Recruitment strategies for sarcopenia trials: lessons from the LACE randomized controlled trial

Miles D. Witham[1,2]* iD, Marcus Achison[3], Terry J. Aspray[1], Alison Avenell[4], Margaret M. Band[3], Peter T. Donnan[5], Jacob George[2], Adrian Hapca[3], Cheryl Hume[3], Paul Kemp[6], Kristina Pilvinyte[3], Avan A. Sayer[1], Karen T. Smith[3], Allan D. Struthers[2] & Deepa Sumukadas[7]

[1]AGE Research Group, NIHR Newcastle Biomedical Research Centre, Newcastle University, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle, UK; [2]Division of Molecular and Clinical Medicine, School of Medicine, University of Dundee, Dundee, UK; [3]Tayside Clinical Trials Unit, University of Dundee, Dundee, UK; [4]Health Services Research Unit, University of Aberdeen, Aberdeen, UK; [5]Division of Population Health and Genomics, School of Medicine, University of Dundee, Dundee, UK; [6]Cardiovascular and Respiratory Interface Section, National Heart and Lung Institute, Imperial College London, London, UK; [7]Department of Medicine for the Elderly, NHS Tayside, Dundee, UK

Abstract

Background   Sarcopenia is rarely diagnosed and is not recorded electronically in routine clinical care, posing challenges to trial recruitment. We describe the performance of four components of a strategy to efficiently recruit participants with sarcopenia to a trial of perindopril and/or leucine for sarcopenia: primary care vs. hospital recruitment, a comparison of central vs. local telephone pre-screening, performance of a questionnaire on physical function conducted as part of the pre-screening telephone call, and performance of bioimpedance measurement to identify low muscle mass.

Methods   Hospital-based recruitment took place through inpatient and outpatient geriatric medicine services. Local research nurses reviewed medical notes and approached potentially eligible patients. Primary care recruitment reviewed primary care lists from collaborating practices, sending mailshots to patients aged 70 and over who were not taking angiotensin-converting enzyme inhibitors. Telephone pre-screening was conducted either by research nurses at each site or centrally by Tayside Clinical Trials Unit. The 10-point SARC-F questionnaire was used for pre-screening. De-identified recruitment information was held on a central electronic tracking system and analysed using SPSS. Bioimpedance was measured using the Akern BIA 101 system, with the Sergi equation used to estimate lean mass.

Results   Fourteen UK sites recruited to the trial. The 1202 sets of notes in hospital-based care were reviewed at these sites; 7 participants (0.6% of total notes screened) were randomized. From primary care, 13 808 invitations were sent; 138 (1.0% of total invited) were randomized. 633/2987 primary care respondents were pre-screened centrally; the mean number of calls per respondent was 2.3. For 10 sites where central and local pre-screening could be compared, the conversion rate from pre-screening to randomization was 18/588 (3.1%) for centralized calls, compared with 73/1814 (4.0%) for local pre-screening calls ($P = 0.29$). A weak relationship was seen between higher (worse) SARC-F score at screening and lower likelihood of progression to randomization ($r = -0.08$, $P = 0.03$). Muscle mass estimates generated using the Sergi equation were systematically biased, and a recalibrated equation for bioimpedance-estimated muscle mass was derived.

Conclusions   Primary care recruitment led to higher response rates and overall numbers randomized than hospital-based recruitment. Centralized pre-screening saved local research nurses' time but did not improve conversion to randomization. SARC-F did not help to target screening activity in this sarcopenia trial, and a recalibration of the equation for estimating muscle mass from bioimpedance measures may improve accuracy of the screening process.

Keywords   Sarcopenia; Randomized controlled trial; Screening; Recruitment; Body composition

Introduction

Sarcopenia is the loss of muscle strength and mass that commonly accompanies advancing age.[1] It is a major health issue thought to affect millions of older people, with a prevalence of between 5% and 10% in those aged 65 and over in the UK according to the 2010 European Working Group on Sarcopenia (EWGSOP) criteria.[2] Sarcopenia is associated with incident disability, falls, hospital admission and longer length of stay, and earlier death.[3–5] The cost of sarcopenia in the UK has been estimated at 2 billion pounds per annum.[6] Existing evidence supports resistance exercise training as an effective intervention,[7] but not all older people are willing or able to undertake such training. New therapies, both pharmacological and non-pharmacological, are therefore needed to treat and prevent this condition.[8]

Sarcopenia is a relatively newly described condition, and as such, it presents a number of challenges when attempting to conduct randomized controlled trials. A diagnosis of confirmed sarcopenia requires both measurement of muscle strength and muscle mass,[1] neither of which are routinely collected in clinical practice. Until recently, no International Classification of Diseases-10 code was available for sarcopenia,[9] and the diagnosis is still not routinely made[10] or recorded in either paper or electronic clinical records. Although older people are familiar with the concept of muscle weakness, few will have heard of the term sarcopenia, and fewer still will recognize that the diagnosis applies to them. Finding and recruiting participants to trials for sarcopenia is therefore more challenging than for conditions with well-established public awareness, diagnostic pathways, and coding systems.

In order to better understand how to find and recruit the target populations for sarcopenia trials, studies are required that evaluate different channels of recruitment, different screening methods, and different ways to efficiently evaluate both muscle strength and muscle mass as part of the screening process. The aim of the work reported later was therefore to better understand how to efficiently recruit participants to future trials of sarcopenia therapies, using data from the multicentre Leucine and Angiotensin Converting Enzyme inhibitors for sarcopenia (LACE) randomized controlled sarcopenia trial.[11] We assessed the performance of four components of our screening pathway: (a) primary care vs. hospital-based care recruitment methods; (b) central vs. local telephone pre-screening; (c) use of a simple telephone physical function questionnaire as part of pre-screening; and (d) ability of bioimpedance measurement to identify those with low muscle mass at the screening visit. We also evaluated whether the recruitment pathway was successful in recruiting a trial population fulfilling the definition of sarcopenia from different guidelines.

Methods

Trial description

The LACE trial was a multicentre, parallel-group, 2 × 2 factorial, double-blind, placebo controlled, randomized trial testing the effect of perindopril and/or leucine in older people with sarcopenia. LACE sought to enrol patients aged 70 and over with sarcopenia, defined as a low muscle mass and low muscle strength (either low grip strength or low gait speed). Exclusion criteria included the current use of, or contraindications to, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers, heart failure, severe chronic obstructive pulmonary disease, other skeletal myopathies, or advanced chronic kidney disease. Participants received perindopril or placebo starting at 2 mg and titrated up to 4 mg once daily after 2 weeks, if tolerated. Participants also received 2.5 g three times a day of leucine or placebo powder with food. All interventions were given for 12 months. The primary outcome for the trial was the between-group difference in the Short Physical Performance Battery[12] measured over the course of the trial; secondary endpoints included muscle mass measured by dual X-ray absorptiometry (DXA) scanning, handgrip strength, quadriceps strength, 6 min walk distance, activities of daily living measured by the Nottingham Extended Activities of Daily Living Scale,[13] quality of life measured with the EQ 5D-3L tool, and falls measured by monthly falls diaries. Blood samples were taken for safety monitoring and studies into biomarkers and mechanisms. The full protocol has been published previously.[11] The trial was funded by the NIHR/MRC Efficacy and Mechanisms Evaluation funding stream (grant 13/53/03). The trial was registered online (www.isrctn.com; ISRCTN90094835). Approval for the study was given by the East of Scotland Research Ethics Committee (reference 14/ES/1099), and by the UK Medicines and Healthcare products Regulatory Agency (EudraCT number 2014-003455-61); the trial was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The sponsor was Tayside Academic Sciences Centre.

Recruitment

The recruitment strategy for the LACE trial used several components. Groups likely to contain a higher than average proportion of people with sarcopenia were identified from primary care or hospital-based care geriatric medicine services. Next, telephone pre-screening was used to exclude those less likely to have sarcopenia, and then finally, in-person screening was conducted to test muscle strength and estimate muscle mass. Recruitment took place at 14 sites across the UK. The recruitment pathway for the LACE trial is show in *Figure* 1 along with the aspects of the pathways assessed in this analysis.

For primary care recruitment, GP practices within easy reach of an hospital-based care centre were approached. Those who agreed to collaborate with participant

Figure 1 Flowchart of recruitment in the Leucine and Angiotensin Converting Enzyme inhibitors for sarcopenia (LACE) trial and four components (in green) of screening pathway assessed. DXA, dual X-ray absorptiometry.
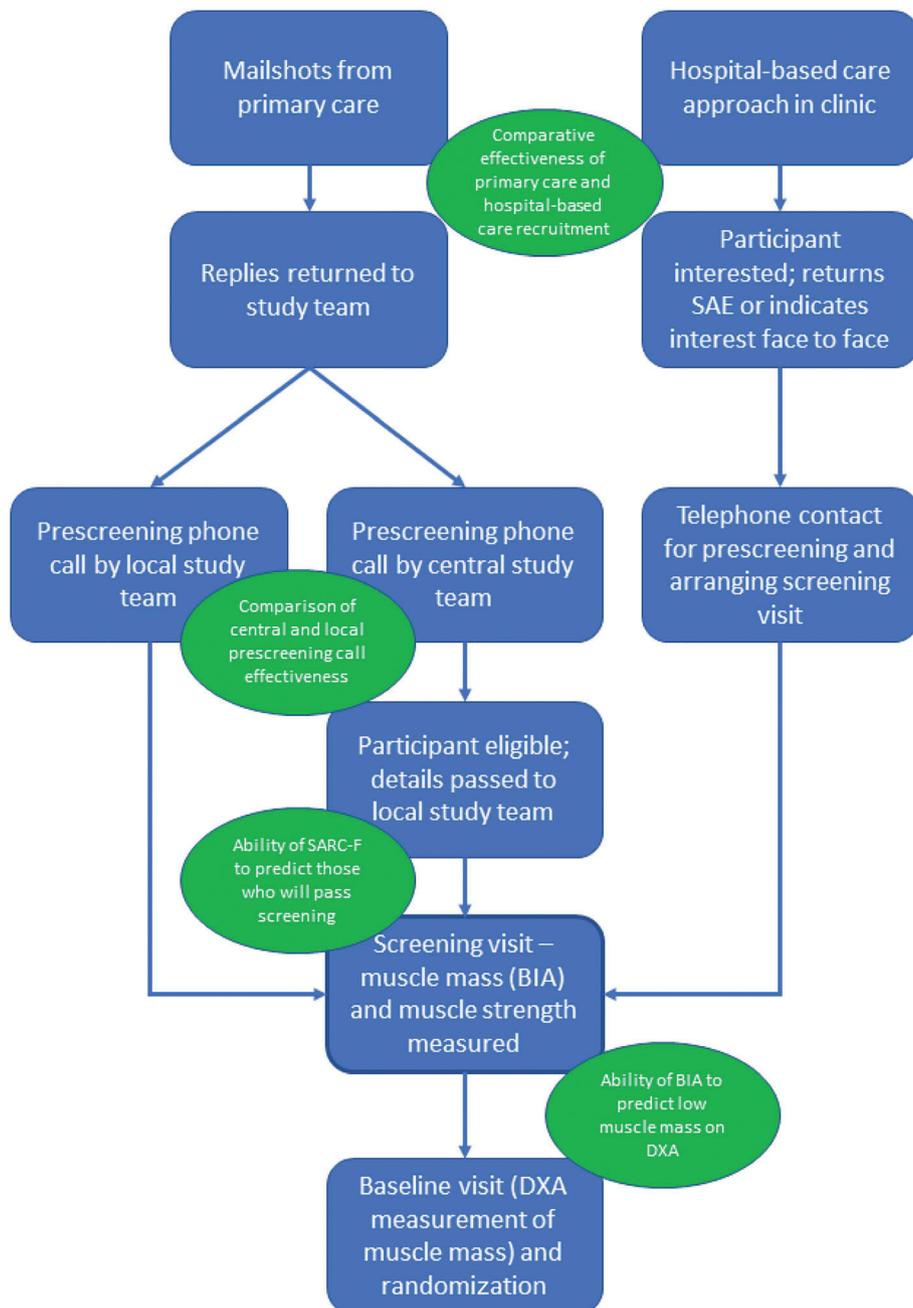
identification reviewed their practice lists to identify patients aged 70 and over; not taking ACE inhibitors; and without heart failure, chronic obstructive pulmonary disease, aortic stenosis, chronic kidney disease Stages 4 or 5, or thyrotoxicosis. Potentially eligible participants were sent a brief (two pages) information sheet with reply slip and paid-for return envelope. Participants who returned the reply slip indicating interest in the trial were then contacted by telephone for pre-screening. Pre-screening telephone calls were conducted by local research nurses for some centres, but for centres lacking the staff capacity to do this, telephone pre-screening was conducted centrally by non-clinical staff in the Tayside Clinical Trials Unit.

Hospital-based recruitment was conducted via inpatient and outpatient geriatric medicine services at each site. Local research nurses reviewed medical notes and then approached potentially eligible patients face-to-face or via letter if time was not available for an approach during clinic.

Pre-screening process

At pre-screening (performed by telephone for most participants, but face-to-face in clinic for some participants in hospital-based care), questions regarding potential exclusion criteria were asked, along with the 10-point SARC-F questionnaire.[14] This questionnaire sums results from five simple questions about everyday function and has been proposed as a screening score to identify patients with sarcopenia. The optimal cut-off for identifying patients with sarcopenia in a UK population is not known. The protocol therefore allowed the threshold score for the SARC-F to be changed during the trial. At the start of the trial, a SARC-F score of 4 or more was required to proceed from pre-screening to a screening visit. This was adjusted after 6 months of recruitment to a threshold of three points to increase the number of participants proceeding to a screening visit. Participants passing the pre-screening process were sent the full information sheet and then invited to attend a face-to-face screening visit.

Screening visit

At the screening visit, muscle mass was measured using the Akern 101 bioimpedance analyser (Akern, Italy). Initially, the Janssen equation[15] was used to derive whole-body lean mass from the bioimpedance measures. After 6 months of recruitment, a comprehensive review of the screening criteria was undertaken in light of slow recruitment and very high (>95%) rates of failed screening visits (20 screening visits but only one participant randomized). After consideration of new information about the accuracy and population specificity of different equations for estimating muscle mass by bioimpedance, we changed to using the Sergi equation[16] to estimate appendicular lean mass. Values from bioimpedance analysis (BIA) (reactance and resistance) are converted by the Sergi equation to predict appendicular skeletal muscle mass (ASMM) index (ASMM/height^2). The Sergi equation was derived from bioimpedance measures using the same BIA system as used for screening in the LACE trial (the Akern BIA 101), compared with DXA appendicular muscle mass; this is in contrast to the Janssen equation that was calibrated against whole-body skeletal muscle measurements from magnetic resonance imaging scanning. The Sergi equation was derived in an older, white, European (but non-UK) population, and independent validation data are lacking on how well the equation can predict DXA-measured muscle mass and hence its utility as a screening tool in sarcopenia trials. In addition, we reviewed muscle mass thresholds for trial inclusion, driven by high screen fail rates, particularly in those with obesity and muscle weakness. We therefore moved from a whole-body lean mass threshold stratified by sex (<13 kg for women, <20.5 kg for men) to appendicular lean mass thresholds stratified by sex and body mass index (BMI), with cutpoints derived from data in the UK Biobank study[17] (Supporting Information, *Table* S1). This change was made to ensure representation of patients with both obesity and sarcopenia, in line with new guidance from the USA.[18]

Muscle strength was measured using handgrip dynamometry (the maximum value of two attempts on each hand was taken). Gait speed was measured over a 4 m course. To be eligible for entry to the trial, participants had to have muscle mass below the sex and BMI-specific threshold, and either a gait speed of <0.8 m/s or a maximum handgrip strength below 20 kg (women) or below 30 kg (men).

Baseline visit

At the baseline visit, baseline data for the primary and secondary outcomes were collected, including appendicular muscle mass measured using whole-body DXA scanning. Scanning was conducted using Hologic or Lunar DXA scanners, using proprietary software. Each scanner was regularly calibrated using a site-specific phantom, but cross-scanner calibration was not performed. DXA for muscle mass has previously been shown to have good repeatability and strong correlation with magnetic resonance imaging-measured muscle mass.[19]

Data processing and analysis

De-identified recruitment information was held on a central electronic tracking system designed and hosted by the University of Dundee Health Informatics Centre. De-identified screening visit and baseline trial visit data were entered by

local research nurses onto OpenClinica (OpenClinica LLC, Waltham, MA, USA); after data cleaning and verification by the Tayside CTU team, screening and baseline data were extracted as flat files without any indication of treatment allocation. All analyses were performed using SPSS v24 (IBM, New York, USA). A two-sided P value of <0.05 was taken as significant for all analyses. Descriptive data were generated for all participants who attended a screening visit and for all participants who underwent baseline visit measurements including DXA scanning. Categorical variables were compared using Pearson's χ^2 test. Correlations were tested using Spearman's rho.

Estimates of ASMM index derived via the Sergi equation at the screening visit were compared with ASMM index measured by DXA at the baseline visit. Bland–Altman plots were generated to compare the difference in estimated and measured ASMM index across the measurement range. Multivariable linear regression using forced entry of variables was used to generate a new study-specific equation relating bioimpedance outputs to DXA-measured ASMM, which was then calibrated to the study population. Finally, as a test of how successful the overall screening process was in identifying the target group for the trial (i.e. those fulfilling the definition of sarcopenia), we calculated the proportion of patients randomized who met the EWGSOP 2010 definition,[20] which formed the original basis for inclusion in LACE. Given recent changes in consensus definitions of sarcopenia since the LACE trial was planned, we also calculated the proportion who met two other definitions—from the updated 2019 EWGSOP guidelines,[21] and the Foundation for the National Institutes of Health consensus definition originating in the USA.[18]

Results

A total of 320 participants attended a screening visit and 145 participants were randomized into the trial between June 2016 and December 2018. Table 1 shows the characteristics of those attending the screening visit and those who were randomized. Of the 2897 individuals who underwent telephone pre-screening, 1746 had a SARC-F score of <3 and were thus ineligible; 241 had other reasons for ineligibility (excessive weight loss, presence of a pacemaker or defibrillator, already taking ACE inhibitors, angiotensin receptor blockers or other prohibited medications, undertaking physiotherapy or unable to walk without human assistance), 255 declined to proceed after discussing the trial by telephone, a further 217 declined to proceed after reading the full trial information, and 118 did not proceed to screening due to trial recruitment closing. Of the 320 attending a screening visit, 129 did not proceed due to failure to meet the screening criteria for sarcopenia.

## Primary care vs. hospital-based screening

Figure 2 shows a comparison of flow through the primary care and hospital-based screening pathways. The proportion of participants randomized from those approached was not significantly higher in primary care than in hospital-based care (138/13808 (1.0%) vs. 7/1202 (0.6%); P = 0.16) but the volume of participants able to be approached and randomized through the primary care pathway was much higher.

Table 1 Characteristics of participants attending screening visit and baseline visit for muscle mass measurement

Characteristic		Attended screening visit (n = 320)		Randomized with valid baseline DXA data (n = 144)
Mean age (years) (SD)		77.7 (5.6)		78.8 (6.0)
Female sex (%)		190 (59)		78 (54)
Mean handgrip strength (kg) (SD)	Men (n = 123)	24.8 (7.0)	Men (n = 66)	23.1 (5.9)
	Women (n = 151)	14.3 (4.4)	Women (n = 78)	13.7 (3.9)
Mean BIA muscle mass[a] (kg/m^2) (SD)	Men (n = 130)	7.49 (1.37)	Men (n = 66)	7.64 (1.34)
	Women (n = 188)	5.79 (1.82)	Women (n = 78)	5.17 (1.17)
Mean SPPB (SD) (n = 282)		6.8 (2.7)		7.0 (2.3)
Mean gait speed (m/s) (SD) (n = 271)		0.76 (0.25)		0.75 (0.23)
Median chair stand time (s) [IQR]		21 [16–28]		22 [17–28]
Proportion (%) with low grip strength (<30 kg M, <20 kg F)		231/274 (84)		135/144 (94)
Proportion (%) with low grip strength (<27 kg M, <16 kg F)		174/274 (64)		104/144 (72)
Proportion (%) with low muscle mass index (BIA) (<7.26 kg/m^2 M, <5.45 kg/m^2 F)		143/318 (45)		73/144 (51)
Low BIA muscle mass on BMI stratum (%)	<18.5 kg/m^2	7/7 (100)		4/4 (100)
	18.5–24.9 kg/m^2	68/81 (84)		29/34 (85)
	25.0–29.9 kg/m^2	100/132 (76)		58/74 (78)
	≥30 kg/m^2	49/98 (50)		18/32 (56)
	Total	224/318 (70)		109/144 (76)

BIA, bioimpedance analysis; BMI, body mass index; DXA, dual X-ray absorptiometry; IQR, interquartile range; SPPB: Short Physical Performance Battery.
[a]ASMM/height^2 estimated using Sergi equation.

Figure 2 Primary care vs. hospital-based care screening yield.

*Primary care*   *Hospital-based care*
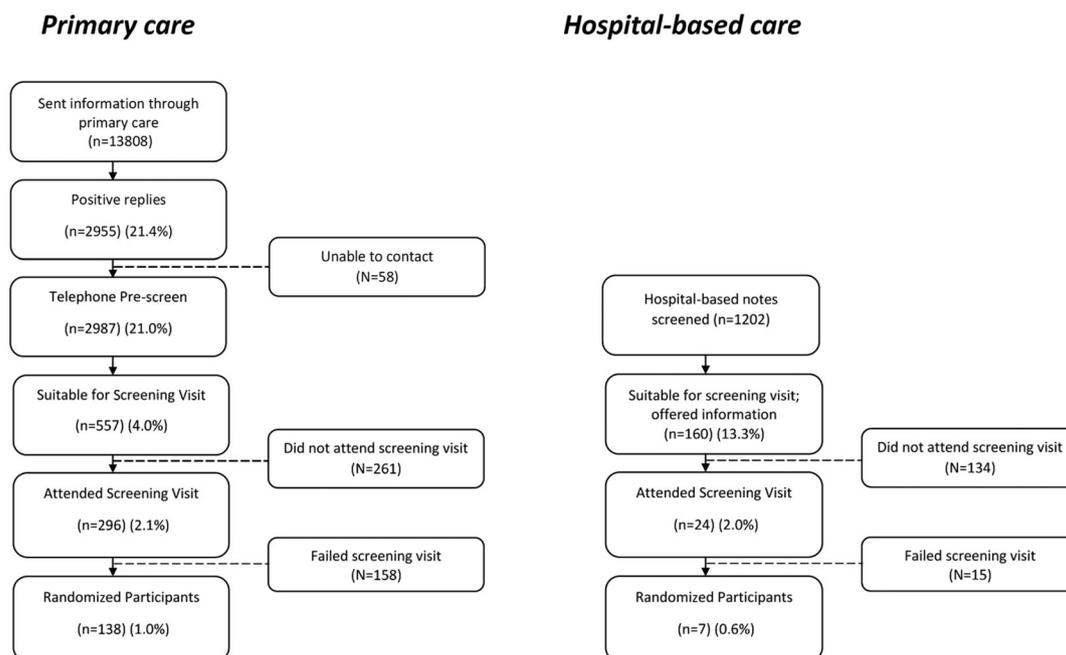
Centralized pre-screening telephone calls

A total of 633/2897 primary care respondents were pre-screened centrally; the mean number of calls per respondent was 2.3. More than one attempt was required to make contact with some respondents as telephone calls went unanswered. At 10 sites, pre-screening was conducted partly by the local study team and partly by central pre-screening to augment the capacity of the local study team to respond to expressions of interest in the study in a timely manner. At these 10 sites, the conversion rate from pre-screening to randomization was 18/588 (3.1%) for centralized calls, compared with 73/1814 (4.0%) for local pre-screening calls ($P = 0.29$).

SARC-F performance as a pre-screening tool

A weak relationship was seen between higher (worse) SARC-F score at pre-screening and lower likelihood of progression to randomization ($r = -0.08$, $P = 0.03$); the association was stronger in men ($r = -0.13$, $P = 0.04$) than in women ($r = -0.05$, $P = 0.29$). Details of conversion rates by SARC-F score are given in *Figure* 3, and a breakdown by sex is shown in *Figure* S1A and S1B. Participants with a SARC-F score of less than 3 did not progress to screening; thus, we were unable to assess the relationship between SARC-F scores of 0 to 2 and likelihood of progression to randomization.

The SARC-F score at pre-screening showed a modest association with handgrip strength for both men ($r = -0.29$,

Figure 3 Conversion rate to screening visits and randomization by SARC-F score at pre-screening.
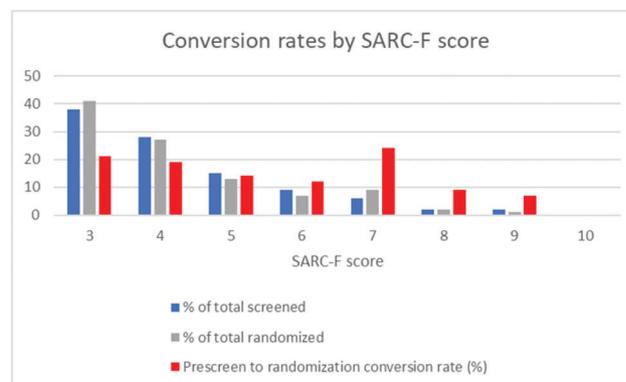
$P < 0.001$) and women ($r = -0.17$, $P = 0.03$). A similar correlation ($r = -0.28$, $P < 0.001$) was seen between SARC-F score and 4 m gait speed at screening. A significant correlation was found between SARC-F and ASMM index measured by bioimpedance for men ($r = -0.19$, $P = 0.04$) but not for women ($r = 0.05$, $P = 0.47$). *Figure* S2A to S2D shows the relationship between SARC-F score at pre-screening and the proportion of participants with low grip strength, low gait speed, and low muscle mass measured by bioimpedance. Even with a SARC-F score of 3, the majority of participants had low muscle strength (as defined by the 2010 and the

2019 EWGSOP thresholds); the proportion with low muscle mass was little different in those with a SARC-F score of 3 or 4 than for those with higher SARC-F scores.

Performance of bioimpedance analysis as a screening test for low muscle mass on dual X-ray absorptiometry

A total of 144 participants underwent DXA at the baseline visit and had usable data. Baseline details are shown for these 144 participants in *Table* 1. *Figure* S3 shows the correlation (r = 0.79, $P < 0.001$) between DXA-measured baseline ASMM index and ASMM index estimated via the Sergi equation from screening BIA data. *Figure* 4 shows the Bland–Altman plot comparing estimated and measured ASMM index; while overall agreement was good, with BIA underestimating ASMM index by only 0.17 kg (SD 1.11), estimates were systematically biased, with greater underestimation of ASMM index at lower ASMM index, and overestimation at higher ASMM indices. The overall bias amounted to 0.5 kg of underestimation for every 1 kg lower ASMM index.

An alternative equation was derived to fit data from the LACE trial, using the results of a linear regression analysis (shown in *Table* S2) with further adjustment to calibrate the new equation with the observed DXA results. The final equation to predict ASMM index as measured by DXA from bioimpedance was:

$$
\begin{aligned}
1.15 \times (10.251 \ & - \ [\text{Age in years} \times 0.011] \\
& + \ [\text{Sex} = 1 \text{ for male}, 0 \text{ for female}] \\
& - \ [\text{Rz} \times 0.003] + [\text{Xc} \times 0.011] \\
& - \ [\text{Height in cm} \times 0.031] \\
& + \ [\text{Weight in kg} \times 0.044]) - 1.275
\end{aligned}
$$

Rz, resistance. Xc, reactance.

Figure S4 shows that Bland–Altman plot comparing this cohort-specific estimate with the measured DXA appendicular skeletal muscle mass index; the mean difference between estimated and measured appendicular skeletal muscle mass index was 0 (SD 0.5) kg/m^2, and no systematic bias was evident.

Proportion of randomized participants meeting different definitions of sarcopenia

Table 2 shows the percentage of randomized participants in the LACE trial with DXA-measured baseline muscle mass that met four different definitions of sarcopenia. The proportion of included women with sarcopenia was lower than the proportion for men for all definitions. Only one-third of included participants met the original 2010 EWGSOP definition, but the number meeting a definition of 'probable sarcopenia'

Figure 4 Bland–Altman plot for agreement between appendicular skeletal muscle mass estimated by bioimpedance (Sergi equation) and measured by DXA at baseline (*n* = 144). ASMMI, appendicular skeletal muscle mass index; BIA, bioimpedance analysis; DXA, dual X-ray absorptiometry. Graph shows fit line with 95% confidence interval, together with mean difference and 95% confidence interval for difference.
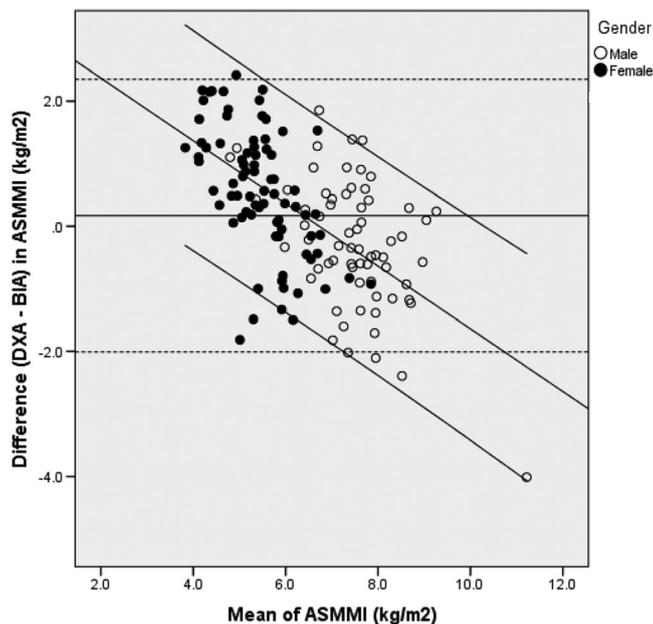
Table 2 Proportion of randomized participants meeting different sarcopenia criteria

	EWGSOP 2010[a]	EWGSOP 2019 low grip[b]	EWGSOP 2019 confirmed sarcopenia[c]	FNIH[d]
Men (%)	30/66 (45)	50/66 (76)	15/66 (23)	27/66 (41)
Women (%)	24/78 (31)	54/78 (69)	17/78 (22)	22/78 (28)
All (%)	54/144 (38)	104/144 (72)	32/144 (22)	49/144 (34)

EWGSOP, European Working Group on Sarcopenia; FNIH, Foundation for the National Institutes of Health.
[a]Low grip strength (<30 kg men or <20 kg women) OR gait speed <0.8 m/s, AND low appendicular muscle mass index (<7.26 kg/m^2 men or <5.45 kg/m^2 women).
[b]Low grip strength (<27 kg men or <16 kg women).
[c]Low grip strength (<27 kg men or <16 kg women) AND low appendicular muscle mass index (<7.0 kg/m^2 men or <5.5 kg/m^2 women).
[d]Low grip strength (<26 kg men or <16 kg women) AND low appendicular lean mass (lean mass in kg divided by body mass index in kg/m^2 < 0.789 for men or <0.512 for women).

based on low grip under the revised (2019) EWGSOP guidelines was nearly three quarters of the total.

Discussion

We found that recruitment via primary care delivered many more participants with sarcopenia than recruitment via hospital-based care, a result of the much higher volume of potential participants that could be reached, rather than a large difference in the proportion of those screened who were eligible to participate. Conducting pre-screening telephone calls using a central team rather than the local site teams performing telephone pre-screening did not lead to a higher rate of conversion to in-person screening visits. The SARC-F tool had limited utility in differentiating those at pre-screening who would progress to randomization. Our results suggest that using BIA and the Sergi equation as a screening tool for low muscle mass is subject to systematic bias in this group of older UK participants, underestimating muscle mass in those with low muscle mass. This is likely to lead to inclusion of participants who do not fulfil the muscle mass criteria for sarcopenia on a more accurate measure such as DXA scanning.

Previous studies have also found recruitment of participants meeting stringent definitions of sarcopenia (based on low muscle strength and low muscle mass) to be difficult. The PROVIDE trial[22] recruited 380 participants and used a two-category definition of sarcopenia based on the ratio of skeletal muscle mass (measured by bioimpedance) to body weight, thus avoiding the need for muscle mass to be below an absolute threshold; only 70% of participants had a hand-grip strength below the 2010 EWGSOP thresholds[20] (<30 kg for men and <20 kg for women).

Strengths of our analysis include our ability to examine multiple components of the screening process. As such, we were able to examine a range of different screening techniques to evaluate which ones appeared successful. A number of limitations also deserve comment. We did not

perform randomization to allocate different screening techniques, either at an individual level or at a site level. Conducting such randomized Studies Within a Trial (SWATs) would have reduced bias and enabled more robust evidence to be generated. However, not all processes within the recruitment process would be amenable to randomization, and additional embedded process evaluations (including evaluations using qualitative methods) would have provided valuable additional contextual information,[23] for instance on how participants made the decision to take part, and on how study teams framed their conversations with potential participants. Such information would be particularly valuable given the significant number of otherwise eligible participants who chose not to attend a screening visit having read the study information or discussed the study during telephone pre-screening. We excluded participants with a SARC-F score of less than 3 at pre-screening and so are unable to comment on the performance of the SARC-F score at these levels; recent data suggest that using a very low SARC-F cut-off (≥1 point) would enable a better balance between sensitivity and specificity for detecting those with probable sarcopenia,[24] thus increasing the number of potentially eligible participants progressing from a pre-screening telephone call to a screening visit, while still enabling exclusion of those unlikely to have sarcopenia.

When we designed the LACE trial, the 2010 EWGSOP criteria[20] for sarcopenia were in use. Guidelines have changed since then, making any comparison of screening tools with these guidelines out of date. We have however also endeavoured to assess our findings against currently used criteria including the updated 2019 EWGSOP guidelines.[21] In terms of our assessment of muscle mass, we did not assess BIA and DXA on the same day, which may have led to additional variability in measurements, as BIA is sensitive to changes in fluid status. Our BIA measures, and the equation we derived from our data, apply only to measures obtained using the Akern BIA 101 system; other BIA systems require their own calibration. Although we were able to derive an equation that more accurately related muscle mass estimated by BIA to that measured by DXA in our study population, this

equation is likely to be overfitted for this study population and requires validating in different samples, albeit those recruited from a population of similar age and composition.[15,25]

What do these results mean for how we should design recruitment pathways for sarcopenia trials? First, recruitment through primary care provides an efficient, if low-yield strategy; many thousands of potential participants can be reached by mailshot at low cost. Searching electronic healthcare databases as part of such a strategy also enables identification of those with common exclusion criteria (such as the use of ACE inhibitors in the LACE trial) at an early stage in the screening process. However, the use of pre-screening questionnaires such as SARC-F to identify those more likely to have sarcopenia appears to add little to the screening process. Pre-screening could be confined to questions about other inclusion and exclusion criteria not addressable in electronic searches, although it is still possible that a lower threshold for the SARC-F would still have utility in excluding those who are unlikely to have sarcopenia. Central pre-screening can support delivery of a high-volume pre-screening strategy but in our study appeared to offer no clear advantage to local pre-screening in terms of the conversion rate from pre-screening to randomization. It is possible that central pre-screening by staff who are clinically trained might be more effective, both in terms of being able to answer questions from potential participants but also in establishing the confidence of potential participants; further study of this issue is required. However, central pre-screening, even by clinically trained staff, does not enable the local study team to start building a relationship with potential participants, which might affect trial retention. It is noteworthy that one-sixth of participants at telephone pre-screening chose not to proceed despite being eligible, highlighting this call as a decision point in need of further study. Local pre-screening telephone calls should therefore be preferred if the volume of calls can be handled by the local team.

The revised EWGSOP guidelines for sarcopenia may enable a change of focus in how we identify and recruit participants for sarcopenia trials. The guidelines now enable a diagnosis of probable sarcopenia to be made solely on the presence of low handgrip strength; low muscle mass is required only as a confirmatory measurement. This change acknowledges that the practical difficulties in measuring muscle mass in clinical practice,[26] and also takes into account that muscle strength rather than size, are the more important factors determining physical function and prognosis.[27] Designing sarcopenia trials to target and enrol those with probable sarcopenia would dispense with the need to screen for low muscle mass before entry and would align research practice with what is feasible and prevalent in clinical practice—grip strength is being measured more widely in geriatric medicine and rehabilitation services now, but muscle mass is not. Targeting those with probable sarcopenia, with the introduction of handgrip strength testing as a routine measure in clinical services, would also enable successful screening and recruitment from hospital-based settings.

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Conflict of interest

None to declare.

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Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Body mass index and sex-specific screening cut-offs for bioimpedance measured muscle mass.
Table S2. Linear regression to predict DXA measured appendicular muscle mass from bioimpedance results (n = 144)Figure S1. Conversion rate to screening visits and randomisation by SARC-F score at pre-screening.
Figure S2. Relationship between SARC-F score and sarcopenia diagnoses at screening visit.
Figure S3. Correlation between appendicular skeletal muscle mass estimated by BIA and measured by DXA at baseline (n = 144).

Figure S4. Bland–Altman plot for agreement between appendicular skeletal muscle mass estimated by bioimpedance (new LACE cohort equation) and measured by DXA at baseline (*n* = 144).

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