Effect of Acipimox on skeletal muscle biochemistry, structure and function in older people with probable sarcopenia: an experimental medicine study

ISRCTN trial database (ISRCTN87404878)

Eleven participants passed screening. The CONSORT diagram (Figure 1) and Table 1 show participant flow through the trial. The first 11 participants completed the final outcome visit and took the study medication correctly; therefore, recruitment was stopped as the target number of participants for analysis had been achieved. Details of the study participants at screening are shown in Table 2. All fulfilled the criteria for probable sarcopenia under the EWGSOP2 guidelines. None of the participants discontinued the study medication prematurely. Median medication adherence was 95% (range 91–104%).

There was no statistically significant difference in the primary outcome of change in NAD concentrations in skeletal muscle between baseline and follow-up [median difference: -0.003 umol/g (IQR -0.058 to 0.210); P=0.26] (Table 3) or secondary outcomes (Table 3 -6) . Nineteen adverse events were reported, none serious (Table 6) .

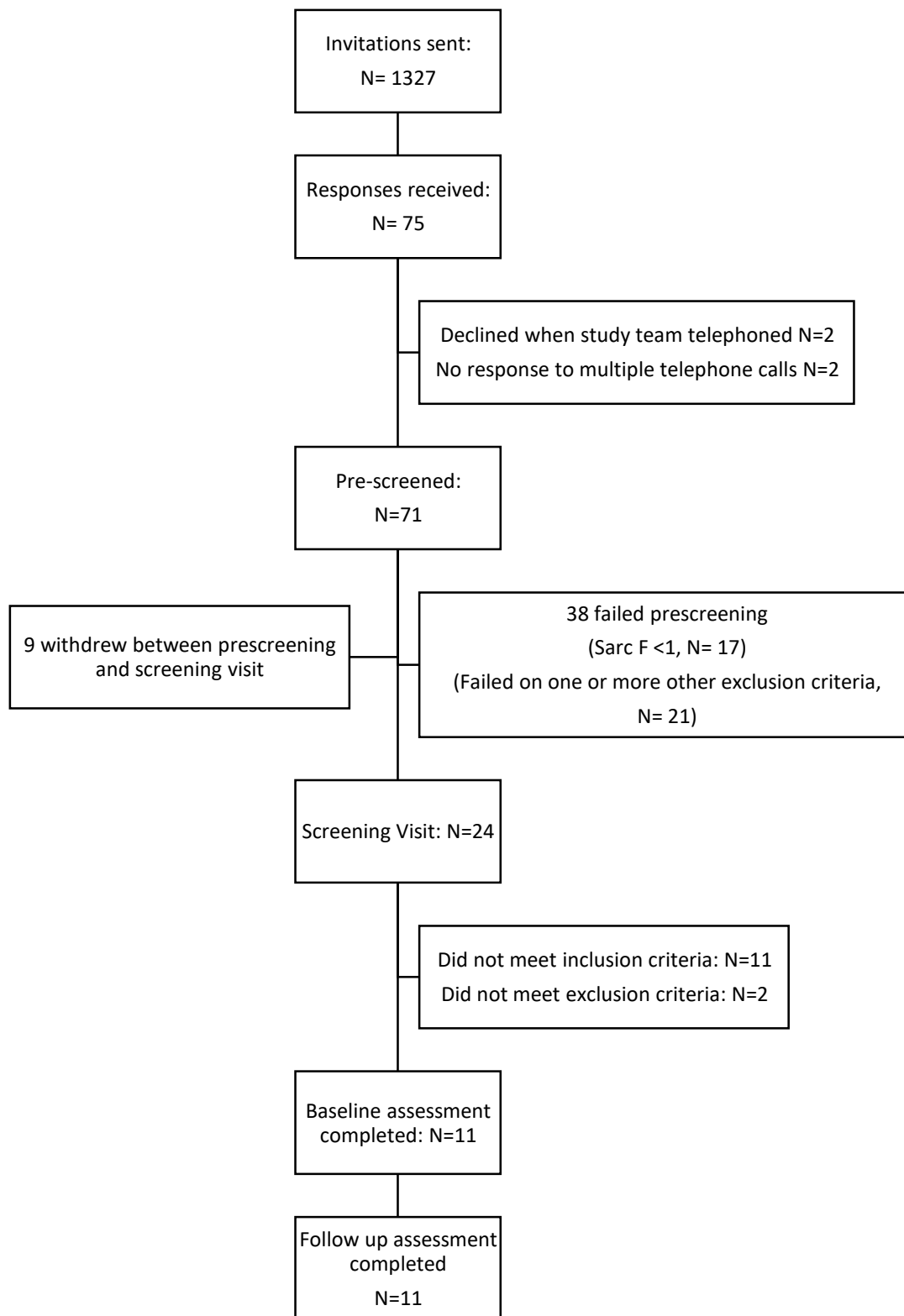**Figure 1 CONSORT Diagram of participant flow through the trial.**

Invitations sent:
N= 1327

Responses received:
N= 75

Declined when study team telephoned N=2
No response to multiple telephone calls N=2

Pre-screened:
N=71

9 withdrew between prescreening and screening visit

38 failed prescreening
(Sarc F <1, N= 17)
(Failed on one or more other exclusion criteria, N= 21)

Screening Visit: N=24

Did not meet inclusion criteria: N=11
Did not meet exclusion criteria: N=2

Baseline assessment completed: N=11

Follow up assessment completed
N=11

Table 1 Reported Exclusion criteria during the screening process.

Reported Exclusion Criteria (some participants reported more than one exclusion criterion)
• Progressive neurological or malignant condition with life expectancy <6 months (N=2)
• Symptomatic (NYHA class II-IV) chronic heart failure (N=5)
• Severe COPD (GOLD stage IV) (N=1)
• 10% weight loss (N=5)
• Taking statin medication or fibrate medication (N=9)
• Use of oral or parenteral anticoagulant medication (N=5)
• Antiplatelet agents other than low-dose aspirin (N=2)
• Allergy to aspirin (N=1)
• Contraindications to MRI scanning (N=2)
• Corticosteroid equivalent to >7.5mg oral prednisolone (N=2)

Table 2 Participant characteristics at screening (n=11)

	N (%)
Mean age (years) (SD)	78.9 (4.3)
Female sex (%)	8 (73)
White British ethnicity	11 (100)
Fried Frailty state • Robust • Pre frail • Frail	5 (45) 5 (45) 1 (9)
Comorbidity	
Cardiovascular or cerebrovascular disease (%)	0 (0)
Diabetes (%)	0 (0)
Atrial Fibrillation (%)	0 (0)
Hypothyroidism (%)	1 (9)
Hyperthyroidism (%)	0 (0)
Anxiety (%)	2 (18)
Depression (%)	2 (18)
Parkinsonism (%)	0 (0)
Chronic obstructive pulmonary disease (%)	2 (18)
Asthma (%)	0 (0)
Osteoarthritis (%)	7 (64)
Mean maximal handgrip strength (men) (kg) (SD)	33.3 (4.2)
Mean maximal handgrip strength (women (kg) (SD)	16.5 (2.3)
Median 5x sit-to-stand time (s) (range)	17.9 (16.0-18.5)
Mean 4m walk speed (m/s) (SD)	0.69 (0.07)
Mean BMI (kg/m^2) (SD)	25.2 (3.5)
Creatinine Clearance (ml/min) (SD)	58.5 (11.6)

Table 3: Change in skeletal muscle measures between baseline and follow-up

	Difference between baseline and follow-up	P
Skeletal muscle NAD (umol/g of tissue) N=8^ Median (IQR)	-0.003 (-0.06 – 0.02)	0.26
Skeletal muscle NADH (umol/g of tissue) N= 7# N=11 Median (IQR)	0.0004 (-0.03 – 0.01)	0.87
Skeletal muscle NAD / NADH ratio N= 7# Median (IQR)	0.15 (-1.04 – 1.73)	0.87
Skeletal muscle ATP (mmol/mg) N= 9¥ Median (IQR)	- 0.63 (-1.65-0.43)	0.17
Skeletal muscle ADP (mmol/mg) N = 9¥ Median (IQR)	-0.02 (-0.18-0.04)	0.26
Skeletal muscle ATP: ATP ratio N=9¥ Median (IQR)	-0.14 (-1.40-0.45)	0.26
Skeletal muscle Mitochondrial DNA copy number N=11 Median (IQR)	-2966 (-9011-3143)	0.33
Quadruple immunofluorescence N= 8* Median (IQR)		
• Complex I: Proportion of positive fibres (%)	0.41 (-0.79 – 0.73)	0.58
• Complex IV: Proportion of positive fibres (%)	0.68 (-0.48 – 34.5)	0.21
Cytochrome C oxidase/ succinate dehydrogenase histochemistry. N= 8* The proportion of SDH fibres staining for COX (%) Median (IQR)	0 (0-0.4)	0.28

^ NAD out of range in samples from 2 participants at baseline and follow and a further 1 participant at follow-up

NADH out of range in samples from 2 participants at baseline and follow and a further 2 participants at follow-up

¥ATP and ADP out of range on samples from 2 participants at baseline and follow-up

* Samples for 2 participants at baseline and a 3rd participant at follow-up did not contain any muscle fibres.

Table 4: Change in strength and physical performance measures between baseline and follow-up

	Difference between baseline and follow-up	P
Maximum Grip strength (Kg)Men N=3 [mean (SD)]	0.18 (2.60)	0.82
Maximum Grip strength (Kg) women N=8 [mean (SD)]		
4m walk speed (m/s) N=11 [mean (SD)]	-0.02 (0.12)	0.67
SPPB Total Score N=11 [mean (SD)]	0.27 (1.79)	0.63
Walking Bouts Per Day (number) N=9 [mean (SD)]	15.6 (75.0)	0.55
Mean daily walking Bout Duration (seconds) N=9 [mean (SD)]	-2.63 (2.21)	0.73
Mean walking speed in short bouts (m/s) N=9 [mean (SD)]	0.02 (0.04)	0.21

Table 5 MR Spectroscopy Measures

	Difference between baseline and follow-up	P
MRI Spectroscopy PCr t½ N=11 [Median (Interquartile range)]	4.6 (0.70-21.0)	0.05
Fat content of lower limb skeletal muscle (%)	-0.06 (-0.27 – 0.12)	0.80

Table 6: Summary of adverse event frequencies

		Number of participants (N=11)
Number of participants with at least one AE		9
Number of participants with at least one AR		5
Number of participants with at least one SAE		0
Number of participants with at least one SAR		0
Number of participants with at least one SUSAR		0
Total number of AEs		19
Number of the most common AEs:	Itch	1
	Soft tissue injury to the leg	1
	Flushing	1
	Cellulitis	2
	Covid 19 Infection	1
	Hematoma	2
	Aching legs	1
	Rash	1
	Bruising to arm	1
	Sciatica	1
	Fall	1
	Constipation	1
	White coat hypertension	1
Number of hospital admissions		0

Number of deaths	0

AE: Adverse event