 April 2014, there were 151 registered trials recruiting individuals with sarcopenia in the WHOICTRP database. Twenty-eight studies were excluded: 3 because the main objective was not sarcopenia but hip fracture, 20 because of their observational design and 5 because they specifically excluded older adults. The analysis focused on the remaining 123 (81.4 %) clinical intervention studies on sarcopenia.

The main characteristics of these clinical trials are described in Table 1. Most trials (116, 94.3 %) were single centre and randomized (115, 93.5 %), and roughly half of them (63, 51.2 %) were double blind. The study population was not specified in 103 trials, being mostly community dwelling when this was stated (only 2 trials were performed in hospitalized subjects and 2 in nursing homes).

Forty-five (36.6 %) of the studies focused on nutritional interventions, 15 (12.2 %) on physical exercise and 24 (19.5 %) on both physical exercise and nutritional intervention; one-third studied hormone replacement of other interventions.

Inclusion and exclusion criteria in these clinical trials are shown in Table 2. Sixty-seven (54.4 %) included

Table 1 Characteristics of ongoing clinical trials on sarcopenia

Characteristics	Frequency (n, %)
Type of study	
Single centre	116 (94.3)
Multiple centres	3 (2.4)
International, multiple centres	4 (3.3)
Study design	
Double blind	63 (51.2)
Single blind	15 (12.2)
Controlled study	16 (13)
Open study	19 (15.4)
Not specified	10 (8.1)
Assignment of treatment	
Randomized	115 (93.5)
Non randomized	5 (4.1)
Not stated	3 (2.4)
Population	
Community	16 (13.0)
Hospitalized	2 (1.6)
Nursing home	2 (1.6)
Not specified	103 (83.7)
Intervention	
Exercise/physical activity	15 (12.2)
Nutritional intervention	45 (36.6)
Exercise plus nutritional intervention	24 (19.5)
Hormone replacement	7 (5.7)
Other	32 (26.0)

Table 2 Inclusion and exclusion criteria used in ongoing clinical trials on sarcopenia

	Frequency (n, %)
Inclusion criteria	
Gender	
Males	34 (27.6)
Females	22 (17.9)
Both	67 (54.4)
Age	
Upper and lower age limits	57 (46.3)
Only lower age limit	64 (52.0)
Not mentioned	2 (1.6)
Health related conditions	
Relatively healthy or normal subjects	71 (57.7)
Population with healthy subjects and subjects with a disease of interest for the study	10 (8.1)
Frail or pre-frail subjects	5 (4.1)
Postmenopausal women	7 (5.7)
Postmenopausal obese women	2 (1.6)
Subjects with impaired mobility or difficulty performing activities of daily living	4 (3.3)
Subjects with low lean mass	4 (3.3)
Subjects with high risk of bone fracture, previous fractures, osteopenia	3 (2.4)
Osteoporosis or frequent falls	7 (5.7)
Other	14 (11.4)
Lifestyle and physical activity	
Sedentary or very light physical activity	11 (8.9)
Moderate to intense exercise and recreational activities	8 (6.5)
Regular activities of daily living or independent living	6 (4.9)
Not mentioned	98 (79.7)
Other criteria	
Bioethical issues	9 (7.3)
Measurement of muscle mass feasible	23 (18.7)
Ability to complete the protocol	9 (7.3)
No language or cognitive problems	4 (3.3)
Ambulatory subjects	2 (1.6)
Exclusion criteria	
Lifestyle	
Smokers	18 (14.7)
Use of alcohol	14 (12.2)
Restricted physical activity	1 (0.8)
Regular or intense exercise	30 (24.4)
Other	15 (12.2)
Use of other study drugs or potential confounding drugs	85 (69.1)
Diseases	
Cardiovascular disorders	77 (62.6)
Neurological and psychiatric diseases	76 (61.8)
Metabolic disorders	72 (58.5)
Other diseases that may potentially influence intervention	88 (71.5)
Present disability	76 (61.8)

subjects of both genders. Sixty-four (52.0 %) used a lower age limit to define the population (age-related sarcopenia), but 57 (46.3 %) also set upper age limits. Definition of the target population was quite heterogeneous: 71 trials (57.7 %) included healthy or normal subjects, while the rest used many different ways to define it. Only 4 studies looked at subjects with low lean mass and none used recent definitions of sarcopenia (low muscle mass and function). Lifestyle and the degree of physical activity of subjects were not described or considered in most cases (98 trials, 79.7 %). Biomarkers were rarely used for inclusion (15 trials, 12.2 %).

The most widely used exclusion criteria, apart from old age the use of other investigational interventions, were cardiovascular diseases (77 trials, 62.2 %), neuropsychiatric disorders (68 trials, 55.3 %), metabolic disorders (72 trials, 58.5 %) and the presence of physical disability (76 trials, 61.8 %). Many trials (30, 24.4 %) also excluded subjects with regular or intense exercise or physical activity at baseline.

Main outcome measures are described in Table 3. Muscle mass and muscle strength were the primary outcome variables in 28.5 and 29.5 % of studies and physical performance in 19.5 %, but only 5 (4.1 %) used these three variables together (muscle mass, muscle strength and physical performance). Biological measures (biopsy, protein synthesis studies and a wide array of biochemical measurements, usually in blood) were used in 26.8 % of the trials. Muscle energy, cognition, cardiovascular risk factors, quality of life and cost were considered in a few studies. Secondary outcomes were wide and not comprehensively listed. Muscle mass 16.3 %, strength 32.5 % and physical performance 25.2 % were used as outcome measures in an additional in the trials, and others mentioned many different biochemical measurements.

Little information and agreement existed in the way muscle and physical performance parameters were measured (Table 3). Most trials did not specify the instrument or test used to measure muscle mass, muscle strength or physical performance 16.3 %. When mentioned, dual-energy X-ray absorptiometry (DXA) was the most usual choice for muscle mass, while test leg flexion, extension or press-isokinetic was the most frequent measures of muscle strength, followed by handgrip strength. Gait speed and the

Table 3 Primary and secondary outcomes and instruments used to measure relevant

	Frequency (n, %)
Outcomes	
Primary outcomes	
Muscle mass	17 (13.8)
Muscle strength	14 (11.4)
Physical performance	12 (9.8)
Muscle function (strength and performance)	6 (4.9)
Muscle mass and strength	6 (4.9)
Muscle mass and physical performance	1 (0.8)
Muscle mass and function (strength and performance)	5 (4.1)
Biopsy	3 (2.4)
Protein synthesis and degradation/biochemical measurements	33 (26.8)
Activities of daily living	3 (2.4)
Bone mineral density	4 (3.3)
Bone mineral density and muscle mass	1 (0.8)
Bone mineral density and muscle strength	5 (4.1)
Other	11 (8.9)
No primary outcome variable mentioned	2 (1.6)
Secondary outcomes	
Muscle mass	4 (3.3)
Muscle strength	15 (12.2)
Physical performance	15 (12.2)
Muscle function (strength and performance)	7 (5.7)
Muscle mass and strength	7 (5.7)
Muscle mass and functionality (strength and performance)	9 (7.3)
Protein synthesis and degradation/biochemical measurements	20 (16.3)
Biopsy	1 (0.8)
Bone mineral density	4 (3.3)
Bone mineral density and muscle strength	2 (1.6)
Other	24 (19.5)
No secondary outcome variables mentioned	15 (12.2)
Measuring instruments	
Muscle Mass	
Dual-energy X-ray absorptiometry (DXA)	14 (11.4)
DXA and Magnetic resonance imaging (MRI)	1 (0.8)
Computed tomography (CT)	1 (0.8)
Anthropometry, DXA and MR	1 (0.8)
Ultrasonography	3 (2.4)
Bioelectrical impedance analysis (BIA)	3 (2.4)
BIA and DXA	1 (0.8)
Not specified	31 (25.2)
Muscle strength	
Leg flexion, extension or press-isokinetic	15 (12.2)
Handgrip strength	10 (8.1)
Bench press	2 (1.6)
Chair test	1 (0.8)
1 RM	2 (1.6)
Handgrip and leg grip strength	4 (3.3)
Chair test and isokinetic	1 (0.8)
Pulmonary peak expiratory flow	3 (2.4)
Not specified	38 (30.9)
Physical performance	
Gait speed (4–6 m)	6 (4.9)
Short Physical Performance Battery (SPPB)	10 (8.1)
Timed up and go (TUG)	3 (2.4)
20-m walk test	1 (0.8)
6-min walk test	4 (3.3)
SPPB and additional test	6 (4.9)
TUG and additional test	5 (4.1)
VO2 max	1 (0.8)
Climb stairs	1 (0.8)
Not specified	20 (16.3)

Short Physical Performance Battery (a validated scale that includes gait speed) were preferred to measure physical performance, but variability was wide and many trials used several measures.

Discussion

The aim of this study was to analyse how active clinical trials for the treatment of sarcopenia are currently designed. The design, inclusion and exclusion criteria, and outcome measures of a large set of trials registered in the WHO database were reviewed for active trials on sarcopenia. We found a large heterogeneity in study design, which calls for urgent action if such trials are expected to lead to solid conclusions that may be applied to clinical practice, and if they are to be compared by meta-analytic techniques.

Despite the rapidly growing number of articles on sarcopenia published in recent years, not so many describe new clinical research [3]. The fact that there were around 150 active trials on the area at the time the WHO database was searched is thus per se a relevant finding, although this number is still far to those found with similar methodology in heart failure or diabetes [14].

Being sarcopenia interventions in an early stage of development, most active research is performed by single centres, with little collaborative or international research. Methodology of many of these studies was not optimal to assess the effects of interventions, as less than half of the

trials were randomized clinical trials. A basic requirement for the design of interventions is the identification of the populations where research subjects are recruited, and this seems to be an important requirement for sarcopenia, as prevalence and characteristics of this condition seem to differ from community to hospitalized to nursing home-dwelling elders [3]. However, most active trials do not describe the population they are targeting. Most trials are exploring exercise and nutrition interventions, as drug trials are in most cases yet in the first steps of development and have not reached phase III [12, 15, 16]. Importantly, some trials are studying both nutrition and exercise, an important point as these interventions seem to be synergic, or at least to have a significant interaction [17].

Inclusion and exclusion criteria in these clinical studies are again heterogeneous, as no standards for trial design have been yet published, neither recommendation issued by medication agencies. Almost half of the interventions are gender specific, which is unusual and shows that many researchers believe that sarcopenia in males and females may behave different [18]. This may also be well justified in trials of hormone-derived drugs, as sex hormone levels clearly differ even in old age. Sarcopenia is considered an age-related condition, so setting a lower age limit makes sense. However, many trials also set an upper age limit, which cannot be explained by science and may well be due to ageism, which has been widely described in research of most age-related conditions [19, 20]. A key aspect to consider when designing sarcopenia trials is the baseline degree of physical activity and the presence of disability, usually defined by inability to walk or to perform activities of daily living. While the later aspect is usually clear, with a tendency to exclude those already disabled, the former is rarely addressed, except for the exclusion of well trained or highly fit subjects from exercise trials. Exclusion of cardiovascular, neurological or metabolic disorders is extremely prevalent in these studies, which may be a problem when results of research have to be transferred to a population where those conditions are more the rule than the exception. Surprisingly, trials do not use the presence of well-defined sarcopenia as the main inclusion criteria. Being the definition of sarcopenia disputed, this may be a major flaw that will limit comparisons between trials.

Sarcopenia is usually defined by low muscle mass and function. However, muscle outcomes are at this time not considered sufficient for drug or interventions approval by medicine agencies, as the links between muscle parameters and relevant clinical outcomes are still not strong enough to allow using them as proxies. Recently, research on exercise has been using physical performance measures as main outcome measure [21], but there is still no consensus or guidance by both researchers and agencies on what outcomes should be considered relevant, with incident disability, disability to walk or perform basic ADLs, nursing home admissions or falls among the most cited candidates. However, the number of trials not using muscle parameters to study a muscle condition seems to be too high. More agreement is shown by basic research studies, where protein synthesis and degradations measures, and biochemical measures are frequently cited.

Finally, there are some relevant aspects in the choice of measuring instruments for muscle mass and function. This is a relevant question, but is poorly disclosed in clinical trial protocols. DXA is emerging as the best research technique to measure muscle mass, although discussion on cut-off points is now very active [22]. Although grip strength is the muscle strength measure with the widest evidence, many researchers choose leg strength measures. Heterogeneity is widest in physical performance, where a wide array of measures, lead by gait speed and SPPB, are used.

This study has some strengths and limitations. Sample size was large, and publication bias did not influence the results. However, only the WHOICTRP registry was analysed, so trials not listed in this registry are missed. The proportion of ongoing trials worldwide that are registered is unknown, but there is no reason to support that findings in nonregistered trials should be different. Besides, the WHOICTRP only displays limited information, with a brief summary of clinical trial protocols that researchers usually fill in. As such, important data might be lacking that have been properly addressed in the final research protocol. This may be the case for outcome measures, with some investigators reporting a wide number of outcomes and other researchers only presenting some basic information. However, the use of the WHOICTRP has showed to be relevant to offer an overview of research in different areas [14, 23]. In addition, we should also mention that the quality of the databases included in the register of the WHO may be irregular, but there is no better global source of information than this.

Sarcopenia is a frequent condition that limits function and quality of life in old age. Interventions that prevent or reverse sarcopenia are needed to avoid negative outcomes linked with this condition [24]. Present research seems to have some limitations in definition of population, trial design and outcome measures used. Consensus built by scientific organizations and regulatory agencies is needed if high-quality research is to be produced in this field. Very recent efforts may be pointing in the right way [13].

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Compliance with ethical standards

Conflict of interest Lilia Patricia Bustamante, Ninfa Ramirez Duran and Carmen Sánchez declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study informed consent is not required.

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