Exercises to improve function of the rheumatoid hand (SARAH): a randomised controlled trial

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Summary

Background **Disease-modifying biological agents and other drug regimens have substantially improved control of disease activity and joint damage in people with rheumatoid arthritis of the hand. However, commensurate changes in function and quality of life are not always noted. Tailored hand exercises might provide additional improvements, but evidence is lacking. We estimated the effectiveness and cost-effectiveness of tailored hand exercises in addition to usual care during 12 months.**

Methods **In this pragmatic, multicentre, parallel-group trial, at 17 National Health Service sites across the UK we randomly assigned 490 adults with rheumatoid arthritis who had pain and dysfunction of the hands and had been on a stable drug regimen for at least 3 months, to either usual care or usual care plus a tailored strengthening and stretching hand exercise programme. Participants were randomly assigned with stratification by centre. Allocation was computer generated and unmasked to participants and therapists delivering treatment after randomisation. Outcome assessors and all investigators were masked to allocation. Physiotherapists or occupational therapists gave the treatments. The primary outcome was the Michigan Hand Outcomes Questionnaire overall hand function score at 12 months. The analysis was by intention to treat. We calculated cost per quality-adjusted life-year. This trial is registered as ISRCTN 89936343.**

Findings **Between Oct 5, 2009, and May 10, 2011, we screened 1606 people, of whom 490 were randomly assigned to usual care (n=244) or tailored exercises (n=246). 438 of 490 participants (89%) provided 12 month follow-up data. Improvements in overall hand function were 3·6 points (95% CI 1·5–5·7) in the usual care group and 7·9 points (6·0–9·9) in the exercise group (mean difference between groups 4·3, 95% CI 1·5–7·1; p=0·0028). Pain, drug regimens, and health-care resource use were stable for 12 months, with no difference between the groups. No serious adverse events associated with the treatment were recorded. The cost of tailored hand exercise was £156 per person; cost per quality-adjusted life-year was £9549 with the EQ-5D (£17 941 with imputation for missing data).**

Interpretation **We have shown that a tailored hand exercise programme is a worthwhile, low-cost intervention to provide as an adjunct to various drug regimens. Maximisation of the benefits of biological and DMARD regimens in terms of function, disability, and health-related quality of life should be an important treatment aim.**

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Introduction

Rheumatoid arthritis has a substantial effect on the quality of life, function, and productivity of millions of people across the world. Its major effects are on the synovial joints, particularly the hands.[1] Best practice mandates aggressive control of joint inflammation with disease modifying drugs (DMARDs) and, more recently, biological agents. These drugs have delivered substantial improvements in disease activity and minimised structural damage.[2,3] However, commensurate changes in disability, health-related quality of life, and joint deformity are not always noted.[4,5]

Hand exercises might enhance the effect of a range of drug regimens in rheumatoid arthritis of the hand, but evidence is lacking. Effective exercise interventions are potentially low-cost compared with other treatments for the disease, but rely on good compliance.[6,7] Results from small randomised controlled trials provide some evidence that exercise can restore or maintain hand function,[8] but larger trials with longer follow-up are needed.

The aim of the Strengthening and Stretching for Rheumatoid Arthritis of the Hand Trial (SARAH) was to estimate, for people whose rheumatoid arthritis is controlled by various drug regimens, the effectiveness and cost-effectiveness of adding an individually tailored, progressive exercise programme for the hands and arms, in addition to best practice usual care.

Methods

Study design and participants

The SARAH trial was a pragmatic, multicentre, investigator-blind, parallel-group randomised controlled trial. A detailed protocol is published elsewhere.[9] The trial was done at 17 National Health Service hospital trusts in

For more on the **SARAH trial materials** see http://www.octru.ox.ac.uk/interventions/SARAHtrial/sarah-trial-materials

England. Participants were adults with rheumatoid arthritis meeting the American College of Rheumatology clinical and immunological criteria,[10] who reported active pain and dysfunction of hands, who were either not on a DMARD regimen, or who had been on a stable DMARD regimen (including biological agents if used) for 3 months or more. Exclusion criteria were upper limb surgery or fracture in the previous 6 months, pregnancy, or waiting for upper limb surgery.

Patients gave written informed consent in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. The trial was approved by the Oxford C Multicentre Research Ethics Committee (REC reference 08/H0606/47).

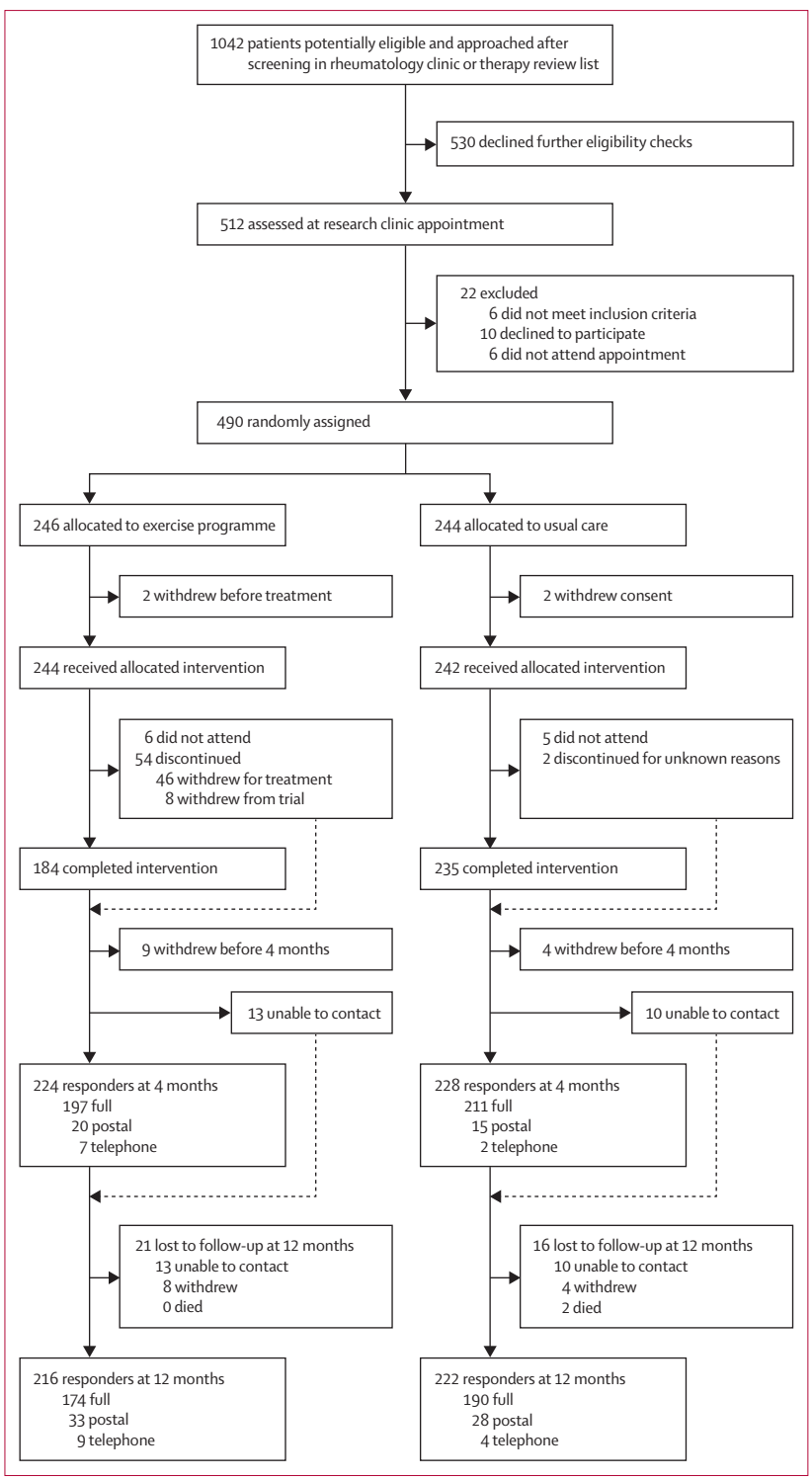

Figure: **Trial profile**

Randomisation and masking

We used a central telephone randomisation service at the Warwick Clinical Trials Unit. The study was individually randomised, with stratification by centre with a variable (random) block length of between two and eight. Allocation was computer generated and unmasked to participants and therapists delivering treatment after randomisation. Outcome assessors and all investigators were masked to group allocation. We asked participants not to disclose allocation to the assessors at follow-up. We asked outcome assessors if they could guess the allocation of participants at the end of each assessment.

The first centre to begin recruitment was the University Hospital of Coventry and Warwickshire, in October, 2009, followed by South Warwickshire NHS Trust; Basingstoke and North Hampshire NHS Trust; Wrightington, Wigan and Leigh NHS Trust; Royal National Hospital for Rheumatic Diseases NHS Trust; Winchester and Eastleigh Healthcare NHS Trust; Poole Hospital NHS Trust; Portsmouth Hospitals NHS Trust; Royal Bournemouth and Christchurch Hospitals NHS Trust; Dorset Primary Care Trust; Worcestershire Acute Hospitals NHS Trust; Nuffield Orthopaedic Centre NHS Trust; George Eliot NHS Trust; Heart of England NHS Trust; Sussex community NHS Trust; University Hospitals of Leicester NHS Trust; and Derby Hospitals NHS Trust. Stratified randomisation ensured that trial groups were parallel; we accumulated participants in both groups from initiation of recruitment.

Procedures

We asked clinicians to identify potentially eligible patients during clinic visits or from clinic records, and to provide a written invitation and information sheet. If willing, patients attended a face-to face-appointment with a research clinician to discuss the trial, check eligibility, and complete baseline assessments and study registration.

We have published a detailed description of the interventions.[11] Usual care was based on international clinical guidance and included joint-protection education and, where indicated, functional splinting.[12,13] A maximum of three sessions of outpatient therapy were allowed, to a maximum of 1·5 h contact time. We provided participants with information sheets published by Arthritis Research UK, and encouraged them to be active.

We added the exercise programme to usual care, and intended the exercises to be done daily at home for a minimum of 12 weeks. The programme included six sessions of face-to-face contact with a physiotherapist or occupational therapist. It included seven mobility exercises and four strength or endurance exercises against resistance provided by bands, balls, or therapeutic putty. Participants had an initial assessment to tailor the exercise prescription to their strength, pain level, and flexibility. We set the initial intensity of exercise at moderate-to-somewhat-hard using a modified Borg Scale.[14] We used a standardised protocol to progress or regress the exercises, aiming to increase both repetitions and resistance over time.[11] We provided participants with an exercise booklet with pictures and instructions describing the exercises, and the necessary resistance materials. We incorporated evidence-based strategies to promote uptake and adherence to the exercise programme, consisting of an exercise contract, diary, patient-led goal-setting, and regular review of goals.[15]

Drug therapy and surgery continued in both groups of the trial as indicated by clinical need. We did not allow manual therapy, resting splints, or electrotherapies in either group because of scarcity of evidence of their effectiveness, or because of evidence of ineffectiveness.[16]

Therapists were trained to deliver both the exercise programme and control interventions. All therapists received 4 h of training covering theoretical and practical application of both interventions, and two short update training sessions during the trial. Therapists detailed the content of all treatment sessions in a standardised log book and clinical records. Every therapist received at least one quality-control assessment per intervention type, and all records were reviewed to ascertain attendance and for documentary evidence of assessment, and of progression or regression of exercises. We defined patient compliance with the intervention as attendance at all face-to-face sessions with the therapist. Participants kept a diary record of exercise completion.

Outcomes

A detailed description of measurements is in the published protocol.[9] Follow-up data were obtained at 4 and 12 months after randomisation at a face-to-face research clinic appointment, supplemented by postal and telephone questionnaires when participants were unable to attend. All questionnaires were completed independently by participants. The primary outcome measure was the overall hand function subscale of the Michigan Hand Outcome Questionnaire (MHQ) at 12 months (range 0–100; high score indicates great function).[17]

Secondary outcomes were other subscales of the MHQ—activities of daily living, pain, work performance, satisfaction, aesthetics and the summed MHQ score (range 0–100; high score indicates good performance). We measured pain using the Troublesomeness questionnaire (range 0–20; high score indicates great pain),[18] and self-reported global change, benefit or harm, and treatment satisfaction questions. We obtained physical ability measures consisting of isometric pinch and grip strength, dexterity, hand and wrist range of motion, and metacarpalphalangeal joint alignment.[9] We measured self-efficacy using the Arthritis Self-efficacy scale (seven items; high score indicates great self-efficacy).[19] We used modified tender and swollen joint count of the hands and wrist (22 joints in total,

For the **protocol** see http://www.octru.ox.ac.uk/interventions/SARAHtrial

	Usual care (n=242)	Exercise (n=246)
Age (years)		
Mean (SD)	63·5 (11)	61·3 (12)
Sex		
Female (%)	186 (76%)	188 (76%)
Ethnic origin		
White	235 (98%)	238 (97%)
Indian	2 (1%)	3 (1%)
Pakistani	1 (<1%)	..
Mixed	1 (<1%)	3 (1%)
Other	1 (<1%)	2 (1%)
In employment		
Full-time employed	22 (9%)	29 (12%)
Part-time employed	30 (12%)	26 (11%)
Self-employed	10 (4%)	11 (5%)
Right/left-hand dominant		
Right	215 (90%)	226 (92%)
Left	23 (9%)	18 (7%)
Years since rheumatoid arthritis diagnosis, estimated by participant (median, IQR)	10 (4, 22)	10 (4, 21)
Baseline ESR (median, IQR)	16 (8, 28)	15 (7, 28)
Baseline CRP (median, IQR)	6 (3, 12)	5 (3, 12)
Drug treatment*		
Biological DMARD	52 (22%)	51 (21%)
Combination nonbiological DMARD	53 (22%)	72 (29%)
Single nonbiological DMARD	118 (49%)	103 (42%)
Other drugs	19 (8%)	19 (8%)
MHQ, mean (SD)		
Overall hand function (both)	52·1 (16·4)	52·1 (15·2)
Activities of daily living (both)	54·1 (25·0)	54·5 (24·5)
Work	48·4 (22·0)	48·2 (22·0)
Pain	51·4 (19·9)	51·9 (21·9)
Aesthetics (both)	58·6 (22·1)	56·9 (22·0)
Satisfaction (both)	43·5 (22·3)	43·9 (19·7)
Overall score	50·9 (16·9)	50·6 (16·4)
SF-12 (mean, SD)		
Aggregate physical scale (PCS)	34·5 (9·5)	33·8 (9·8)
Aggregate mental scale (MCS)	48·9 (11·0)	48·1 (10·7)
Pain/troublesomeness (mean, SD)		
Overall score	48·5 (21·5)	46·0 (22·2)
Confidence in tasks overall score (self-efficacy)	68·7 (19·1)	67·0 (20·3)
Clinical assessment (mean, SD)		

(Table 1 continues on next page)

	Usual care (n=242)	Exercise (n=246)
(Continued from previous page)		
MCP joint deformity in degrees	7·4 (9·4); n=238	6·8 (8·4); n=245
Active wrist ROM score in degrees†	90·1 (31·7); n=239	88·0 (29·6); n=245
Combined finger flexion in mm‡	12·8 (16·1); n=238	13·0 (16·1); n=245
Composite finger extension in mm†	20·2 (25·5); n=231	21·3 (24·4); n=244
Thumb opposition score†	8·0 (2·1); n=241	8·2 (2·2); n=246
Swollen joint count	4·1 (4·8); n=241	4·2 (4·8); n=246
Tender joint count	4·8 (5·1); n=241	5·0 (5·40); n=246
Dexterity: nine-hole peg test (s)	27·3 (9·4); n=240	27·2 (8·2); n=246
Maximum full-hand grip force (Newtons)	130·3 (73·1); n=240	134·2 (83·3); n=245
Maximum pinch grip force (Newtons)	39·1 (19·6); n=237	40·2 (21·1); n=243

Data are N (%), median (IQR), or mean (SD). DMARD=disease-modifying drugs. ESR=erythrocyte sedimentation rate. MHQ=Michigan Hand Outcome Questionnaire. PCS=physical component score. MCS=mental component score. MCP=metacarpalphalangeal. ROM=range of motion. *Not mutually exclusive. †Highest score=greatest movement. ‡Lowest score=greatest movement.

Table 1: **Baseline characteristics**

	Usual care	Exercise
Treatments delivered		
Median number of sessions	1 (1–2)	6 (5–6)
Did not attend any sessions	7/242 (3%)	8/246 (3%)
Attended assessment session only*	135/242 (56%)	8/246 (3%)
Part completion of treatment	10/242 (4%)	46/246 (19%)
Full completion of treatment	225/242 (93%)	184/246 (75%)
Time from randomisation to last treatment (months)	1·1 (0·5–1·7)	3·2 (2·7–4·0)
Self-reported exercise (≥1–2 sessions per week)		
At 4 months	137/222 (62%)	174/216 (81%)
At 12 months	123/216 (57%)	128/206 (62%)
Treatment session components		
Provided joint protection advice	224/235 (95%)	220/238 (92%)
Provided ACR booklets	220/235 (94%)	222/238 (93%)
Provided functional splinting	103/235 (44%)	98/238 (41%)
Modified or reviewed functional splinting?	81/235 (34%)	111/238 (47%)
Helped patient complete exercise diary?	NA	223/238 (94%)
Helped patient complete personal exercise guide?	NA	201/238 (85%)
Median number of exercises progressed	NA	8 (3–10)
Ran through discharge advice	NA	169/238 (71%)
Discussed continuing with exercise programme	NA	169/238 (71%)

Data are median (IQR), or n/N who completed questionnaires or treatment logs (%). ACR=American College of Rheumatology. NA=not applicable. *No follow-up sessions were attended (usual care were expected to have between one and three sessions).

Table 2: **Details of the interventions provided in the groups assigned to usual care and to exercise**

according to Fuchs and colleagues[20]) to assess changes in disease activity, along with erythrocyte sedimentation rate (ESR)and C-reactive protein (CRP) obtained from patient records. Health-related quality of life (Short Form-12[21] [range 0–100; high scores indicate high quality of life] and EuroQol EQ-5D[22] [range 0–1]) were obtained for the health economics analysis. We obtained self-assessment of exercise compliance using a five-item questionnaire. We classified serious adverse events (death, life threatening events, hospitalisation, medical intervention, and disability) as related, unrelated, and possibly related to treatment, as were all adverse events reported by clinicians, researchers, or participants.

Statistical analysis

A previous efficacy study, in which a similar outcome measure was used, reported a standardised mean difference (SMD) of 0·4 (moderate).[23] For this larger, more pragmatic multicentre trial, an SMD of 0·3 in the primary outcome would be realistic and meaningful, and similar to worthwhile effects in other pragmatic studies of rheumatoid arthritis.[24] To show this difference with 80% power at the 5% significance level, we needed data for a total of 352 participants (using SAS procedure GLMPOWER). Allowing for a 25% drop-out rate in follow-up, we sought to recruit at least 469 participants. The original sample size calculation did not include inflation for therapist effects, although we included assessment for these effects in the final analysis.

The analysis was by intention to treat. We estimated means, standard deviations, and proportions to provide descriptive data for every group. We estimated treatment effects using generalised linear modelling, adjusted for baseline score, age, sex, and pre-randomisation drug regimens (no DMARD, single non-biological DMARD, combination non-biological DMARD, or biological DMARD). We estimated therapist effects from a random effect nested within every centre. We used statistical tests of interaction to do prespecified subgroup analyses on baseline drug regimen (no DMARD, single non-biological DMARD, combination non-biological DMARD, or biological DMARD) and disease duration (<5 years or ≥5 years) because we believed that these could most affect response to the interventions. We used published score-specific guidance to manage missing data,[17,25] and investigated the effects of missing data using multiple imputation analysis. We used complier-average causal effect analysis (CACE) to estimate the effects of patient compliance on the primary outcome.[26] We did the analyses using SAS version 9.2 software. One interim review was planned at 1 year after start of recruitment. As expected at this time, the 12 month data were insufficient to test the primary outcome hypothesis, so the Independent Data Monitoring Committee based any consideration of stopping the trial only on treatment uptake at 4 months and adverse event reports.

Therapists or research clinicians recorded adverse drug reactions and serious adverse events at follow-up appointments, or participants themselves recorded events. They recorded these reactions and events on a specific event notification form and classified them through discussions with local investigators and the trial lead. We requested as much information as possible from the participants, especially about the potential attribution of the event.

We estimated intervention costs from individual patient attendance records, averaged across participants attending at least one treatment session, and included equipment, therapist time, and training costs. We obtained data for use of health-care resources at 4 and 12 months and applied published unit costs to these services.[27] We estimated quality-adjusted life-years (QALYs) from EQ 5D and SF-6D data. We estimated the incremental cost per QALY gained using complete case analysis and with several imputations for missing data, using recognised methods for economic analyses.[28]

Role of the funding source

The funder approved the design and appointed trial steering and data monitoring committees to oversee the study. The funder had no role in data analysis, data interpretation, or the decision to submit for publication.

	Mean change from baseline (95% CI)		Mean treatment difference (95% CI)	p value	Number of participants confirmed
	Usual care	Exercise			
Overall hand function exercise (MHQ)					
4 months	4·04 (2·17–5·91)	8·73 (6·83–10·64)	4·71 (2·32–7·11)	0·0001	449
12 months	3·56 (1·45–5·68)	7·93 (5·98–9·88)	4·28 (1·49–7·06)	0·0028	438
CACE at 12 months	NA	NA	5·23 (2·62–8·01)	0·0001	..
MHQ ADL (both hands)					
4 months	2·57 (−0·40–4·74)	7·86 (5·44–10·28)	5·66 (2·64–8·69)	0·0003	448
12 months	2·27 (−0·04–4·59)	5·89 (3·66–8·13)	3·48 (0·31–6·66)	0·0321	436
MHQ work					
4 months	5·27 (2·62–7·92)	6·12 (3·68–8·56)	1·04 (−2·39–4·48)	0·5518	445
12 months	3·11 (0·23–5·98)	8·12 (5·36–10·87)	4·62 (0·82–8·42)	0·0175	436
MHQ satisfaction (both hands)					
4 months	6·66 (4·01–9·31)	9·59 (6·86–12·32)	3·61 (0·12–7·09)	0·0430	445
12 months	7·06 (4·16–9·95)	10·36 (7·53–13·18)	3·38 (−0·37 to 7·13)	0·0784	436
MHQ pain*					
4 months	−5·11 (−7·58 to −2·63)	−7·60 (−9·94 to −5·26)	−3·30 (−6·50 to −0·11)	0·0433	445
12 months	−6·01 (−8·74 to −3·29)	−8·26 (−10·83 to −5·70)	−2·40 (−5·92 to 1·12)	0·1814	437
MHQ aesthetics (both hands)					
4 months	2·84 (0·27–5·41)	3·52 (0·89–6·14)	0·39 (−2·96 to 3·74)	0·8209	442
12 months	3·37 (0·42–6·33)	4·70 (1·81–7·59)	1·01 (−2·70 to 4·72)	0·5933	437
MHQ summed score					
4 months	4·34 (2·67–6·00)	7·28 (5·65–8·91)	3·17 (0·91–5·43)	0·0063	451
12 months	4·22 (2·23–6·21)	7·59 (5·75–9·43)	3·21 (0·53–5·89)	0·0195	438
SF 12 Mental Component Score					
4 months	0·58 (−0·56 to 1·73)	0·46 (−0·66 to 1·59)	−0·16 (−1·58 to 1·27)	0·8299	443
12 months	0·41 (−0·89 to 1·71)	2·19 (0·75–3·63)	1·59 (−0·06 to 3·23)	0·0593	423
SF 12 Physical Component Score					
4 months	0·91 (0·03–1·80)	2·04 (1·01–3·08)	1·18 (−0·11 to 2·46)	0·0743	443
12 months	0·03 (−0·96 to 1·03)	1·19 (0·23–2·14)	0·93 (−0·35 to 2·22)	0·1555	423
EQ-5D health state					
4 months	0·01 (−0·03 to 0·04)	0·04 (0·01–0·07)	0·02 (−0·02 to 0·06)	0·3813	448
12 months	0·02 (−0·01 to 0·06)	0·03 (0·00–0·06)	0·00 (−0·03 to 0·04)	0·8714	434
Troublesomeness					
4 months	−4·64 (−7·23 to −2·05)	−5·44 (−7·91 to −2·97)	−2·70 (−5·91 to 0·50)	0·0993	439
12 months	−4·54 (−7·35 to −1·73)	−4·32 (−7·15 to −1·49)	−1·61 (−5·21 to 1·99)	0·3810	423
Self-efficacy					
4 months	2·04 (−0·10 to 4·19)	5·78 (3·40–8·17)	3·38 (0·45–6·30)	0·0244	442
12 months	1·11 (−1·44 to 3·66)	5·19 (2·45–7·92)	3·21 (−0·19 to 6·62)	0·0651	422

MHQ=Michigan Hand Outcome Questionnaire. CACE=complier-average causal effect analysis. ADL=activities of daily living. SF-12=short form-12. EQ-5D=EuroQol EQ-5D.
*High score=great pain.

Table 3: **Estimates of effect in primary outcome and patient-reported secondary outcome measures**

	Mean change from baseline (95% CI)		Mean treatment difference (95% CI)	p value	Number of participants confirmed
	Usual care	Exercise			
Full-hand grip force (Newtons)					
4 months	7·35 (2·43–12·28)	15·55 (10·17–20·93)	9·29 (2·01–16·57)	0·0129	400
12 months	9·57 (3·66–15·48)	15·77 (10·11–21·42)	6·41 (−1·87 to 14·70)	0·1303	355
Pinch grip force (Newtons)					
4 months	3·15 (1·60–4·70)	4·92 (2·74–5·4)	1·57 (−0·59 to 3·73)	0·1547	396
12 months	2·35 (0·63–4·06)	5·33 (2·99–7·68)	3·01 (0·13–5·88)	0·0411	351
Active wrist ROM score (degrees)*					
4 months	2·75 (0·63 to 4·87)	4·84 (2·65 to 7·02)	1·58 (−1·25 to 4·41)	0·2750	401
12 months	4·21 (1·73 to 6·68)	4·56 (2·13 to 7·00)	0·27 (−2·72 to 3·26)	0·8587	356
Combined finger flexion finger (mm)†					
4 months	−3·39 (−4·54 to −2·25)	−4·45 (−5·82 to −3·07)	−0·93 (−2·43 to 0·58)	0·2281	398
12 months	−3·20 (−4·51 to −1·89)	−3·92 (−5·48 to −2·36)	−0·64 (−2·40 to 1·13)	0·4793	355
Composite finger extension (mm)*					
4 months	1·45 (−0·17 to 3·07)	4·04 (1·98 to 6·09)	2·55 (0·05 to 5·04)	0·0462	390
12 months	1·45 (−0·76 to 3·65)	4·81 (2·77 to 6·84)	4·05 (1·13 to 6·96)	0·0068	346
Thumb opposition score*					
4 months	0·18 (0·00 to 0·35)	0·31 (01·3 to 0·50)	0·13 (−0·10 to 0·37)	0·2725	403
12 months	0·12 (−0·07 to 0·30)	0·16 (−0·04–0·37)	0·10 (−0·16 to 0·36)	0·4416	359
Dexterity: nine-hole peg test (s)					
4 months	−0·74 (−1·50 to 0·03)	−1·39 (−1·97 to −0·81)	−0·64 (−1·53 to 0·26)	0·1643	403
12 months	−0·09 (−0·92 to 0·74)	−1·33 (−1·86 to −0·80)	−1·19 (−2·15 to −0·23)	0·0156	358
Swollen joint count (both hands)					
4 months	−0·12 (−0·73 to 0·48)	−1·05 (−1·58 to −0·53)	−0·87 (−1·50 to −0·23)	0·0077	405
12 months	−1·02 (−1·71 to −0·34)	−1·13 (−1·69 to −0·56)	−0·07 (−0·74 to 0·61)	0·8844	360
Tender joint count (both hands)					
4 months	−0·38 (−1·02 to 0·27)	−1·27 (−1·86 to −0·68)	−1·03 (−1·77 to −0·29)	0·0069	405
12 months	−1·15 (−1·86 to −0·43)	−0·96 (−1·69 to −0·23)	0·12 (−0·77 to 1·00)	0·7955	360
MCP joint deformity (degrees)					
4 months	−0·59 (−1·32 to 0·15)	−0·92 (−1·57 to −0·27)	−0·66 (−1·53 to 0·21)	0·1357	398
12 months	−0·32 (−1·01 to 0·36)	−0·70 (−1·41 to 0·01)	−0·56 (−1·50 to 0·37)	0·2369	355
Erythrocyte sedimentation rate [log transformation]					
4 months	−0·09 (−0·20 to 0·02)	−0·04 (−0·15 to 0·07)	−0·06 (−0·23 to 0·11)	0·4864	276
12 months	−0·10 (−0·23 to 0·03)	−0·04 (−0·18 to 0·10)	−0·02 (−0·18 to 0·15)	0·8323	252
C-reactive protein [log transformation]					
4 months	−0·18 (−0·32 to −0·03)	0·04 (−0·11 to 0·19)	0·32 (0·08 to 0·55)	0·0093	322
12 months	−0·12 (−0·29 to 0·05)	−0·14 (−0·29 to 0·02)	−0·03 (−0·24 to 0·19)	0·8185	291

ROM=range of motion. MCP=metacarpalphalangeal. *High score=great movement. †Low score=less movement.

Table 4: **Estimates of effect in physical performance and clinical secondary outcome measures**

The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Oct 5, 2009, and May 10, 2011, we screened 1606 people, of whom 512 were potentially eligible and willing to be randomly assigned (figure). After excluding 22 people at the formal eligibility check, we randomly assigned the remaining 490 patients to usual care (n=244) or to the tailored exercise programme (n=246). Two participants recruited to the group assigned to usual care withdrew their consent for any data to be used. Most participants were recruited from outpatient clinics (198 [81%] of 246 in the group assigned to exercise and 199 [82%] of 242 in the group assigned to usual care). The other participants were recruited from mailing patients on consultant and therapy review lists.

Outcomes were obtained for about 90% of participants at 12 months (figure). Participants lost to follow-up seemed to be younger and more likely to be men than those retained in the study (appendix p 3). The loss to follow-up was slightly greater in the group assigned to exercise. Data quality was good, with few missing data. 408 (90%)of responses were taken with face-to-face clinical assessment at 4 months and 364 (83%) at 12 months. Postal responses contributed 35 (8%) at 4 months and 61 (14%) at 12 months, and telephone responses contributed nine (2%) at 4 months and 13 (3%) at 12 months, with no difference between groups.

103 reports of serious adverse events were reported, but none were regarded as related to treatment: two deaths, in usual care; three life-threatening conditions, one in the group assigned to usual care and two in the group assigned to exercise; ten hospital admissions, three in the group assigned to usual care and seven in the group assigned to exercise; two needing medical intervention, one in the group assigned to usual care and one in the group assigned to exercise; 86 reported disability, 38 in the group assigned to usual care and 48 in the group assigned to exercise, all accounted for by flares of rheumatoid disease. Two patients had transient exacerbation of arm pain in the group assigned to exercise. Outcome assessors correctly guessed allocation in 54% of cases (50% representing an equal chance), but the correct guesses did not affect the effect estimates.

Table 1 shows baseline characteristics. More than 90% of participants were treated with biological or non-biological DMARDs. In the group assigned to exercise, as compared with usual care, slightly more participants were using a combination of non-biological DMARDs before randomisation, and fewer used a single DMARD. The most common biological DMARDs used were adalimumab (42 [40%] of 104 participants on biologicals) and etanercept (34 [32%]), and methotrexate was the most commonly used non-biological DMARD (used by 342 [81%] of 424 participants either monotherapy or combination). Drugs other than biological or non-biological DMARDs (such as analgesics or mild opiates) were prescribed for a small proportion of participants (38 [8%] of 488).

Table 2 details treatments received. 48 therapists provided treatment. Treatment was initiated after baseline assessment at a median of 20 days (IQR 12–34) for the group assigned to exercise and 19 days (13–33) for

the group assigned to usual care. Nearly all participants completed treatment in the usual care group and 184 (75%) participants attended all six sessions in the intervention group. Participants in the exercise group reported greater compliance with daily or any exercise at 4 months; this difference narrowed at 12 months.

Comparison of treatment attendance and content across the two trial groups indicated that therapists complied well with the protocol (table 2). No significant therapist effects were recorded (intraclass coefficient <0·0001).

Table 3 provides estimates of treatment effect for patient-reported outcomes. The exercise group's improvement was more than double that of the usual care group. The difference between groups was 4·3 (95% CI 1·5–7·1; effect size 0·3). In the CACE analysis the between-group difference in the primary outcome was increased. Changes in secondary outcomes mirrored these trends, with significant differences in MHQ of activities of daily living, work, and satisfaction subscales, MHQ summed score, and self-efficacy. No significant deterioration was recorded in pain or aesthetics in either group during the 12 months, and no between-group differences. Participant's global ratings of change in their hands, wrists, or both, were improved in the group assigned to exercise at both 4 and 12 months, (p<0·0001, Wilcoxon test). 92 (45%) of 206 participants assigned to the exercise group reported improvement compared with 45 (21%) of 216 participants assigned to usual care at 12 months. 165 (81%) of 204 participants in the exercise group reported benefit compared with 135 (63%) of 213 participants in the group assigned to usual care at 12 months (p<0·0001, Wilcoxon test). Participant ratings of satisfaction with treatment also favoured the intervention group at both timepoints (p=0·0347 at 12 months, Wilcoxon test).

Table 4 provides estimates of treatment effect for impairment and disease activity outcomes. Small but significant improvements were noted in the number of tender and swollen joints in the group assigned to exercise at 4 months but not at 12 months; however, no substantial difference was recorded between groups in CRP, ESR, or MCP joint deformity. Hand muscle strength and dexterity were significantly improved in the exercise group over or at the 12 month timepoint. Flexibility improved in both groups.

The cost of a full course of exercise therapy was £156 per participant. Allowing for other health-care use during follow-up, the mean cost was £103 (95% CI −£622 to 838) higher with intervention than with usual care. QALY gains were 0·01 for the EQ5D (95% CI −0·03 to 0·05) and 0·02 (95% CI 0·01–0·04) for the SF6D. For complete case analysis the incremental cost per QALY gain was £9549 for the EQ-5D (£17 941 with multiple imputations) and £7440 for the SF-6D (£23 228 with multiple imputations).

We noted no significant subgroup effects, and no significant interaction between treatment and medication, or duration of rheumatoid arthritis (table 5).

	Treatment effect (95% CI)	Number of participants confirmed	p (interaction)
Time since diagnosis			
<5 years	−6·08 (0·22–11·94)	115	0·4822
≥5 years	−3·72 (0·21–7·22)	276	..
Baseline medication regimen			
Biological DMARD only	4·70 (−1·12–10·52)	92	0·6261
Combination non-biological DMARD	6·20 (−0·09–12·49)	114	..
Single non-biological DMARD	4·20 (0·10–8·50)	199	..
No DMARD	−1·84 (−12·04 to 8·37)	33	..

DMARD=disease-modifying drugs.

Table 5: **Estimates of treatment effect in pre-specified sub-group analyses at 12 months**

***Panel:* Research in context**

Systematic review

We searched Medline, Embase, CINAHL, AMED, Physiotherapy Evidence Database (PEDro), OTseeker, Web of Science, and WHO International Clinical Trials Registry Platform from date of inception of the search databases to Dec 12, 2013, using search strings for condition, intervention, and body area, and to identify randomised trials. We identified six randomised controlled trials (378 participants) addressing hand exercises, and an additional trial investigating a general arm intervention (108 participants).[29] We also identified a narrative review[8] including four randomised studies, all of which were identified in our searches. At the outset of the SARAH trial the value of hand exercises was unknown. All the studies reported positive effects on one or more impairments of muscle strength, and range of motion or pain. The duration of follow-up and methods of measurement were highly variable, making conclusions difficult to draw. Only one study reported effects on hand function, and these were positive. Quality of studies was generally poor with either unclear or high risk of bias in several aspects of most studies. All studies apart from one were underpowered and with short-term follow up.

Interpretation

The SARAH trial contributes additional, high-quality evidence from a large and methodologically robust trial to support the use of hand exercises in management of people with rheumatoid arthritis affecting the hands.

Discussion

These results showed that a tailored hand exercise programme is a worthwhile, low-cost intervention as an adjunct to a range of drug regimens (panel). Maximisation of the benefits of biological and DMARD regimens in terms of function, disability, and health-related quality of life should be an important treatment aim.

Our participants were representative of the population of people with rheumatoid arthritis in the UK in terms of age and sex.[12] Minority UK ethnic groups were, however, under-represented. We recruited people who were stable on a drug regimen before exercises, recognising that patients can find exercises very difficult when experiencing pain and poor symptom control. However, participants were not patients with burnt-out quiescent disease. More than half needed or were receiving either combination DMARDs or biologicals, and showed substantial tenderness and joint swelling in the hands.

In comparison with a good quality, usual-care control intervention of joint protection advice and splinting, exercise doubled the treatment effect in important areas of overall hand function, activities of daily living function, work, satisfaction (as measured by MHQ subscales) and confidence to self-manage symptoms. This was a pragmatic trial and we prespecified a modest difference for the primary outcome (standardised difference 0·3 equating to a small-to-moderate effect[30]) and this difference was achieved without worsening of pain, worsening deformity, or change in medication use. Compliance measured by treatment attendance was high, and compliance with home exercise seemed to be good, especially during the first 4 months. Responses in impairment level measures were generally favourable, although not absolutely consistent. The most likely explanation for these findings is the variable presentation in impairments between participants and the individual tailoring of each programme.

The costs of the intervention were small compared with the annual cost of providing drug regimens. For example, in the UK the cost of biological drugs for rheumatoid arthritis is £7000–10 000 per patient per year.[31] Within-trial cost-effectiveness analysis indicated that hand exercises are likely to be a cost-effective use of National Health Service resources, being within or below the accepted thresholds of £20 000–30 000 per QALY that suggest a cost-effective alternative to usual care in the UK. We are likely to have underestimated cost-effectiveness because the analysis was limited to a time horizon of 1 year.

Methodological limitations of this study are similar to many other rehabilitation trials in that participant and clinician masking is impossible with exercise interventions. The sustained effect of the intervention at 1 year after randomisation and at least 6 months after completion of face-to-face contact suggests that the effects are not placebo or non-specific effects. Sensitivity analyses showed that loss to follow-up and un-masking is highly unlikely to have affected the results because the primary outcome was obtained by questionnaire independently of clinician or investigator involvement. However, in the health economic analysis, when, despite good follow-up, multiple imputation indicates greater uncertainty, probably because of the combination of a fairly small QALY gain and very wide variation in the costs of rheumatoid-related health care for individual patients.

Scrutiny of attendance and treatment logs as well as patient-reported health-care use indicated that contamination between the groups was unlikely. Although we prespecified subgroup analyses, the sample size of the study was not powered for such analyses, and the findings that disease duration and prerandomisation drug regimen do not significantly affect treatment effect should be interpreted with caution. Other possible criticisms are that we did not use the full American College of Rheumatologists recommended core set of disease activity measures.[32] We excluded two of the seven American College of Rheumatologists criteria related to global rating of disease, because they were not applicable to the intervention. We asked clinicians to use a pragmatic and inclusive approach to identification of participants, but because of Data Protection Law, we have minimum data for people who declined to participate. Hence we cannot rule out selection biases. Recall bias is possible for some questionnaires, but should be equally distributed across groups. We made no adjustment for testing of multiple hypotheses, choosing instead accepted methods of a prespecified primary outcome. We accounted for potential confounders in the stratified randomisation and through baseline covariate adjustment. Centre was addressed through the randomisation method; baseline function, DMARD usage, age, sex, and therapist were addressed in the pre-specified analyses; and interactions with time since original diagnosis, type of referral, ESR, and CRP, were also investigated.

Thus, an exercise regimen for the hand and upper limb is effective in restoration and retaining of hand function in rheumatoid arthritis, with associated positive effects on activities of daily living, work, and physical and emotional roles during a 12 month follow-up.

Contributors

SEL, EMW, PJH, JA, CM, VN, AR, MRU, and MAW conceived the trial and design. SEL, EMW, PJH, SD, and MAW acquired the data and provided administrative, technical, and material support. SEL, JA, MD, MJG, JL, CM, VN, AR, MRU, and MAW analysed and interpreted the data. SEL, PJH, MD, JL, CM, and MAW drafted the Article. CM, MD, MG, and JL did the statistical analysis. SEL, JA, CMcC, AR, and MRU obtained funding. SEL, JA, JL, AR, and MU supervised the study. All authors revised the Article. SEL was the chief investigator.

Declaration of interests

We declare no competing interests.

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Towards evidence-based hand exercises in rheumatoid arthritis

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Rheumatoid arthritis is the most common inflammatory joint disease, affecting about 0·5% of the global population, and causes disability, including pain and activity limitation. Almost 80% of patients with rheumatoid arthritis have hand dysfunction,[1] which is related to restricted participation in society, including disability at work.[2] Improved drug treatment has enhanced inflammation control in rheumatoid arthritis during the past decade, but unfortunately does not remove disability.[3-5] To take full advantage of improved inflammation control, it is important now to explore possible windows of opportunity for cost-effective rehabilitation measures to maximise the benefits of drug treatment and reduce disability.

We read with interest the results of Sarah Lamb and colleagues' trial[6] in *The Lancet*. This is an important study, especially because the feasibility of strength training for rheumatoid hands has been questioned, as has its potential to increase damage and deformity due to potential disturbance of the delicate mechanics of the hand by inflammatory processes.[7,8] This novel, well designed study, with full statistical power, aimed to investigate whether exercise improves hand function beyond the functional gains obtained by usual care. The investigators randomly assigned 490 adults with rheumatoid arthritis reporting hand pain or dysfunction in UK hospitals to usual care, or to a tailored programme of strengthening and stretching hand exercises. In terms of the trial's primary outcome, the Michigan Hand Outcomes Questionnaire overall function score at 12 months, hand function improved by 3·6 points in the usual care group and 7·9 points in the exercise group (mean difference 4·3, 95% CI 1·5–7·1). The study contributes high quality evidence for the use of hand exercises in the management of patients with rheumatoid arthritis on contemporary medical treatment. Furthermore, the authors define hand exercise as a cost-effective intervention by current criteria applied in the UK, which is important because the drugs for this target group of patients with rheumatoid arthritis have become very expensive. The use of hand exercise also has potential to be integrated into e-health, via a web-based solution or interactive monitoring, which could further increase cost-effectiveness and adherence.[9]

We thus commend Lamb and colleagues for their effort to design and carry out a randomised controlled trial on tailored hand exercise. The positive results might, however, be jeopardised by threats to the external validity of the study. The study sample might have been biased to include patients especially motivated because participation involved acceptance of either intervention or control conditions. They might also have been especially adherent to hand exercise because they were willing to travel to hospital over a long period, while also following a daily exercise programme at home. This bias often occurs in rehabilitation studies, but is rarely paid attention to,[10] and might partly have contributed to the positive results.

The assessed hand exercise intervention with focus on mobility, strength, and endurance was based, by a systematic and rigorous process, on existing scientific evidence, best clinical practice, and theoretical knowledge from exercise physiology and behavioural science. This is a thoughtful and adequate strategy for a first major randomised controlled trial in the specialty, and resulted in a positive outcome. However, complex interventions such as muscular exercise include many potential combinations of targeted muscles or muscle groups; strength, endurance, or coordination exercises; and static or dynamic muscle work done eccentrically or concentrically in open or closed chains. We therefore look forward to future studies comparing the programme assessed by Lamb and colleagues with alternative programmes to explore whether hand

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exercise interventions can be further optimised for patients with rheumatoid arthritis.

Because the exercise programme assessed by Lamb and colleagues might challenge therapists' existing views on adequate hand treatment in rheumatoid arthritis, and thus in present clinical practice, steps need to be taken to overcome the well known difficulties with therapists' protocol adherence and their resistance to change of practice.[11] In implementation of the programme assessed by Lamb and colleagues into clinical practice, it should thus be recognised that clinical therapists, like the study therapists, need both initial training and brief subsequent booster sessions to ensure appropriate delivery of the intervention. This recognition might be especially important because the programme includes not only hand exercises but also use of extensive behavioural change support techniques, which are not yet self-evident parts of physical therapy and occupational therapy practice.

We believe that Lamb and colleagues' study[6] represents an important contribution to future clinical treatment guidelines and, if implementation issues are properly addressed, that it will improve hand function therapy in patients with rheumatoid arthritis.

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