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Hand exercises for patients with rheumatoid arthritis – an extended follow-up of the SARAH randomised controlled trial

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2 figures and 4 tables

Abstract

Objectives:

The SARAH [Stretching And strengthening for Rheumatoid Arthritis of the Hand] randomised controlled trial evaluated the effectiveness of a hand exercise programme and demonstrated it was clinically and cost effective at 12 months. The aim of this extended follow-up was to evaluate the effects of the SARAH programme beyond 12 months.

Methods:

Using postal questionnaires, we collected the Michigan Hand Questionnaire (MHQ) hand function (primary outcome), ADL and work subscales, pain troublesomeness, self-efficacy, self-reported hand exercise performance and health related quality of life. Mean difference in hand function scores were analysed by a linear model, adjusted for baseline score.

Results:

Two thirds (n=328/490, 67%) of the original cohort provided data for the extended follow-up. The mean follow-up time was 26 months (range 19-40 months).

There was no difference in change in hand function scores between the two groups at extended follow-up [mean difference (95%CI) 1.52 (-1.71 to 4.76)]. However, exercise group participants were still significantly improved compared to baseline (p=0.0014) unlike the best practice usual care group (p=0.1122). Self-reported performance of hand exercises had reduced substantially.

Conclusions:

Participants undertaking the SARAH exercise programme had improved hand function compared to baseline more than 2 years after randomisation. Hand function remained better than the control group but the between group difference was no longer statistically significant. The reduction in hand function compared to earlier follow-up points coincided with a reduction in self-reported performance of hand exercises. Further intervention to promote long term adherence may be warranted.

Strengths and limitations of this study

There was a lack of evidence regarding the long term effectiveness of hand exercises for improving hand function in patients with rheumatoid arthritis (RA) beyond 12 months.

This paper reports on the extended follow up (average follow up of 26 months) of a trial evaluating the effectiveness of a an individually tailored, progressive stretching and strengthening hand exercise programme for people with RA.

The benefits of the exercises evident at 12 months follow up had reduced but not completely diminished, however, so had adherence with the exercise programme.

This study highlights the importance of supporting patients with RA to maintain regular exercise.

The extended follow up was not planned at the start of the trial so the response rate is lower than that of the main trial.

INTRODUCTION

Rheumatoid arthritis (RA) is the most common inflammatory polyarthritis[1]. Hand dysfunction is common and to address this, exercises are recommended[2, 3]. Recommendations include exercises for enhancing flexibility, muscle strength and managing functional impairments[2]. Limited evidence of the effectiveness of hand exercises for people with RA[4-8] led to the commissioning of the Stretching and Strengthening for Rheumatoid Arthritis of the Hand (SARAH) Trial (ISRCTN89936343)[9, 10]. The SARAH Trial demonstrated that an individually tailored, progressive stretching and strengthening hand exercise programme improved hand function and was cost-effective compared to usual care over a 12 month period[11, 12]. However, there remained a lack of evidence regarding the long term effect of hand exercises.

Adherence to any exercise programme is crucial[13]. Support provided by health professionals enhances adherence with exercises but adherence is challenging when unsupervised[14]. The SARAH exercise programme was prescribed by a physiotherapist or occupational therapist who provided a maximum of six supervisory sessions during a three month period. During the sessions exercises were tailored to ensure maximal effect, and adherence promoted using a well-recognised behavioural framework[15]. It was intended that participants would carry out exercises daily at home during and beyond the supervised period.

The aim of the extended follow-up study was to estimate adherence to the intervention after the three month supervisory period, and the clinical effects of the SARAH exercise programme beyond 12 months.

METHODS

Study design

A pragmatic, multi-centre, randomised controlled trial carried out in 17 National Health Service (NHS) Hospitals in the United Kingdom[11] .

Participants

Participants were adults (≥18 years) with RA affecting their hands, who were either not on a disease-modifying anti-rheumatic drugs (DMARD) regime, or who had been on a stable DMARD regimen (including biologic agents) for three months or more. RA was defined using the American College of

Rheumatology criteria[16] . People who had upper limb surgery or fracture in the previous six months, were waiting for upper limb surgery or were pregnant were excluded.

Study procedures

Potential participants were approached during clinic visits or from clinic records (October 2009 and May 2011) and provided with a written invitation and information sheet. A researcher arranged an appointment to discuss the trial, check eligibility, and if appropriate, complete baseline assessments and randomise participants. Follow-up data was collected 4 and 12 months after randomisation at face to face appointments. The extended follow-up (>12 months) was an addition to the original study protocol [9]. Approval was granted for all elements of the study by the Oxford C Multicenter Research Ethics Committee [REC reference 08/H0606/4] and by hospital Research and Development departments. Extended follow-up questionnaires were posted to all participants (unless they had withdrawn from the study or were deceased) between September 2012 and January 2013 so the time for extended follow-up varied between participants. Informed consent was provided by all participants. Participants who agreed to participate in the extended follow-up completed a response form indicating their consent and returned this with their questionnaire. Participants could request to complete the questionnaire over the phone. If participants did not respond to the extended follow-up invitation one reminder letter was sent.

Interventions

The control intervention was best practice usual care consisting of joint protection education, advice on whole body mobility exercises and, if appropriate, functional splinting delivered over a maximum of three appointments. Participants in the intervention arm received best practice usual care and an individually tailored exercise programme, in which moderate to high intensity strengthening and stretching exercises were prescribed. Therapists used supervisory sessions to provide advice, check tolerability, progress or regress exercises and promote adherence. Treatments are described in detail elsewhere [10].

Data collection

Baseline measures

Measurements collect at baseline are described elsewhere[12]. These included demographics, Michigan Hand Outcome Questionnaire (MHQ) [17-19], pain troublesomeness[20], Arthritis Self-efficacy Scale[21], the EuroQol EQ5D[22], the 12 item short form health survey (SF-12)[23], impairment (grip strength, dexterity, hand and wrist range of motion and joint alignment),

Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP), modified tender and swollen joint count of the hands and wrist[24] and medication use.

Outcome measures

We reduced the number of questionnaires included in the extended follow-up because of the postal mode of administration. This included the primary outcome (Michigan Hand Questionnaire (MHQ) hand function subscale) for which scores ranged from 0 to 100, with higher scores indicating better performance. Secondary outcomes were the activities of daily living (ADL) and work MHQ subscales, pain troublesomeness [20], participant-rated improvement, Arthritis Self-efficacy[21], the EuroQol EQ5D[22] and the 12 item short form health survey (SF-12)[23]. To assess adherence with the exercise programme, all participants were asked to report how often they performed hand exercises for their RA.

Sample size estimates

The SARAH trial was sized to detect a small to moderate effect size of 0.3 in the primary outcome at 12 months. This was based on a previous smaller efficacy study of exercise that reported a standardised difference of 0.4 (8). We modified this effect downward to account for the SARAH trial being a pragmatic multicenter trial and to reflect worthwhile effects found in other pragmatic studies of RA[25]. To show this difference with 80% power at the 5% significance level, we required data on a total of 352 participants (using SAS procedure GLMPOWER) for analysis. Allowing for a 25% loss to follow-up, at least 469 participants were needed.

Randomisation

We used a central telephone randomisation service at the Warwick Clinical Trials Unit. Randomisation was stratified by center, and used a variable block length. Allocation was computer-generated and revealed once the participant was registered into the trial. It was not possible to blind participants and therapists delivering treatments to treatment allocation but follow-up data was collected by blinded research staff.

Statistical analysis

The analysis was intention to treat. Descriptive statistics were generated to compare people completing extended follow-up and those not, and the characteristics of randomised groups to identify any selection and retention biases. We only report earlier outcomes (baseline, 4 and 12 months) for those participants that took part in the extended follow-up. For all outcomes, we estimated within and between group differences at each time point (as well as overall) using a linear

model. Estimates of treatment effect were reported as the mean difference and 95% confidence interval. All models were adjusted for baseline MHQ score and pre-randomisation drug regime (Biologic DMARDs, Combination non-biologic DMARDs, Single non-biologic DMARD, No DMARD). The inclusion of time-to-follow up allowed adjustment for variable amounts of follow-up, and an estimation of the impact of duration of follow-up on the treatment effect. Multiple imputation estimates for MHQ overall hand function were also calculated for the extended follow-up time-point and adjusted for hospital, age and sex. The multiple imputation took account of the MHQ hand function score for all time-points, and baseline data (age, CRP, ESR, SF12 physical and mental summary scores, pain troublesomeness, confidence, impairment measurements, and DMARD group).

Secondary outcome measures of change in pain, quality of life and self-efficacy were analysed in a similar manner. Patient rated improvement was compared using the Wilcoxon test. Report of current exercise performance was categorised as at least 3 times per week, less than 3 times per week and no exercise and was analysed using Pearson's chi-squared.

Statistical analyses used SAS V9.2 software (SAS Institute Inc., USA).

RESULTS

Characteristics of the sample

The baseline characteristics are given in Table 1. Just over two-thirds of the original cohort (n=328 67%) provided data (Figure 1). On average, participants completed the extended follow-up 26 months after randomisation, with no difference between the groups [exercise: median time of 25.8 months (IQR 22.0-30.8); best practice usual care: median time of 26 months (IQR 22.2-29.9); P=0.6522]. An analysis performed to see if the time of extended follow-up (which varied from 19 to 40 months after randomisation) was associated with outcome showed there was no significant time effect (p=0.1399).

The two groups at extended follow-up were similar in age, gender, disease duration and baseline EQ-5D scores.

Figure 1 – CONSORT Flow diagram

The characteristics of participants who did and did not respond to the extended follow-up are provided in Table 1. The average age of responders was 63.6 years (SD 10.9) and 75.6% (248/328) were women, which was similar to the demographic of the entire sample at baseline. However, non-

responders had worse hand function at baseline than responders (scores 48.1 and 54.0 respectively). The proportion of participants reporting that they were performing hand exercises for their RA at earlier follow-up points was higher amongst responders compared to non-responders (Table 1) although the difference was not statistically significant (p=0.1323 and p=0.2598). Most notably, a greater proportion of non-responders in the exercise arm reported doing no exercise at 12 months compared to those who responded (44.4% versus 24.5% respectively; p=0.0488).

Table 1 – Characteristics of participants completing and not completing the extended follow-up by arm

Characteristic by arm	Participants completing the extended follow-up	Participants not completing the extended follow-up	Participants completing the extended follow-up	Participants not completing the extended follow-up	Participants completing the extendedfollow-up	Participants not completing the extended follow-up
Study arm	**Exercise programme**		**Usual Care**		**Combined**	
Age at randomisation, Mean (SD)	62.9 (11.0)	58.6 (14.0)	64.3 (10.8)	61.5 (12.1)	63.6 (10.9)	59.8 (13.2)
Sex, F (%)	77.4	74.7	74.0	81.2	75.6	77.5
Ethnic Origin, n (%)						
White	85 (93.4)	153 (98.7)	66 (95.7)	169 (98.3)	151 (93.4)	322 (98.5)
Indian	2 (2.2)	1 (0.7)	-	2 (1.2)	2 (1.3)	3 (0.9)
Pakistani	-	-	1 (1.5)	-	1 (0.6)	-
Mixed	2 (2.2)	1 (0.7)	1 (1.5)	-	3 (1.9)	1 (0.3)
Other	2 (2.2)	-	1 (1.5)	1 (0.6)	3 (1.9)	1 (0.3)
Disease duration (years), Mean (SD)	12.4 (10.8)	14.4 (10.4)	14.7 (12.5)	12.4 (10.7)	13.7 (11.8)	13.5 (10.6)
Baseline ESR Median (IQR)	13.0 (7.0, 26.0)	21.0 (9.0,30.0)	17.0 (9.0, 30.0)	13.0 (8.0, 27.0)	15.0 (8.0,28.0)	18.5 (8.0, 28.5)
Baseline CRP Median (IQR)	5.0 (3.0,11.0)	6.5 (3.0,13.0)	6.0, (3.0,13.0)	6.0 (3.0, 11.0)	5.0 (3.0, 12.0)	6.0 (3.0, 12.0)
Medications, n (%)						
Biologic DMARD	30 (19.4)	22 (24.2)	35 (20.2)	17 (24.6)	65 (19.8)	39 (24.4)
Combination non-biologic DMARD	46 (29.7)	26 (28.6)	42 (24.3)	11 (15.9)	42 (26.8)	37 (23.1)
Single non-biologic DMARD	66 (42.6)	37 (40.7)	85 (49.1)	33 (47.8)	85 (46.0)	70 (43.8)
Other medications	13 (8.4)	6 (6.6)	11 (6.4)	8 (11.6)	11 (3.4)	14 (8.8)
Baseline MHQ hand function, Mean (SD)	53.9 (15.1)	48.9 (14.8)	54.1 (15.6)	47.0 (17.4)	54.0 (15.4)	48.1 (15.9)
Baseline SF12 physical summary score, Mean (SD)	35.4 (9.7)	31.1 (9.4)	35.4 (9.7)	32.1 (8.5)	35.4 (9.7)	31.5 (9.0)
Baseline SF12 mental summary score,	49.7 (10.5)	45.5 (10.7)	50.4 (10.4)	45.1 (11.7)	50.1 (10.4)	45.3 (11.1)

Mean (SD)						
Baseline EQ5D health state, Mean (SD)	0.6 (0.3)	0.5 (0.3)	0.6 (0.2)	0.5 (0.3)	0.6 (0.3)	0.5 (0.3)
Baseline pain troublesomeness score, Mean (SD)	43.1 (20.5	50.9 (24.2)	46.0 (21.1)	54.6 (21.6)	44.6 (20.9)	52.5 (23.1)
Baseline self-efficacy – confidence to manage their condition, Mean (SD)	69.5 (18.2)	62.5 (23.0)	71.3 (17.7)	62.2 (21.0)	70.5 (17.9)	62.4 (22.1)
Participant reported frequency of hand exercises at 4 months, n (%)						
At least 3 times a week	107 (71.8)	44 (67.7)	80 (48.2)	25 (45.5)	187 (59.4)	69 (57.5)
Less than 3 times a week	26 (17.5)	11 (16.9)	36 (21.7)	5 (9.1)	62 (19.7)	16 (13.3)
No exercises	16 (10.7)	10 (15.4)	50 (30.1)	25 (45.5)	66 (21.0)	35 (29.2)
Participant reported frequency of hand exercises at 12 months, n (%)						
At least 3 times a week	61 (40.4)	18 (33.3)	66 (39.1)	18 (38.3)	127 (39.7)	36 (35.6)
Less than 3 times a week	53 (35.1)	12 (22.2)	35 (20.7)	9 (19.1)	88 (27.5)	21 (20.8)
No exercises	37 (24.5)	24 (44.4)	68 (40.2)	20 (42.6)	105 (32.8)	44 (43.6)
Change in MHQ hand function baseline to 12 months, Mean (SD)	7.2 (13.6)	9.8 (16.8)	3.2 (16.0)	4.8 (16.3)	5.1 (15.0)	7.5 (16.7)
Change in SF12 physical summary score baseline to 12 months, Mean (SD)	0.8 (7.2)	2.3 (6.3)	-0.1 (7.6)	0.5 (6.7)	0.3 (7.5)	1.5 (6.5)
Change in SF12 mental summary score baseline to 12 months, Mean (SD)	2.1 (9.9)	2.4 (12.4)	0.2 (9.5)	1.1 (10.8)	1.1 (9.7)	1.8 (11.7)
Change in EQ5D health state baseline to 12 months, Mean (SD)	0.0 (0.2)	0.0 (0.2)	0.0 (0.2)	0.0 (0.3)	0.0 (0.2)	0.0 (0.3)

Intervention adherence

Exercise programme participants reported substantially reducing their frequency of hand exercises over time with 71.4% reporting that they exercised 3 times per week at 4 months and only 31.4% at the extended follow-up (Table 2). They had reported performing hand exercises for their RA more frequently than best practice usual care participants at both the 4 and 12 months follow-up. At extended follow-up there was no longer a clear difference between the two groups in their reports of hand exercises.

Table 2 Participant reported frequency of hand exercises for their RA [n(%)] for those that responded to the extended follow-up

	4 Months		12 Months		Extended follow-up	
	Usual Care	Exercise programme	Usual Care	Exercise programme	Usual Care	Exercise programme
Participant reported frequency of hand exercises						
At least 3 times a week	80 (48.2)	107 (71.8)	66 (39.1)	61 (40.4)	60 (34.9)	48 (31.4)
Less than 3 times a week	36 (21.7)	26 (17.5)	35 (20.7)	53 (35.1)	38 (22.1)	48 (31.4)
No exercises	50 (30.1)	16 (10.7)	68 (40.2)	39 (24.5)	74 (43.0)	57 (37.3)
Not answered	3	3	2	2	1	2
P trend (Wilcoxon)	<0.0001		0.0884		0.7715	

Primary outcome – hand function

Figure 2 and Table 3 shows the change in MHQ hand function subscale scores over time for those completing the extended follow-up. Best practice usual care resulted in small but statistically significant improvements in hand function at 4 and 12 months, in comparison to baseline values. However, the within group difference between baseline and extended follow-up was not statistically significant [Mean MHQ hand function subscale score at baseline = 54.1 (SD15.65); extended follow-up = 56.1 (SD18.85); p=0.1122].

Figure 2 Mean change from baseline over time for the primary and secondary outcomes for those who responded to the extended follow-up. Error bars represent the standard error. For the number of participants providing data for each outcome at each time point please refer to Table 3.

Table 3 Estimates of effect in primary outcome and patient reported secondary outcome measures for those who responded to the extended follow-up.

	Mean change from Baseline (95% CI) Usual Care	Exercise programme	Mean treatment difference (95% CI)	P value	Number of participants confirmed
MHQ Overall hand function					
4 Months	3.27 (1.15 to 5.39)	9.27 (7.19 to 11.34)	6.24 (3.56 to 8.92)***	<0.0001	320
12 Months	3.19 (0.79 to 5.59)	7.18 (5.02 to 9.33)	3.91 (0.71 to 7.10)*	0.0171	324
Extended follow-up	1.97 (-0.45 to 4.39)	3.76 (1.50 to 6.02)	1.52 (-1.71 to 4.76)	0.3567	327
MHQ ADL (both hands)					
4 Months	3.37 (0.94 to 5.79)	8.29 (5.61 to 10.96)	5.07 (1.73 to 8.42)**	0.0032	319
12 Months	2.53 (-0.12 to 5.18)	5.34 (2.71 to 7.97)	2.83 (-0.90 to 6.56)	0.1375	323
Extended follow-up	2.34 (0.03 to 4.66)	3.15 (0.30 to 6.01)	0.72 (-2.88 to 4.32)	0.6948	324
MHQ Work					
4 Months	4.91 (1.91 to 7.91)	8.26 (5.47 to 11.04)	3.04 (-0.96 to 7.04)	0.1370	316
12 Months	2.97 (-0.05 to 5.99)	7.70 (4.73 to 10.68)	4.44 (0.30 to 8.57)*	0.0363	323
Extended follow-up	5.81 (2.97 to 8.65)	7.76 (4.67 to 10.84)	2.06 (-2.10 to 6.22)	0.3318	315
SF 12 Mental Component Score (MCS)					
4 Months	0.70 (-0.62 to 2.02)	1.09(-0.18 to 2.37)	0.51 (-1.16 to 2.18)	0.5488	319
12 Months	0.21 (-1.21 to 1.64)	2.12 (0.54 to 3.69)	1.63 (-0.22 to 3.49)	0.0857	322
Extended follow-up	0.21 (-1.23 to 1.66)	0.27 (-1.25 to 1.78)	0.22 (-1.71 to 2.15)	0.8252	326
SF 12 Physical Component Score (PCS)					
4 Months	0.62 (-0.39 to 1.63)	1.84 (0.65 to 3.02)	1.37 (-0.12 to 2.86)	0.0719	319
12 Months	-0.09 (-1.24 to 1.06)	0.76 (-0.39 to 1.92)	0.72 (-0.79 to 2.23)	0.3519	321
Extended follow-up	-0.51 (-1.66 to 0.64)	0.19 (-1.16 to 1.54)	0.50 (-1.24 to 2.25)	0.5720	326
EQ-5D Health state					
4 Months	0.0 (-0.03 to 0.04)	0.06 (0.02,0.09)	0.03 (-0.01 to 0.07)	0.1654	319
12 Months	0.02 (-0.02 to 0.05)	0.04 (0.00 to 0.07)	0.00 (-0.04 to 0.05)	0.8239	.322
Extended follow-up	-0.01 (-0.05 to 0.02)	-0.01 (-0.05 to 0.03)	-0.01 (-0.06 to 0.04)	0.6893	324

Pain troublesomeness score†					
4 Months	-4.79 (-7.76 to -1.82)	-5.57 (-8.25 to -2.90)	-2.51 (-6.22 to 1.21)	0.1872	315
12 Months	-4.68 (-7.83 to -1.53)	-5.03 (-8.16 to -1.90)	-1.58 (-5.65 to 2.48)	0.4454	322
Extended follow-up	-3.79 (-6.93 to -0.64)	0.20 (-2.98 to 3.38)	3.23 (-0.83 to 7.28)	0.1199	326
Self-efficacy – confidence to manage their condition					
4 Months	2.38 (-0.15 to 4.62)	6.58 (3.74 to 9.42)	3.41 (0.5 to 6.29)*	0.0209	319
12 Months	1.30 (-1.32 to 3.92)	5.46 (2.29 to 8.62)	3.19 (0.71 to 6.98)	0.1113	321
Extended follow-up	0.22 (-2.34 to 2.78)	2.96 (0.03 to 5.90)	2.30 (-1.20 to 5.79)	0.1988	323

***p<0.001; ** p<0.01; *p<0.05; ; † Higher score = more pain

Exercise resulted in substantial improvements from baseline, with the peak effect at 4 months. For both 4 and 12 months differences between the exercise and best practice usual care group were statistically and clinically significant. By the extended follow-up time point the exercise intervention was still associated with a significant within group improvement in hand function in comparison to baseline [Mean MHQ hand function subscale score at baseline =53.9 (SD15.1); extended follow-up = 57.7 (SD18.04); p=0.0014]. However, the difference between exercise and best practice usual care interventions was no longer statistically significant (Table 3).

Secondary outcomes

MHQ ADL and MHQ work subscales

Significant within group differences were observed in both groups for the MHQ ADL and MHQ work subscales at the extended follow-up compared to baseline ($p<0.05$ and $P<0.001$ for best practice usual care and the exercise arms respectively). Greater improvement from baseline was seen in the exercise arm (Figure 2 and Table 3).

There was a statistically significant between group difference in the MHQ ADL subscale at 4 and 12 months and the MHQ work subscale at 12 months favouring the exercise arm but this difference was no longer significant at the extended follow-up.

Health-related Quality of Life (SF-12 and EQ-5D)

There were no observable within group differences or between group differences at any follow-up time point as measured by the SF-12 or the EQ-5D (Figure 2 and Table 3).

Pain troublesomeness

There were statistically significant within group changes at the 4 and 12 months follow-up with both groups reporting less pain compared to baseline and this continued in the best practice usual care arm at extended follow-up (p=0.0196). However, the pain scores reported at extended follow-up in the exercise arm were similar to baseline scores (p=0.9039).

There was no statistically significant between group difference in pain troublesomeness scores at any follow-up time point (Figure 2 and Table 3).

Self-efficacy

At extended follow-up there was a significant within group change in self-efficacy observed in the exercise arm but not the best practice usual care arm. Participants in the exercise group reported higher self-efficacy scores compared to their baseline scores (p=0.0496) but this was not the case for the best practice usual care (p=0.8675).

Respondents in the exercise arm reported higher self-efficacy scores at 4 months follow-up compared to the best practice usual care group but this difference was diminished at 12 months and extended follow-up so the between group difference was no longer evident (Figure 2 and Table 3).

Participant rated improvement

Participant rated improvement in the exercise arm were significantly higher at 4 and 12 months follow-up than the best practice usual care group but there was no difference between the two groups at the extended follow-up (Table 4).

Table 4 Patient reported secondary outcome measures [n (%)] for those that responded to the extended follow-up

	4 Months		12 Months		Extended follow-up	
	Usual Care	Exercise programme	Usual Care	Exercise programme	Usual Care	Exercise programme
Participant rated improvement						
Completely recovered	1 (0.6)	-	2 (1.2)	1 (0.7)	1 (0.6)	-
Much improved	18 (10.8)	34 (22.8)	14 (8.2)	31 (20.5)	22 (12.8)	25 (16.3)
Slightly improved	34 (20.4)	48 (32.2)	23 (13.5)	38 (25.2)	17 (9.9)	24 (15.7)
No change	65 (38.9)	45 (30.2)	69 (40.6)	47 (31.1)	75 (43.6)	58 (37.9)
Slightly worsened	41 (24.6)	17 (11.4)	49 (28.8)	22 (14.6)	41 (23.8)	35 (22.9)
Much worsened	8 (4.8)	5 (3.4)	12 (7.1)	9 (6.0)	15 (8.7)	7 (4.6)
Vastly worsened	-	-	1 (0.6)	3 (2.0)	1 (0.6)	4 (2.6)
P trend (Wilcoxon)	<0.0001		<0.0001		0.2018	

Multiple imputation

Multiple imputation was used to evaluate the impact of missing data and the estimate of treatment difference from baseline to extended follow-up was 1.75 (-1.20, 4.70), p=0.2433. This is similar to the non-imputed analysis suggesting that missing data was not a major influence on the study findings.

DISCUSSION

We have evaluated the long term outcomes of an individually tailored exercise programme compared to best practice usual care for adults with RA of the hand. Between group differences had

diminished over an average follow-up time of 26 months but generally functional scores favoured the exercise group. Both groups had improved hand function compared to baseline but this was only statistically significant in the exercise group. We interpret this to mean that although functional improvements due to the exercises had reduced, they had not diminished completely. Exercise arm participants completed treatment with their therapist approximately 3 months after randomisation so for some participants it had been 2 years since attending treatment. Therefore, it is very encouraging that some benefit still persisted. We aimed to estimate exercise adherence beyond the supervised period and the data shows that by the extended follow-up many participants in the exercise arm were no longer exercising as intended. RA is a progressive disease so regular exercise of sufficient intensity is needed to maintain muscle strength. It is likely that participants were no longer achieving a sufficient dose to maintain functional improvements.

Another study of upper limb exercises demonstrated a similar reduction of benefit over time where gains observed at 12 weeks were no longer evident at 26 weeks follow-up[26] with an assumption it was due to reduced adherence but this data was not collected.

Another proposed mechanism by which the intervention improved function was by bolstering self-efficacy. This effect had also diminished which may be due to the fact it had been 2 years since attending treatment.

One outcome favoured the best practice usual care (pain troublesomeness scores). There was no between group differences but the best practice usual care group had a small but statistically significant reduction in pain compared to baseline unlike the exercise group. However, the reduction in pain was small and we are confident the exercises did not increase pain while improving function. There was no difference in adverse events reported[11] and we conclude that the exercise programme is safe.

Clinical implications and further research

The SARAH exercise programme is an effective adjunct to the medical management of RA for patients with hand problems, but the benefit from the exercise programme did reduce over time as participants reported doing less exercises. These findings raise important questions regarding how patients might be supported to exercise long term which is probably necessary to maintain functional gains.

Further research is needed to establish how ongoing support could be provided. Patients with RA are seen frequently in rheumatology outpatient clinics with the National Institute for Health and Care

Excellence (NICE) recommending annual reviews for patients with RA[27]. Staff could monitor patient's exercise participation during these appointments. However, there is uncertainty amongst health professionals about providing advice about exercise to patients with RA[28, 29]. Specialist rheumatology nurses play an important role in monitoring and supporting patients, yet, EULAR recommendations for specialist rheumatology nurses do not mention exercise[30]. There is a need to educate health professionals and patients about the importance of regular exercise. It is safe for patients with RA to exercise[26, 31] and health professionals need to be confident to advise on exercise regimes, referring to therapists when needed. Patients with RA have to continually modify their treatment in response to changes in their condition. This also applies to exercise which presents another challenge. The SARAH programme is manualised, with clear instructions for progressing/regressing exercises allowing patients to modify exercises when needed. Participant feedback was that this was easy to follow[12] so these types of resources could be made available to health professionals and patients to help patients to exercise regularly.

Methodological limitations

The response rate was lower than the main study. This was not unexpected as this follow-up was not planned at the outset of the study so participants were unaware they would receive the postal questionnaire. We only contacted participants by post so as not to place undue pressure on them to respond and only phoned those who requested to complete the questionnaire by phone. As a consequence, the analysis is underpowered to detect a difference in the primary and secondary outcomes. Loss to follow-up could introduce bias and there were some differences in responders and non-responders, but these were equal across treatment groups. Most notably non-responders had poorer hand function at baseline which may have influenced their outcomes. Non-responders also reported lower levels of exercise adherence at earlier follow-up especially in the exercise arm. Multiple imputation techniques estimated the effect of missing data and the results were largely similar indicating that missing data did not overly influence the findings. Overall, we are confident that the participants providing data were a good representation of the total cohort.

In conclusion, a hand exercise programme is an effective adjunct to current drug management to improve hand function. Participants in the exercise group had improved hand function compared to baseline more than 2 years after randomisation. Hand function had reduced over time which coincided with a reduction in hand exercises highlighting the importance of promoting long term exercise adherence amongst patients with RA.

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Trial Steering Committee

Prof Alison Hammond (Chair), Dr Chris Deighton, Dr Chris McCarthy, Prof Sallie Lamb, Dr Mark Williams, Mr John Wright (User representative)

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CONTRIBUTING STATEMENT

EW: Design of the trial, data collection, interpretation of the data, drafting and revising of the paper, final approval of the version to be published.

CC: Data analysis and interpretation, drafting and revising the paper, final approval of the version to be published.

PH: Design of the study, data collection, interpretation of the data, revision of the paper, final approval of the version to be published.

SD: Trial administration, data collection, revision of the paper, final approval of the version to be published.

MW: Design of the study, data collection and interpretation of the data, revision of the paper, final approval of the version to be published.

SL: Conception and design of the trial, data analysis and interpretation, drafting and revising of the paper, final approval of the version to be published.

COMPETING INTERESTS

None.

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DATA SHARING STATEMENT

The data is available on request from the Chief Investigator (Professor Sarah Lamb).

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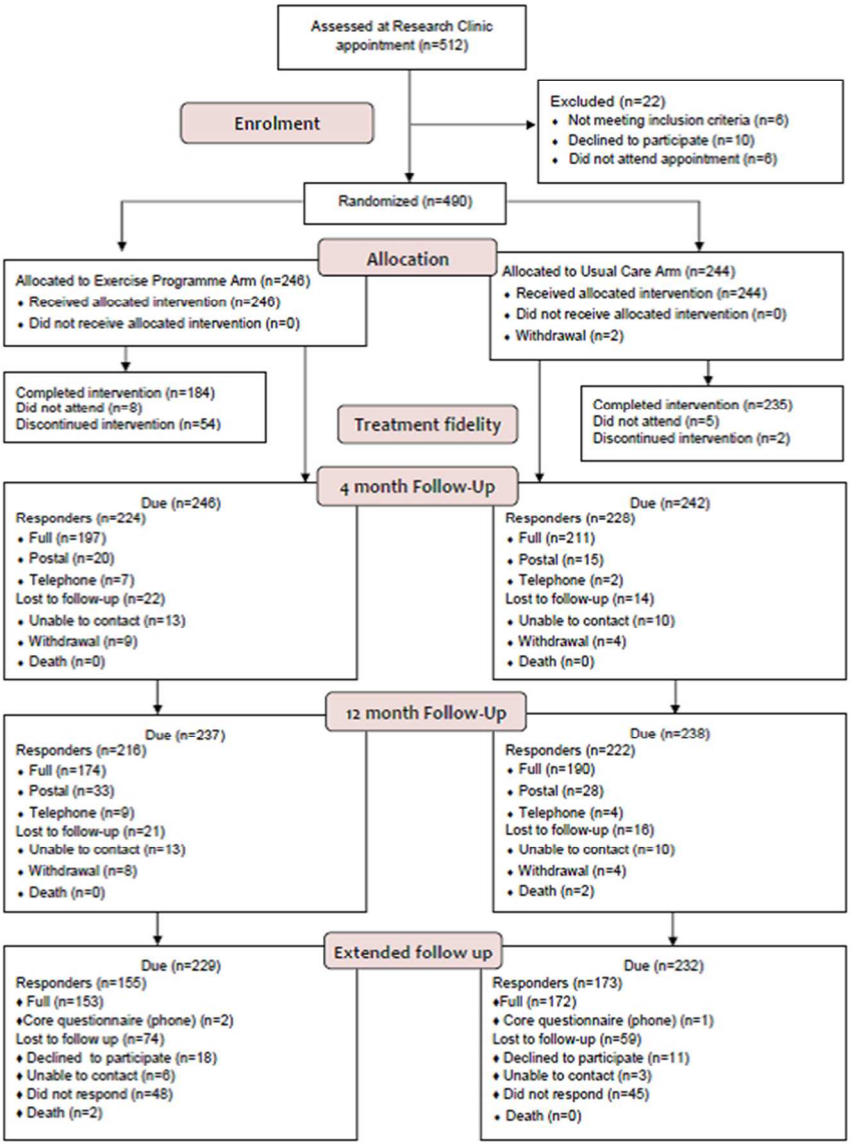

Figure 1 Consort Flow Chart

157x206mm (96 x 96 DPI)

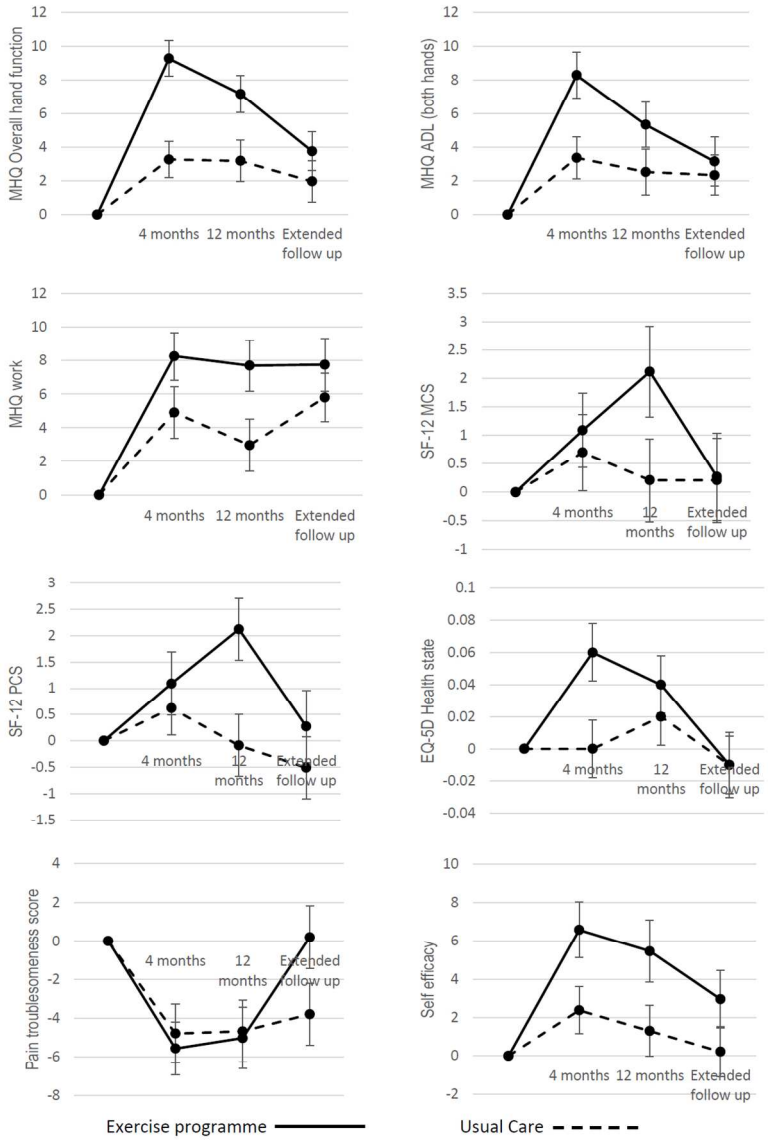

Figure 2 Mean change from baseline over time for the primary and secondary outcomes for those who responded to the extended follow-up.

333x491mm (96 x 96 DPI)

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2 Abstract
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	4-5
	4b	Settings and locations where the data were collected	4-5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5 – reference provided for intervention paper
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	5-6
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	6
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9		6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to	6

		interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	6
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	6-7
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	6-7
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	7, Figure 1, Tables 1-4
	13b	For each group, losses and exclusions after randomisation, together with reasons	Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	5
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Tables 2-4 5
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Tables 2-4
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	16
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	17 Adverse events reported in main trial paper – reference provided
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	18
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	18
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	16-18
Other information			

Registration	23	Registration number and name of trial registry	4
Protocol	24	Where the full trial protocol can be accessed, if available	4
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	20-21

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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Hand exercises for patients with rheumatoid arthritis – an extended follow-up of the SARAH randomised controlled trial

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Hand exercises for patients with rheumatoid arthritis – an extended follow-up of the SARAH randomised controlled trial

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Key words: exercise, adherence, rheumatoid arthritis, hand function

Word count: 2948

2 figures and 4 tables

Abstract

Objectives:

The SARAH [Stretching And strengthening for Rheumatoid Arthritis of the Hand] randomised controlled trial evaluated the effectiveness of a hand exercise programme and demonstrated it was clinically and cost effective at 12 months. The aim of this extended follow-up was to evaluate the effects of the SARAH programme beyond 12 months.

Methods:

Using postal questionnaires, we collected the Michigan Hand Questionnaire (MHQ) hand function (primary outcome), ADL and work subscales, pain troublesomeness, self-efficacy and health related quality of life. All participants were asked how often they performed hand exercises for their rheumatoid arthritis. Mean difference in hand function scores were analysed by a linear model, adjusted for baseline score.

Results:

Two thirds (n=328/490, 67%) of the original cohort provided data for the extended follow-up. The mean follow-up time was 26 months (range 19-40 months).

There was no difference in change in hand function scores between the two groups at extended follow-up [mean difference (95%CI) 1.52 (-1.71 to 4.76)]. However, exercise group participants were still significantly improved compared to baseline (p=0.0014) unlike the best practice usual care group (p=0.1122). Self-reported performance of hand exercises had reduced substantially.

Conclusions:

Participants undertaking the SARAH exercise programme had improved hand function compared to baseline more than 2 years after randomisation. This was not the case for the control group. However, scores were no longer statistically different between the groups indicating the effect of the programme had diminished over time. This reduction in hand function compared to earlier follow-up points coincided with a reduction in self-reported performance of hand exercises. Further intervention to promote long term adherence may be warranted.

Strengths and limitations of this study

There was a lack of evidence regarding the long term effectiveness of hand exercises for improving hand function in patients with rheumatoid arthritis (RA) beyond 12 months.

This paper reports on the extended follow up (average follow up of 26 months) of a trial evaluating the effectiveness of a an individually tailored, progressive stretching and strengthening hand exercise programme for people with RA.

The benefits of the exercises evident at 12 months follow up had reduced but not completely diminished, however, so had adherence with the exercise programme.

This study highlights the importance of supporting patients with RA to maintain regular exercise.

The extended follow up was not planned at the start of the trial so the response rate is lower than that of the main trial.

INTRODUCTION

Rheumatoid arthritis (RA) is the most common inflammatory polyarthritis[1]. Hand dysfunction is common and to address this, exercises are recommended[2, 3]. Recommendations include exercises for enhancing flexibility, muscle strength and managing functional impairments[2]. Limited evidence of the effectiveness of hand exercises for people with RA[4-8] led to the commissioning of the Stretching and Strengthening for Rheumatoid Arthritis of the Hand (SARAH) Trial (ISRCTN89936343)[9, 10]. The SARAH Trial demonstrated that an individually tailored, progressive stretching and strengthening hand exercise programme improved hand function and was cost-effective compared to usual care over a 12 month period[11, 12]. However, there remained a lack of evidence regarding the long term effect of hand exercises.

Adherence to any exercise programme is crucial[13]. Support provided by health professionals enhances adherence with exercises but adherence is challenging when unsupervised[14]. The SARAH exercise programme was prescribed by a physiotherapist or occupational therapist who provided a maximum of six supervisory sessions during a three month period. The median number of sessions actually attended by participants was 5 (interquartile range 5-6). During the sessions exercises were tailored to ensure maximal effect, and adherence promoted using a well-recognised behavioural framework[15]. It was intended that participants would carry out exercises daily at home during and beyond the supervised period.

The aim of the extended follow-up study was to estimate adherence to the intervention after the three month supervisory period, and the clinical effects of the SARAH exercise programme beyond 12 months.

METHODS

Study design

A pragmatic, multi-centre, randomised controlled trial carried out in 17 National Health Service (NHS) Hospitals in the United Kingdom[11] .

Participants

Participants were adults (≥18 years) with RA affecting their hands, who were either not on a disease-modifying anti-rheumatic drugs (DMARD) regime, or who had been on a stable DMARD regimen (including biologic agents) for three months or more. RA was defined using the American College of

Rheumatology criteria[16] . People who had upper limb surgery or fracture in the previous six months, were waiting for upper limb surgery or were pregnant were excluded.

Study procedures

Potential participants were approached during clinic visits or from clinic records (October 2009 and May 2011) and provided with a written invitation and information sheet. A researcher arranged an appointment to discuss the trial, check eligibility, and if appropriate, complete baseline assessments and randomise participants. Follow-up data was collected 4 and 12 months after randomisation at face to face appointments. The extended follow-up (>12 months) was an addition to the original study protocol [9]. Approval was granted for all elements of the study by the Oxford C Multicenter Research Ethics Committee [REC reference 08/H0606/4] and by hospital Research and Development departments. Extended follow-up questionnaires were posted to all participants (unless they had withdrawn from the study or were deceased) between September 2012 and January 2013 so the time for extended follow-up varied between participants. Informed consent was provided by all participants. Participants who agreed to participate in the extended follow-up completed a response form indicating their consent and returned this with their questionnaire. Participants could request to complete the questionnaire over the phone. If participants did not respond to the extended follow-up invitation one reminder letter was sent.

Interventions

The control intervention was best practice usual care consisting of joint protection education, advice on whole body mobility exercises and, if appropriate, functional splinting delivered over a maximum of three appointments. Participants in the intervention arm received best practice usual care and an individually tailored exercise programme, in which moderate to high intensity strengthening and stretching exercises were prescribed. Therapists used supervisory sessions to provide advice, check tolerability, progress or regress exercises and promote adherence. Treatments are described in detail elsewhere [10].

Data collection

Baseline measures

Measurements collect at baseline are described elsewhere[12]. These included demographics, Michigan Hand Outcome Questionnaire (MHQ) [17-19], pain troublesomeness[20], Arthritis Self-efficacy Scale[21], the EuroQol EQ5D[22], the 12 item short form health survey (SF-12)[23], impairment (grip strength, dexterity, hand and wrist range of motion and joint alignment),

Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP), modified tender and swollen joint count of the hands and wrist[24] and medication use.

Outcome measures

We reduced the number of outcomes included in the extended follow-up because of the postal mode of administration. Data collection was limited to self-reported measures and we were not able to include physical measures such as strength and dexterity that were measured at previous follow up time points. To reduce participant burden were did not use the whole Michigan Hand Questionnaire (MHQ) and excluded lengthy health resource use questions. Outcome measures for the main trial are described in detail elsewhere[11].

We collected the primary outcome (MHQ hand function subscale) for which scores ranged from 0 to 100, with higher scores indicating better performance. Secondary outcomes were the activities of daily living (ADL) and work MHQ subscales, pain troublesomeness [20], participant-rated improvement, Arthritis Self-efficacy[21], the EuroQol EQ5D[22] and the 12 item short form health survey (SF-12)[23]. To assess adherence with the exercise programme, all participants were asked to report how often they performed hand exercises for their RA.

Sample size estimates

The SARAH trial was sized to detect a small to moderate effect size of 0.3 in the primary outcome at 12 months. This was based on a previous smaller efficacy study of exercise that reported a standardised difference of 0.4 (8). We modified this effect downward (to 0.3) to account for the SARAH trial being a pragmatic multicenter trial and to reflect worthwhile effects found in other pragmatic studies of RA[25]. To show this difference with 80% power at the 5% significance level, we required data on a total of 352 participants (using SAS procedure GLMPOWER) for analysis. Allowing for a 25% loss to follow-up, at least 469 participants were needed.

Randomisation

We used a central telephone randomisation service at the Warwick Clinical Trials Unit. Randomisation was stratified by center, and used a variable block length. Allocation was computer-generated and revealed once the participant was registered into the trial. It was not possible to blind participants and therapists delivering treatments to treatment allocation but follow-up data was collected by blinded research staff.

Statistical analysis

The analysis was intention to treat. Descriptive statistics were generated to compare people completing extended follow-up and those not, and the characteristics of randomised groups to identify any selection and retention biases. We only report earlier outcomes (baseline, 4 and 12 months) for those participants that took part in the extended follow-up. For all outcomes, we estimated within and between group differences at each time point (as well as overall) using a linear model. Estimates of treatment effect were reported as the mean difference and 95% confidence interval. All models were adjusted for baseline MHQ score and pre-randomisation drug regime (Biologic DMARDs, Combination non-biologic DMARDs, Single non-biologic DMARD, No DMARD). The inclusion of time-to-follow up allowed adjustment for variable amounts of follow-up, and an estimation of the impact of duration of follow-up on the treatment effect. Multiple imputation estimates for MHQ overall hand function were also calculated for the extended follow-up time-point and adjusted for hospital, age and sex. The multiple imputation took account of the MHQ hand function score for all time-points, and baseline data (age, CRP, ESR, SF12 physical and mental summary scores, pain troublesomeness, confidence, impairment measurements, and DMARD group).

Secondary outcome measures of change in pain, quality of life and self-efficacy were analysed in a similar manner. Patient rated improvement was compared using the Wilcoxon test. Report of current exercise performance was categorised as at least 3 times per week, less than 3 times per week and no exercise and was analysed using Pearson's chi-squared.

Statistical analyses used SAS V9.2 software (SAS Institute Inc., USA).

RESULTS

Characteristics of the sample

The baseline characteristics are given in Table 1. Just over two-thirds of the original cohort (n=328 67%) provided data (Figure 1). On average, participants completed the extended follow-up 26 months after randomisation, with no difference between the groups [exercise: median time of 25.8 months (IQR 22.0-30.8); best practice usual care: median time of 26 months (IQR 22.2-29.9); P=0.6522]. An analysis performed to see if the time of extended follow-up (which varied from 19 to 40 months after randomisation) was associated with outcome showed there was no significant time effect (p=0.1399).

The two groups at extended follow-up were similar in age, gender, disease duration and baseline EQ-5D scores.

Figure 1 – CONSORT Flow diagram

The characteristics of participants who did and did not respond to the extended follow-up are provided in Table 1. The average age of responders was 63.6 years (SD 10.9) and 75.6% (248/328) were women, which was similar to the demographic of the entire sample at baseline. However, non-responders had worse hand function at baseline than responders (scores 48.1 and 54.0 respectively). The proportion of participants reporting that they were performing hand exercises for their RA at earlier follow-up points was higher amongst responders compared to non-responders (Table 1) although the difference was not statistically significant (p=0.1323 and p=0.2598). Most notably, a greater proportion of non-responders in the exercise arm reported doing no exercise at 12 months compared to those who responded (44.4% versus 24.5% respectively; p=0.0488).

Table 1 – Characteristics of participants completing and not completing the extended follow-up by arm

Characteristic by arm	Participants completing the extended follow-up	Participants not completing the extended follow-up	Participants completing the extended follow-up	Participants not completing the extended follow-up	Participants completing the extendedfollow-up	Participants not completing the extended follow-up
Study arm	**Exercise programme**		**Usual Care**		**Combined**	
Age at randomisation, Mean (SD)	62.9 (11.0)	58.6 (14.0)	64.3 (10.8)	61.5 (12.1)	63.6 (10.9)	59.8 (13.2)
Sex, F (%)	77.4	74.7	74.0	81.2	75.6	77.5
Ethnic Origin, n (%)						
White	85 (93.4)	153 (98.7)	66 (95.7)	169 (98.3)	151 (93.4)	322 (98.5)
Indian	2 (2.2)	1 (0.7)	-	2 (1.2)	2 (1.3)	3 (0.9)
Pakistani	-	-	1 (1.5)	-	1 (0.6)	-
Mixed	2 (2.2)	1 (0.7)	1 (1.5)	-	3 (1.9)	1 (0.3)
Other	2 (2.2)	-	1 (1.5)	1 (0.6)	3 (1.9)	1 (0.3)
Disease duration (years), Mean (SD)	12.4 (10.8)	14.4 (10.4)	14.7 (12.5)	12.4 (10.7)	13.7 (11.8)	13.5 (10.6)
Baseline ESR Median (IQR)	13.0 (7.0, 26.0)	21.0 (9.0,30.0)	17.0 (9.0, 30.0)	13.0 (8.0, 27.0)	15.0 (8.0,28.0)	18.5 (8.0, 28.5)
Baseline CRP Median (IQR)	5.0 (3.0,11.0)	6.5 (3.0,13.0)	6.0, (3.0,13.0)	6.0 (3.0, 11.0)	5.0 (3.0, 12.0)	6.0 (3.0, 12.0)
Medications, n (%)						
Biologic DMARD	30 (19.4)	22 (24.2)	35 (20.2)	17 (24.6)	65 (19.8)	39 (24.4)
Combination non-biologic DMARD	46 (29.7)	26 (28.6)	42 (24.3)	11 (15.9)	42 (26.8)	37 (23.1)
Single non-biologic DMARD	66 (42.6)	37 (40.7)	85 (49.1)	33 (47.8)	85 (46.0)	70 (43.8)
Other medications	13 (8.4)	6 (6.6)	11 (6.4)	8 (11.6)	11 (3.4)	14 (8.8)
Baseline MHQ hand function, Mean (SD)	53.9 (15.1)	48.9 (14.8)	54.1 (15.6)	47.0 (17.4)	54.0 (15.4)	48.1 (15.9)
Baseline SF12 physical summary score, Mean (SD)	35.4 (9.7)	31.1 (9.4)	35.4 (9.7)	32.1 (8.5)	35.4 (9.7)	31.5 (9.0)
Baseline SF12 mental summary score,	49.7 (10.5)	45.5 (10.7)	50.4 (10.4)	45.1 (11.7)	50.1 (10.4)	45.3 (11.1)

Mean (SD)						
Baseline EQ5D health state, Mean (SD)	0.6 (0.3)	0.5 (0.3)	0.6 (0.2)	0.5 (0.3)	0.6 (0.3)	0.5 (0.3)
Baseline pain troublesomeness score, Mean (SD)	43.1 (20.5	50.9 (24.2)	46.0 (21.1)	54.6 (21.6)	44.6 (20.9)	52.5 (23.1)
Baseline self-efficacy – confidence to manage their condition, Mean (SD)	69.5 (18.2)	62.5 (23.0)	71.3 (17.7)	62.2 (21.0)	70.5 (17.9)	62.4 (22.1)
Participant reported frequency of hand exercises at 4 months, n (%)						
At least 3 times a week	107 (71.8)	44 (67.7)	80 (48.2)	25 (45.5)	187 (59.4)	69 (57.5)
Less than 3 times a week	26 (17.5)	11 (16.9)	36 (21.7)	5 (9.1)	62 (19.7)	16 (13.3)
No exercises	16 (10.7)	10 (15.4)	50 (30.1)	25 (45.5)	66 (21.0)	35 (29.2)
Participant reported frequency of hand exercises at 12 months, n (%)						
At least 3 times a week	61 (40.4)	18 (33.3)	66 (39.1)	18 (38.3)	127 (39.7)	36 (35.6)
Less than 3 times a week	53 (35.1)	12 (22.2)	35 (20.7)	9 (19.1)	88 (27.5)	21 (20.8)
No exercises	37 (24.5)	24 (44.4)	68 (40.2)	20 (42.6)	105 (32.8)	44 (43.6)
Change in MHQ hand function baseline to 12 months, Mean (SD)	7.2 (13.6)	9.8 (16.8)	3.2 (16.0)	4.8 (16.3)	5.1 (15.0)	7.5 (16.7)
Change in SF12 physical summary score baseline to 12 months, Mean (SD)	0.8 (7.2)	2.3 (6.3)	-0.1 (7.6)	0.5 (6.7)	0.3 (7.5)	1.5 (6.5)
Change in SF12 mental summary score baseline to 12 months, Mean (SD)	2.1 (9.9)	2.4 (12.4)	0.2 (9.5)	1.1 (10.8)	1.1 (9.7)	1.8 (11.7)
Change in EQ5D health state baseline to 12 months, Mean (SD)	0.0 (0.2)	0.0 (0.2)	0.0 (0.2)	0.0 (0.3)	0.0 (0.2)	0.0 (0.3)

Intervention adherence

Exercise programme participants reported substantially reducing their frequency of hand exercises over time with 71.4% reporting that they exercised 3 times per week at 4 months and only 31.4% at the extended follow-up (Table 2). They had reported performing hand exercises for their RA more frequently than best practice usual care participants at both the 4 and 12 months follow-up. At extended follow-up there was no longer a clear difference between the two groups in their reports of hand exercises.

Table 2 Participant reported frequency of hand exercises for their RA [n(%)] for those that responded to the extended follow-up

	4 Months		12 Months		Extended follow-up	
	Usual Care	Exercise programme	Usual Care	Exercise programme	Usual Care	Exercise programme
Participant reported frequency of hand exercises	n=169	n=152	n=171	n=155	n=173	n=155
At least 3 times a week	80 (48.2)	107 (71.8)	66 (39.1)	61 (40.4)	60 (34.9)	48 (31.4)
Less than 3 times a week	36 (21.7)	26 (17.5)	35 (20.7)	53 (35.1)	38 (22.1)	48 (31.4)
No exercises	50 (30.1)	16 (10.7)	68 (40.2)	39 (24.5)	74 (43.0)	57 (37.3)
Not answered	3	3	2	2	1	2
P trend (Wilcoxon)	<0.0001		0.0884		0.7715	

Primary outcome – hand function

Figure 2 and Table 3 shows the change in MHQ hand function subscale scores over time for those completing the extended follow-up. Best practice usual care resulted in small but statistically significant improvements in hand function at 4 and 12 months, in comparison to baseline values. However, the within group difference between baseline and extended follow-up was not statistically significant [Mean MHQ hand function subscale score at baseline = 54.1 (SD15.65); extended follow-up = 56.1 (SD18.85); p=0.1122].

Figure 2 Mean change from baseline over time for the primary and secondary outcomes for those who responded to the extended follow-up. Error bars represent the standard error. For the number of participants providing data for each outcome at each time point please refer to Table 3.

Table 3 Estimates of effect in primary outcome and patient reported secondary outcome measures for those who responded to the extended follow-up.

	Mean change from Baseline (95% CI) Usual Care	Exercise programme	Mean treatment difference (95% CI)	P value	Number of participants confirmed
MHQ Overall hand function					
4 Months	3.27 (1.15 to 5.39)	9.27 (7.19 to 11.34)	6.24 (3.56 to 8.92)***	<0.0001	320
12 Months	3.19 (0.79 to 5.59)	7.18 (5.02 to 9.33)	3.91 (0.71 to 7.10)*	0.0171	324
Extended follow-up	1.97 (-0.45 to 4.39)	3.76 (1.50 to 6.02)	1.52 (-1.71 to 4.76)	0.3567	327
MHQ ADL (both hands)					
4 Months	3.37 (0.94 to 5.79)	8.29 (5.61 to 10.96)	5.07 (1.73 to 8.42)**	0.0032	319
12 Months	2.53 (-0.12 to 5.18)	5.34 (2.71 to 7.97)	2.83 (-0.90 to 6.56)	0.1375	323
Extended follow-up	2.34 (0.03 to 4.66)	3.15 (0.30 to 6.01)	0.72 (-2.88 to 4.32)	0.6948	324
MHQ Work					
4 Months	4.91 (1.91 to 7.91)	8.26 (5.47 to 11.04)	3.04 (-0.96 to 7.04)	0.1370	316
12 Months	2.97 (-0.05 to 5.99)	7.70 (4.73 to 10.68)	4.44 (0.30 to 8.57)*	0.0363	323
Extended follow-up	5.81 (2.97 to 8.65)	7.76 (4.67 to 10.84)	2.06 (-2.10 to 6.22)	0.3318	315
SF 12 Mental Component Score (MCS)					
4 Months	0.70 (-0.62 to 2.02)	1.09(-0.18 to 2.37)	0.51 (-1.16 to 2.18)	0.5488	319
12 Months	0.21 (-1.21 to 1.64)	2.12 (0.54 to 3.69)	1.63 (-0.22 to 3.49)	0.0857	322
Extended follow-up	0.21 (-1.23 to 1.66)	0.27 (-1.25 to 1.78)	0.22 (-1.71 to 2.15)	0.8252	326
SF 12 Physical Component Score (PCS)					
4 Months	0.62 (-0.39 to 1.63)	1.84 (0.65 to 3.02)	1.37 (-0.12 to 2.86)	0.0719	319
12 Months	-0.09 (-1.24 to 1.06)	0.76 (-0.39 to 1.92)	0.72 (-0.79 to 2.23)	0.3519	321
Extended follow-up	-0.51 (-1.66 to 0.64)	0.19 (-1.16 to 1.54)	0.50 (-1.24 to 2.25)	0.5720	326
EQ-5D Health state					
4 Months	0.0 (-0.03 to 0.04)	0.06 (0.02,0.09)	0.03 (-0.01 to 0.07)	0.1654	319
12 Months	0.02 (-0.02 to 0.05)	0.04 (0.00 to 0.07)	0.00 (-0.04 to 0.05)	0.8239	.322
Extended follow-up	-0.01 (-0.05 to 0.02)	-0.01 (-0.05 to 0.03)	-0.01 (-0.06 to 0.04)	0.6893	324

Pain troublesomeness score†					
4 Months	-4.79 (-7.76 to -1.82)	-5.57 (-8.25 to -2.90)	-2.51 (-6.22 to 1.21)	0.1872	315
12 Months	-4.68 (-7.83 to -1.53)	-5.03 (-8.16 to -1.90)	-1.58 (-5.65 to 2.48)	0.4454	322
Extended follow-up	-3.79 (-6.93 to -0.64)	0.20 (-2.98 to 3.38)	3.23 (-0.83 to 7.28)	0.1199	326
Self-efficacy – confidence to manage their condition					
4 Months	2.38 (-0.15 to 4.62)	6.58 (3.74 to 9.42)	3.41 (0.5 to 6.29)*	0.0209	319
12 Months	1.30 (-1.32 to 3.92)	5.46 (2.29 to 8.62)	3.19 (0.71 to 6.98)	0.1113	321
Extended follow-up	0.22 (-2.34 to 2.78)	2.96 (0.03 to 5.90)	2.30 (-1.20 to 5.79)	0.1988	323

***p<0.001; ** p<0.01; *p<0.05; ; † Higher score = more pain

Exercise resulted in substantial improvements from baseline, with the peak effect at 4 months. For both 4 and 12 months differences between the exercise and best practice usual care group were statistically and clinically significant. By the extended follow-up time point the exercise intervention was still associated with a significant within group improvement in hand function in comparison to baseline [Mean MHQ hand function subscale score at baseline =53.9 (SD15.1); extended follow-up = 57.7 (SD18.04); p=0.0014]. However, the difference between exercise and best practice usual care interventions was no longer statistically significant (Table 3).

Secondary outcomes

MHQ ADL and MHQ work subscales

Significant within group differences were observed in both groups for the MHQ ADL and MHQ work subscales at the extended follow-up compared to baseline ($p<0.05$ and $P<0.001$ for best practice usual care and the exercise arms respectively). Greater improvement from baseline was seen in the exercise arm (Figure 2 and Table 3).

There was a statistically significant between group difference in the MHQ ADL subscale at 4 and 12 months and the MHQ work subscale at 12 months favouring the exercise arm but this difference was no longer significant at the extended follow-up.

Health-related Quality of Life (SF-12 and EQ-5D)

There were no observable within group differences or between group differences at any follow-up time point as measured by the SF-12 or the EQ-5D (Figure 2 and Table 3).

Pain troublesomeness

There were statistically significant within group changes at the 4 and 12 months follow-up with both groups reporting less pain compared to baseline and this continued in the best practice usual care arm at extended follow-up (p=0.0196). However, the pain scores reported at extended follow-up in the exercise arm were similar to baseline scores (p=0.9039).

There was no statistically significant between group difference in pain troublesomeness scores at any follow-up time point (Figure 2 and Table 3).

Self-efficacy

At extended follow-up there was a significant within group change in self-efficacy observed in the exercise arm but not the best practice usual care arm. Participants in the exercise group reported higher self-efficacy scores compared to their baseline scores (p=0.0496) but this was not the case for the best practice usual care (p=0.8675).

Respondents in the exercise arm reported higher self-efficacy scores at 4 months follow-up compared to the best practice usual care group but this difference was diminished at 12 months and extended follow-up so the between group difference was no longer evident (Figure 2 and Table 3).

Participant rated improvement

Participant rated improvement in the exercise arm were significantly higher at 4 and 12 months follow-up than the best practice usual care group but there was no difference between the two groups at the extended follow-up (Table 4).

Table 4 Patient reported secondary outcome measures [n (%)] for those that responded to the extended follow-up

	4 Months		12 Months		Extended follow-up	
	Usual Care	Exercise programme	Usual Care	Exercise programme	Usual Care	Exercise programme
Participant rated improvement	**n=167**	**n=149**	**n=170**	**n=151**	**n=172**	**n=153**
Completely recovered	1 (0.6)	-	2 (1.2)	1 (0.7)	1 (0.6)	-
Much improved	18 (10.8)	34 (22.8)	14 (8.2)	31 (20.5)	22 (12.8)	25 (16.3)
Slightly improved	34 (20.4)	48 (32.2)	23 (13.5)	38 (25.2)	17 (9.9)	24 (15.7)
No change	65 (38.9)	45 (30.2)	69 (40.6)	47 (31.1)	75 (43.6)	58 (37.9)
Slightly worsened	41 (24.6)	17 (11.4)	49 (28.8)	22 (14.6)	41 (23.8)	35 (22.9)
Much worsened	8 (4.8)	5 (3.4)	12 (7.1)	9 (6.0)	15 (8.7)	7 (4.6)
Vastly worsened	-	-	1 (0.6)	3 (2.0)	1 (0.6)	4 (2.6)
P trend (Wilcoxon)	<0.0001		<0.0001		0.2018	

Multiple imputation

Multiple imputation was used to evaluate the impact of missing data and the estimate of treatment difference from baseline to extended follow-up was 1.75 (-1.20, 4.70), p=0.2433. This is similar to the non-imputed analysis suggesting that missing data was not a major influence on the study findings.

DISCUSSION

We have evaluated the long term outcomes of an individually tailored exercise programme compared to best practice usual care for adults with RA of the hand. Between group differences had

diminished over an average follow-up time of 26 months but generally functional scores favoured the exercise group. Both groups had improved hand function compared to baseline but this was only statistically significant in the exercise group. We interpret this to mean that although functional improvements due to the exercises had reduced, they had not diminished completely. Exercise arm participants completed treatment with their therapist approximately 3 months after randomisation so for some participants it had been 2 years since attending treatment. Therefore, it is very encouraging that some benefit still persisted. We aimed to estimate exercise adherence beyond the supervised period and the data shows that by the extended follow-up many participants in the exercise arm were no longer exercising as intended. RA is a progressive disease so regular exercise of sufficient intensity is needed to maintain muscle strength. It is likely that participants were no longer achieving a sufficient dose to maintain functional improvements.

Another study of upper limb exercises demonstrated a similar reduction of benefit over time where gains observed at 12 weeks were no longer evident at 26 weeks follow-up[26] with an assumption it was due to reduced adherence but this data was not collected.

Another proposed mechanism by which the intervention improved function was by bolstering self-efficacy. This effect had also diminished which may be due to the fact it had been 2 years since attending treatment.

One outcome favoured the best practice usual care (pain troublesomeness scores). There was no between group differences but the best practice usual care group had a small but statistically significant reduction in pain compared to baseline unlike the exercise group. However, the reduction in pain was small and we are confident the exercises did not increase pain while improving function. There was no difference in adverse events reported[11] and we conclude that the exercise programme is safe.

Clinical implications and further research

The SARAH exercise programme is an effective adjunct to the medical management of RA for patients with hand problems, but the benefit from the exercise programme did reduce over time as participants reported doing less exercises. These findings raise important questions regarding how patients might be supported to exercise long term which is probably necessary to maintain functional gains.

Further research is needed to establish how ongoing support could be provided. Patients with RA are seen frequently in rheumatology outpatient clinics with the National Institute for Health and Care

Excellence (NICE) recommending annual reviews for patients with RA[27]. Staff could monitor patient's exercise participation during these appointments. However, there is uncertainty amongst health professionals about providing advice about exercise to patients with RA[28, 29]. Specialist rheumatology nurses play an important role in monitoring and supporting patients, yet, EULAR recommendations for specialist rheumatology nurses do not mention exercise[30]. There is a need to educate health professionals and patients about the importance of regular exercise. It is safe for patients with RA to exercise[26, 31] and health professionals need to be confident to advise on exercise regimes, referring to therapists when needed. Consideration should be given to how we can ensure all health professionals who see patients with RA can encourage adherence to exercise, for example, nurses or therapists working within primary care settings and not just specialist rheumatology clinics.

Patients with RA have to continually modify their treatment in response to changes in their condition. This also applies to exercise which presents another challenge. The SARAH programme is manualised, with clear instructions for progressing/regressing exercises allowing patients to modify exercises when needed. Participant feedback was that this was easy to follow[12] so these types of resources could be made available to health professionals and patients to help patients to exercise regularly.

Methodological limitations

The response rate was lower than the main study. This was not unexpected as this follow-up was not planned at the outset of the study so participants were unaware they would receive the postal questionnaire. We only contacted participants by post so as not to place undue pressure on them to respond and only phoned those who requested to complete the questionnaire by phone. As a consequence, the analysis is underpowered to detect a difference in the primary and secondary outcomes. Loss to follow-up could introduce bias and there were some differences in responders and non-responders, but these were equal across treatment groups. Most notably non-responders had poorer hand function at baseline and reported lower levels of exercise adherence at earlier follow-up especially in the exercise arm. It could be expected that responders would have better outcomes compared to non-responders resulting in an overestimate of the treatment effect. However, multiple imputation techniques estimated the effect of missing data and the results were largely similar indicating that missing data did not overly influence the findings. Overall, we are confident that the participants providing data were a good representation of the total cohort. The other factor that may have influenced findings was the disease status of participants. RA is a fluctuating condition so disease status at the time of follow up may have influenced outcomes but

this information was not available. In conclusion, a hand exercise programme is an effective adjunct to current drug management to improve hand function. Participants in the exercise group had improved hand function compared to baseline more than 2 years after randomisation. Hand function had reduced over time which coincided with a reduction in hand exercises highlighting the importance of promoting long term exercise adherence amongst patients with RA.

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EW: Design of the trial, data collection, interpretation of the data, drafting and revising of the paper, final approval of the version to be published.

CC: Data analysis and interpretation, drafting and revising the paper, final approval of the version to be published.

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COMPETING INTERESTS

None.

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DATA SHARING STATEMENT

The data are available on request from the Chief Investigator (Professor Sarah Lamb).

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FIGURES

Figure 1 – CONSORT Flow diagram

Figure 2 Mean change from baseline over time for the primary and secondary outcomes for those who responded to the extended follow-up. Error bars represent the standard error. For the number of participants providing data for each outcome at each time point please refer to Table 3.

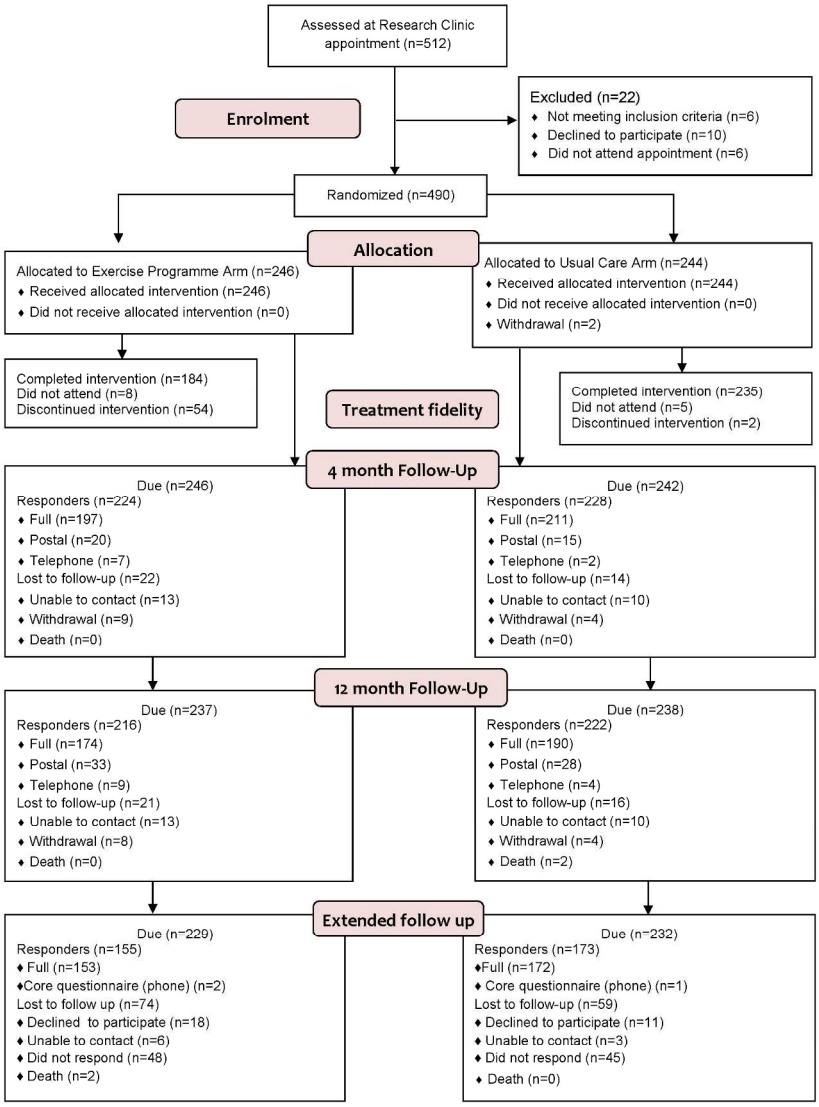
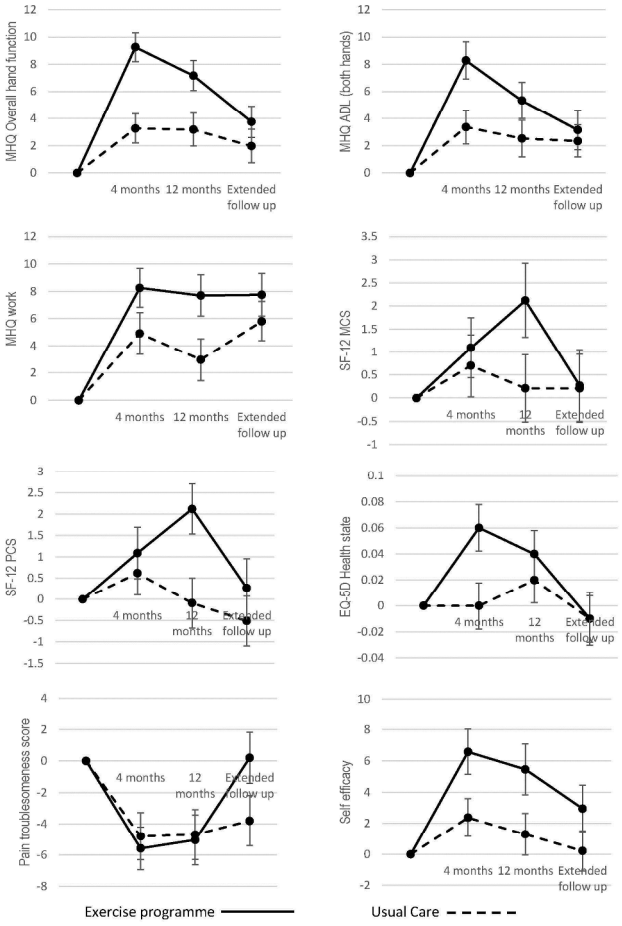


Figure 1 Consort Flow Chart

215x279mm (300 x 300 DPI)



Graphs

210x297mm (300 x 300 DPI)

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2 Abstract
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	4-5
	4b	Settings and locations where the data were collected	4-5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5 – reference provided for intervention paper
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	5-6
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	6
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9		6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to	6

		interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	6
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	6-7
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	6-7
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	7, Figure 1, Tables 1-4
	13b	For each group, losses and exclusions after randomisation, together with reasons	Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	5
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Tables 2-4 5
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Tables 2-4
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	16
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	17 Adverse events reported in main trial paper – reference provided
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	18
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	18
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	16-18
Other information			

Registration	23	Registration number and name of trial registry	4
Protocol	24	Where the full trial protocol can be accessed, if available	4
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	20-21

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.