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The PSSMAR study. Postacute sarcopenia: Supplementation with β-hydroxyMethylbutyrate after resistance training: Study protocol of a randomized, double-blind controlled trial

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1. Introduction

Sarcopenia is a geriatric syndrome characterized by the loss of skeletal muscle mass and strength that occurs with advancing age [1,2]. Sarcopenia is progressive and widespread, and can lead to disability, hospitalization [3–5], worsening quality of life, and death [1,4,6–10]. The great interest this entity arouses is due to its high prevalence and its serious consequences [11–15] .

According to the European Working Group on Sarcopenia in Older People (EWGSOP), diagnosis of sarcopenia is based on clinical criteria: presence of low muscle mass associated with low muscle function and/or low physical performance [1,6]. Despite progress in addressing sarcopenia, there have been very few randomized double-blind clinical trials, evidence regarding treatment effectiveness is limited, and further research is required [6]. In addition, recommendations for the conduct of clinical trials for drugs to treat or prevent sarcopenia [16,17] and reports on pharmacological interventions in frailty and sarcopenia have been developed only recently by consensus of international experts [18,19].

Mechanisms involved in the physiopathology of sarcopenia include, among others, protein synthesis, proteolysis, protein intake, malnutrition, poor blood flow to muscles, and metabolic resistance [1,20–22]. Inactivity can result in anabolic resistance and the subsequent progression from healthy aging to frailty [23,24]. This anabolic resistance can be counteracted by dietary supplementation with a metabolite of leucine, β-hydroxymethylbutyrate (β-HMB) [6,25,26,19,27], which helps to decrease proteolysis and muscle damage during exercise training, both in younger and older individuals [28–30]. A daily dose of 3 g β-HMB diminishes the level of enzymes indicating muscle damage by 20% in urine and by 20%–60% in serum. The beneficial effects of β-HMB depend on serum concentrations, which are at their maximum 2–3 h after intake. The effects of one 3 g dose per day have been demonstrated to obtain the best results [29], with no adverse effects observed in hepatic enzyme function, lipid profile, renal function, or the immune system with 3 g of β-HMB during resistance training [31]. The use of higher doses does not increase fat-free mass or muscle strength [28] .

Resistance exercise is an effective modality for aging men and women and could be considered the most effective and secure to improve muscle strength and physical performance [32,33]. The benefits of resistance training combined with dietary supplementation suggest a potential role for this approach in the management of sarcopenia [34–38].

The use of β-HMB, ingested in combination with the amino acids glutamine and arginine, has been shown to preserve lean body mass in chronic disease conditions such as cancer and acquired immune

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deficiency syndrome (AIDS) [39,40]. In healthy older adults, β- HMB supplementation preserves muscle mass over 10 days of bed rest [41]. It has been suggested that β-HMB may stimulate protein synthesis directly by the mammalian TOR (M-TOR) signalling pathway mechanism [42].

Despite progress in addressing sarcopenia, there have been very few randomized double-blind clinical trials, the evidence regarding treatment effectiveness is limited, and further research is required [6,16,27]. The effects of nutritional supplementation in acute patients, during hospitalization and the post-acute period, are of particular interest, as this population has a high risk of malnutrition and sarcopenia [19,27]. However, the effects of adding β-HMB to a program of resistance training in sarcopenic elderly patients during the post-acute period remain unknown.

Objective: The aim of this study is to assess the effects on muscle mass, strength, and physical performance of an intervention with β-HMB supplementation in addition to resistance training during the post-acute period in older adults with sarcopenia.

Hypothesis: A 12-week post-acute intervention based on β-HMB supplementation together with resistance training will improve muscle mass, strength, and physical performance in older deconditioned patients with sarcopenia after an acute process.

2. Methods

2.1. Study design

This is a prospective, randomized, double-blind, placebo-controlled study with 2 parallel groups. The study has been designed to determine the efficacy of β-HMB supplementation in addition to 12 weeks of resistance training in older patients with sarcopenia after an acute process (post-acute period), following the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) [43] guidelines (additional file 1). Eligible subjects will be randomized to one of two groups: intervention group or control group. No major changes to methods or eligibility criteria after trial commencement are planned.

2.2. Subjects

2.2.1. Inclusion criteria

Inclusion criteria will be men and women aged ≥60 years, sarcopenia diagnosis and case-finding criteria according to EWGSOP guidelines [1,6], discharge from post-acute care geriatric unit for rehabilitation treatment, ambulatory prior to the recent acute process, cognitive situation that allows understanding and following an active physical rehabilitation program (Mini-Mental Status Examination ≥21/30) [44], voluntary participation, and being able and willing to provide an informed consent.

2.3. Exclusion criteria

Potential participants will be excluded if they have active malignancy (exceptions: basal or squamous-cell skin carcinoma or carcinoma in situ of the uterine cervix), major lower limb surgery within the past 6 months (knee or hip arthroplasty), contraindication for resistance training, have regularly performed resistance exercise in the last 6 months, use of any medications interfering with the nutritional intervention (e.g., steroids, free amino acid supplements), serious clinical conditions that compromise and endanger the patient's life, and β-HMB contraindication, intolerance, or allergy [37]. Inclusion and exclusion criteria are listed in Table 1.

2.4. Settings and locations

Recruitment and initial assessment will be carried out in the post-acute care geriatric unit at Centre Forum, Parc Salut Mar, Barcelona, Spain. Sarcopenia assessment will be performed in the Exercise Assessment Laboratory, Physical Medicine and Rehabilitation Department, Hospital de l'Esperança, Parc Salut Mar. Resistance training will be prescribed and administered by a physical therapist in the outpatient rehabilitation area of the Physical Medicine and Rehabilitation Department, Hospital de l'Esperança, Parc Salut Mar. Statistical analysis will be conducted at the Hospital del Mar Medical Research Institute (IMIM). Study sites and phases are summarized in Table 2.

2.5. Interventions

Patients in the intervention group will receive daily supplementation with β-HMB during 12 weeks. Patients in the control group will receive a daily placebo during the same period of time. All patients in both groups will participate in the usual resistance training program 3 days per week during these 12 weeks.

a) Nutritional supplementation

In the intervention group, patients will receive a 3 g dose of β-HMB after each resistance training session [29,30] and will be instructed to take the β-HMB or placebo soluble powder at the same hour on non- training days (12-week total, 252 g). Three g of β-HMB are equivalent to 60 g of leucine. Patients in the control group will receive the same amount of placebo (maltodextrine, a 100% hydrosoluble product, easy to mix, that can be sprinkled with other ingredients to improve the taste or be dissolved in water) in similar posology and with similar organoleptic characteristics. Both groups will receive lime-flavoured substances, which will disguise the potentially unpleasant taste of leucine. β-HMB and placebo will be packaged in indistinguishable envelopes and boxes, with an identification code for each patient and group. Patients in the intervention program who do not participate in a minimum of 70% of the exercise program, receiving a minimum of 70% of the β-HMB dose, will be excluded from analysis.

b) Exercise program

Participants in both groups will follow the same exercise program based on a physical intervention that has been shown to be effective in our local area [45]. The program, consisting of 3 progressive resistance training sessions per week during 12 weeks, will include exercises of lower and upper limbs; training intensity will be that which allows the patient to perform 2 series of 15 repetitions separated by intervals of 3 min. Each session will begin with a 5-min warm-up, followed by 30 min of strength training (10 min, upper limbs; 20 min, lower limbs) and 5 min of cool-down. Most of the exercises will be done while seated or with the use of a chair as a support aid. Balance exercises also will be included weekly, following the American College of Sports Medicine recommendations [46], and will be supervised by a physiotherapist.

2.6. Outcome measures

Timeline, study sites, and outcome measures are summarized in Table 2. The outcome measures will be considered for the diagnosis of sarcopenia according to EWGSOP criteria [1]. The main outcome variable is change in lean body mass, in Kg, at 12-week follow-up, which will be measured by electrical impedance (Bodystat 1500, Bodystat Ltd, Isle of Man, British Isles) [47] and by percentages of the reference values for the European population [48]. For the purpose of this study, values less than 80% of the reference data will be considered decreased.

Secondary variables include changes in handgrip strength, physical performance, nutritional status including clinical biomarkers,

Table 1
Inclusion and exclusion criteria for patient participation.

Inclusion	Exclusion
≥ 60 years old	Kidney or liver severe failure
Discharge from the post-acute care geriatric unit[a]	Active malignancy[b]
Ambulatory prior to the acute process	Major lower limb surgery in the past 6 months (knee or hip arthroplasty)
MMSE ≥21/30	Contraindication for resistance training in the past 6 months
Voluntary participation and informed consent	Following a resistance training program regularly/performed regular exercise over the past 6 months
Sarcopenia diagnosis following EWGSOP criteria	Actively pursuing weight loss
	Need for oral or parenteral supplementation
	Use of any medications interfering with the nutritional intervention
	Contraindication, intolerance, or allergy to β-hydroxymethylbutyrate
	Clinical conditions that compromise and endanger the patient's life

[a] Patients are eligible for referral to this post-acute care geriatric unit if medically stable (absence of acute infection, absence of symptomatic worsening of chronic disease and absence of acute confusion) and judged able to participate in physical therapy after an acute process, as indicated by initial comprehensive geriatric assessment performed by an interdisciplinary care team.
[b] Active malignancy (exception for basal or squamous cell skin carcinoma or carcinoma in situ of the uterine cervix).
MMSE Mini-Mental State Examination; *EWGSOP* European Working Group on Sarcopenia in Older People.

and functional status. Handgrip strength, expressed in Kg and as a percentage of normal values described for the Spanish population [49], will be measured by a hand-held dynamometer (JAMAR®, Nottinghamshire, UK) as previously described [50]. Patients will perform a maximum voluntary isometric contraction of finger flexor muscles; the highest value of three reproducible manoeuvres (<15% variability between values) will be used for analysis. For the purpose of this study, values less than 80% of the reference data, adjusted for age and sex, will be considered decreased [49]. Physical performance will be assessed with gait speed in the 4-m walk test [51–54] and with the Short Physical Performance Battery [1,55,56]. Participants will be instructed to stand with both feet touching the starting line and to begin walking with usual aids (canes or walkers) at their usual pace after a verbal command. The 4-m walk test has been used extensively in previous studies, with validity and sensitivity to change confirmed in large epidemiological studies [51]. For the purpose of this analysis, low walking speed will be defined as walking slower than 0.8 m/s [52].

Nutritional status will be screened by the Mini-Nutritional Assessment Short-Form (MNA-SF), where a score of 0–7 points reflects malnutrition status, 8–11 risk of malnutrition, and 12–14 normal nutrition [57–60]. Criteria recently published by the European Society of Parenteral and Enteral Nutrition (ESPEN) will be used to determine the presence of malnutrition [61,62]: body mass index (BMI, weight/height [2]) <18.5 kg/m^2 or a combined finding of unintentional weight loss and at least one of two other measures, reduced BMI or a low fat-free mass index. Unintentional weight loss is defined as either >10% of habitual weight over an indefinite time, or >5% over 3 months. Reduced BMI is defined as <20 kg/m^2 in participants younger than 70 years and <22 kg/m^2 in older participants. Low FFMI will be considered if <15 kg/m^2 and <17 kg/m^2 in women and men, respectively [61–63]. Nutritional profile based on analysis of blood samples will include laboratory reference values of our institution for the following: total proteins and serum albumin levels, adipo-metabolic profile (low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, total cholesterol, triglycerides, glycosylated haemoglobin), renal profile (creatinine, urea and glomerular filtration rate estimated by the Chronic Kidney Disease Epidemiology Collaboration equation), homocysteine-related markers (folic acid and vitamin B12) thyroid hormones (thyroid-stimulating hormone [TSH], T4), iron profile (serum iron, ferritin, transferrin, transferrin saturation percentage), and calcium profile (serum calcium, vitamin D-25-OH).

Functional status will be assessed by the Barthel index [64] and average length of stay (in both acute and post-acute care units). The Barthel index before hospital admission will be determined by anamnesis with patients and confirmed by caregivers, medical records, and general practitioner as appropriate; during the post-acute care unit stay, Barthel index will be recorded by the interdisciplinary geriatric team. Functional changes will be calculated by rehabilitation impact indices [65–67], as follows: Absolute Functional Gain, calculated by subtracting the Barthel index at admission from the Barthel index at discharge [AFG = Barthel index at discharge—Barthel index at admission] [68,69]; Relative Functional Gain (RFG, achieved percentage of potential gain) corrected with premorbid functional status [RFG = AFG/(Barthel index premorbid—Barthel index at admission) × 100] [65,66,70]; and Rehabilitation Efficiency index (REI = AFG/length of stay) [65,66,71,72,67]. Instrumental activities of daily living will be assessed by the Lawton index [73], a geriatric assessment test widely used in sarcopenia studies [74–77].

Adherence to the resistance training program will be controlled and registered by a trained physical therapist; patients will be encouraged to record their medication intake and any of the potential adverse events in a diary. Other variables to be collected include age, sex, comorbidity assessed by the Charlson index [78,79], and hospital readmissions.

2.7. Study protocols

Upon admission to the post-acute care unit, demographic and clinical data will be registered by a member of the research group, who will also be responsible for the initial geriatric assessment, initial nutritional assessment, and screening for malnutrition (MNA-SF). Blood samples will be extracted at admission and at discharge in the post-acute care geriatric unit and at the end of the 12-week intervention by a nurse trained in the standardized protocol. Rehabilitation impact indices will be calculated by the interdisciplinary team at discharge from post-acute care. Patients who are eligible for inclusion and do not meet any exclusion criteria will be referred for baseline muscle function assessment after discharge from post-acute care. The study outcomes of muscle function, rehabilitation impact indices, and malnutrition will be assessed at baseline, at weeks 4 and 12, and at 1-year follow-up. The PSSMAR Study Flow diagram is shown in Fig. 1. In summary, the initial demographic, clinical, geriatric, and nutritional assessment will be completed and recorded in the post-acute care unit before the intervention begins. Sarcopenia and malnutrition will be assessed using ESPEN criteria and recorded before the intervention begins, at 4-week follow-up, at the end of the 12-week intervention, and at 1-year follow-up.

2.8. Randomization and blinding

Participant randomization to study groups will be performed independently by the hospital pharmacist, blinded to patient iden-

Table 2
Variables for included patients, assessment scales, timeline and study settings.

	Baseline		4-week follow-up	12-week follow-up (end-point)	1-year follow-up
Study settings	Post-acute care unit, Geriatric Dept.	Muscle Assessment Laboratory, Rehabilitation Dept.	Muscle Assessment Laboratory, Rehabilitation Dept.	Muscle Assessment Laboratory, Rehabilitation Dept.	Muscle Assessment Laboratory, Rehabilitation Dept.
- **SARCOPENIA**	– – –	x	x	x	x
OUTCOME		x	x	x	x
VARIABLES		x	x	x	x
- **Primary outcome: Change in muscle mass**					
- **Secondary outcome variables:**					
- Muscle strength					
- Physical performance (gait speed)					
Nutritional assessment	x	–	–	–	x
	–	x	x	x	x
MNA-SF	x	–	–	x	x
Malnutrition, ESPEN criteria					
Blood tests					
- **Functional status**	x	– – – – –	x	x	x
- Instrumental	x		– – –	– – –	– – –
activities of daily	x		x	x	x
living (Lawton index)	x				
- Basic activities of daily living (Barthel index):	–				
- Prior to the acute process					
- At admission to post-acute care					
- At discharge from post-acute care					
- During follow-up					
Rehabilitation impact indices	x	x	x	x	x
	x	x	x	x	x
Absolute Functional Gain (AFG)	x	x	x	x	x
Relative Functional Gain (RFG)					
Rehabilitation Efficiency index (REI)					
Clinical incidents, hospital readmissions	x	x	x	x	x
Adherence to supplementation	–	x	x	x	–
Adherence to resistance training	–	–	x	x	–
Adverse events	–	–	x	x	x

[a]Statistical analysis will be performed at Hospital del Mar Medical Research Institute (IMIM).
The sign "X" means test or probe performed and registered; the sign "-"means test not performed.
AFG = Barthel index at discharge − Barthel index at admission (see text).
RFG = [(Barthel index at discharge − Barthel index at admission)/(Barthel index-premorbid − Barthel index at admission) x 100] (see text).
REI = [(Barthel index at discharge − Barthel index at admission)/length of stay] (see text).
MMSE Mini-Mental State examination; *MNA-SF* Mini-Nutritional Assessment Short-form; *ESPEN* European Society of Parenteral and Enteral Nutrition.

tity. When a new patient meets the eligibility criteria, a researcher will inform the pharmacist, who will assign the anonymized patient record to one of the study groups using a random number generator program designed by the Informatics Department. Doses of β-HMB and placebo will be packaged indistinguishably. Patients and the interdisciplinary researchers will be blinded to study group assignments over the entire study period and until data analysis is complete. The interdisciplinary team and the patients will be instructed not to analyse or compare the contents of the daily doses or in any way seek to identify them. After data analysis has been completed, results will be released to all patients and to participating clinicians and researchers.

2.9. Statistical analysis

Quantitative variables will be presented as mean and standard deviation (SD), unless otherwise stated. Univariate analysis will be performed using X^2, Fisher exact, Student t, or Mann-Whitney *U* tests, depending on the variables analysed. Treatment effect will be analysed by changes in muscle mass, muscle strength, and gait

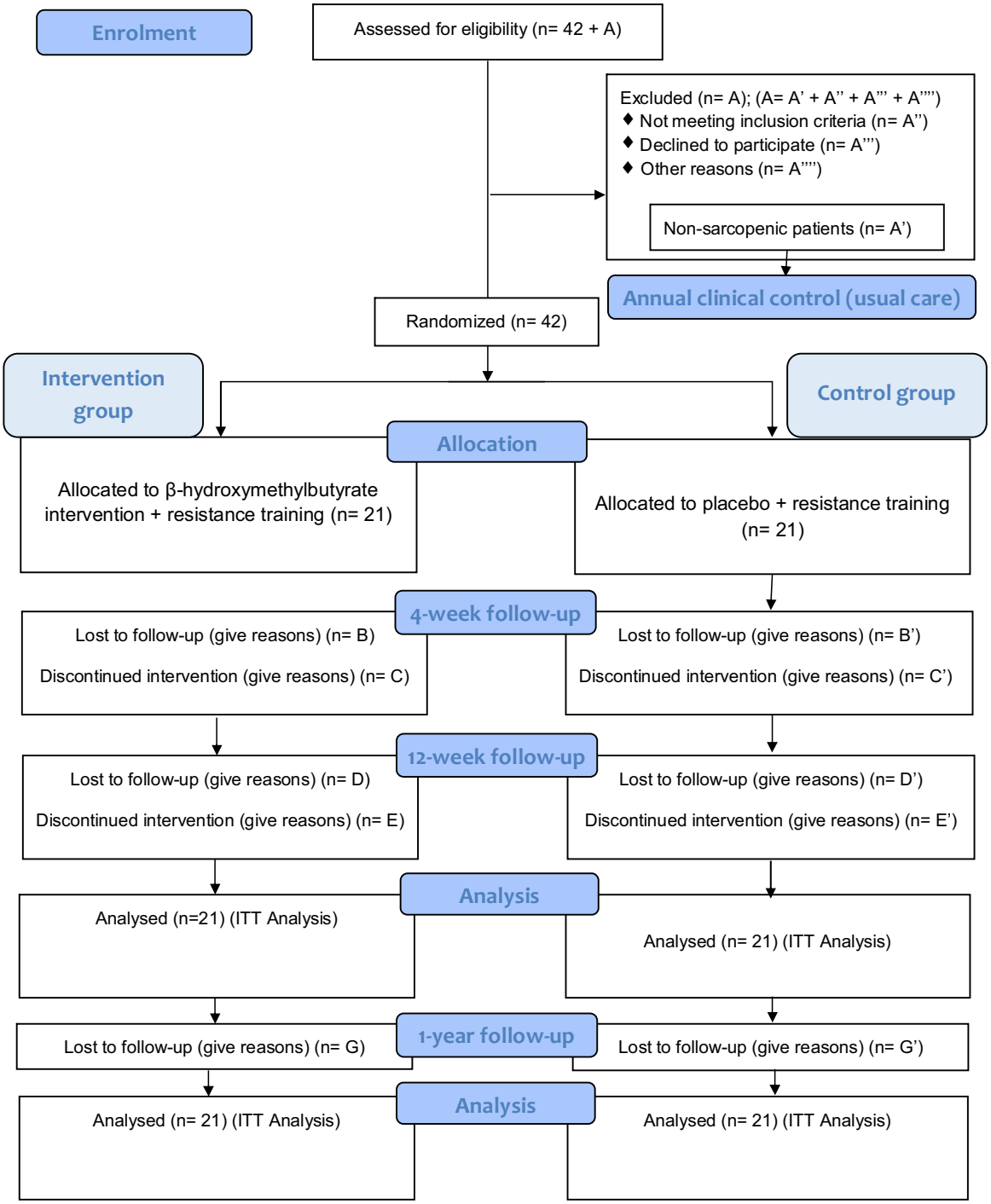

Fig. 1. The PSSMAR Study Flow Diagram.

speed pre- and post-intervention. Changes during follow-up will be assessed by analysis of variance using mixed repeated measures and a one-factor design for the analysis of values over time. Effect size will be reported using Cohen term d index. Number of patients needed to treat (NNT) to counteract one patient affected by sarcopenia over a 12-week follow-up will be calculated. The study outcomes will be analysed by intention-to-treat and the results over the follow-up period will be reported. Potential scenarios of non-compliance and non-adherence with respect to the intervention and of patients receiving the wrong product or concomitant treatments will be considered in the interpretation of results. Additional univariate analyses (e.g., subgroup and adjusted analyses) according to sex, age, and malnutrition as defined by the ESPEN consensus will be performed. No missing data imputation will be performed, as the sample size has been previously adjusted. Sample size calculation incorporated a maximum 10% loss to follow-up. The level of significance will be set at $p \leq 0.05$. Data analysis will be performed using IBM SPSS Statistics v.21.

2.10. Estimation of sample size

Sample size has been calculated in terms of the PSSMAR Study objective: to identify significant differences in sarcopenia components (changes in muscle mass, strength, and physical performance) in older patients with sarcopenia after an acute process (post-acute period). Accepting an alpha risk of 0.05 and a beta risk of 0.2 in two-sided testing, we estimated that 38 participants (190 in each group, intervention and control) are necessary to recognize as statistically significant an increase of 1 (standard deviation, 1.2) Kg in fat-free mass. The sample size was overestimated to allow potential losses of 10%, requiring a final sample of 42 patients (21 in each group); this relatively low percentage of loss reflects the expected adherence to usual care and follow-up in our Geriatric and Physical Medicine and Rehabilitation outpatient clinics for the duration of the study.

2.11. Ethics

National and international research ethics guidelines will be followed, including the Deontological Code of Ethics, Declaration of Helsinki (Fortaleza, 2013), and Spain's confidentiality law concerning personal data (*Ley Orgánica* 15/1999, 13 December, *Protección de Datos de Carácter Personal*). Detailed, understandable oral and written information will be provided to patients and family members, and informed consent to participate will be signed by all participants. In patients with dementia, written informed consent will be obtained from the main caregiver. The PSSMAR Study protocol and the informed consent process have been reviewed and approved by the Clinical Ethics Committee of the *Institut Hospital del Mar díInvestigacions Mèdiques*, Barcelona, Spain (*Comité Etico de Investigación Clínica Parc de Salut Mar*: reference number 2015/6288/I). Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines will be followed [43] (Additional file 1). This trial was registered at www.clinicaltrials.gov with code NCT02679742 on February 9, 2016.

3. Discussion

This is a protocol for a randomized controlled trial that is in the process of development; no data are yet available. The intervention is focused on patients already affected by sarcopenia. Positive results are anticipated, although it has been suggested that the response of skeletal muscle to protein supplementation depends on the status of skeletal muscle mass; in the case of sarcopenic older adults, they will probably respond less to the anabolic stimulus compared to nonsarcopenic or healthy adults [41,80,81]. In some studies, this limitation is partially addressed by categorizing sarcopenic patients [37]; a nutritional intervention with high protein-enriched diet (ricotta cheese) obtained positive results and good stimulus response in community-dwelling, nonsarcopenic patients [81]; however, anabolic resistance obtained nonsignificant results in a similar population of patients with sarcopenia [80]. In our study, diabetes and "older old" age will not be exclusion criteria, in contrast to other published results [41]. In addition, patients with renal failure will not be excluded; β-HMB supplementation is not contraindicated in renal failure, as protein supplementation could be [37].

One of the main limitations of all previous studies has been the high rate of withdrawal from treatment; in our study, we will try to address this issue in three ways. First, our patients will be participating in the usual clinical follow-up after hospitalization in both the Geriatrics and the Physical Medicine and Rehabilitation departments, which makes it less likely that they will drop out. Second, we will administer soluble products. Other studies provided nutritional supplementation in tablet format; in order to administer 3 g of β-HMB, up to 20 pills daily would be necessary. Of course, this would be impractical and could have promoted study withdrawals [27]. Third, a lime-flavoured and scented soluble product will be administered to both groups, which will address the organoleptic characteristics of leucine.

The β-HMB and placebo will be administered after each exercise session because this sequence allows greater use of dietary protein-derived amino acid for de novo muscle protein synthesis, as has been shown in both young and elderly men [82]. The position statement of the International Society of Sports Nutrition (ISSN) on the use of β-HMB as a nutritional supplement to enhance recovery concluded that it can attenuate exercise-induced skeletal muscle damage in trained and untrained populations [83]. Mechanisms of action include inhibition of proteolysis and increased protein synthesis. The ISSN also reports that chronic consumption of β-HMB is safe in both young and elderly populations. A daily β- HMB dose of 38 mg/kg enhances skeletal muscle hypertrophy, strength, and power in both untrained and trained populations when the appropriate exercise prescription is utilized. In sedentary elderly populations, increased lean body mass and physical performance were observed, and there was a trend toward greater decreases in fat mass when β-HMB was taken in conjunction with a structured exercise program.

Our results will highlight the response to the intervention in older deconditioned patients participating in a rehabilitation program after an acute process, which could affect the generalizability of our results to other populations. Nevertheless, considering the high comorbidity and deconditioning in our post-acute care unit's mostly aged, functionally limited, frail patient population, the probability of a high impact of the anabolic resistance component in this sample should provide evidence of the potential applicability of trial results to similar populations.

Separate lines of research have shown that resistance training 2 to 3 times a week improves physical function and reduces functional limitations, disability, and muscle weakness in older people [32] and that β-HMB supplementation decreases proteolysis and muscle damage [6,25,26][28–30]. To our knowledge, this will be the first randomized controlled trial to combine β-HMB supplementation and resistance training to counteract sarcopenia in older adults during the post-acute period.

3.1. Repercussions of the PSSMAR study

The lack of randomized controlled trials on sarcopenia treatment during the post-acute period and the few studies available on the effectiveness of β-HMB in sarcopenic patients point to the potential scientific contributions of our study. Interventions to manage and treat sarcopenia are urgently needed [1,6,15,17,21,16], and even if no significant effects or changes are observed, the study is expected to increase knowledge about effective sarcopenia management and treatment during the post-acute period.

***Author**'s contributions*

DS-R and EM participated in the design of the study and drafted the manuscript. NR-M and JMM conceived of the study and helped to draft the manuscript. SM participated in the design of the study and performed the statistical analysis. OV-I, RM, and FE participated in study design and coordination. All authors read and approved the final manuscript.

Conflict of interest

None declared.

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Provenance and peer review

This article has been peer reviewed.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.maturitas.2016.08.019.

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