Progressive exercise compared with best-practice advice, with or without corticosteroid injection, for rotator cuff disorders: the GRASP factorial RCT

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He was previously lead researcher for the NIHR Research for Patient Benefit-funded RaCeR (Rehabilitation following Rotator Cuff Repair) study (PB-PG-081620009) and chief investigator for the NIHR Doctoral Fellowship-funded SELF study (DRF-2011-04-090). Sarah E Lamb reports grants from the NIHR HTA programme during the conduct of the study and was a member of the following boards: HTA Additional Capacity Funding Board (2012–15); HTA Clinical Trials Board (2010–15); HTA End of Life Care and Add on Studies (2015); HTA Funding Boards Policy Group (formerly Clinical Studies Group) (2010–15); HTA Maternal, Newborn and Child Health Methods Group (2013–15); HTA post-board funding teleconference (2010–15); HTA Primary Care Themed Call board (2013–14); HTA Prioritisation Group (2010–15); and the NIHR Clinical Trials Unit Standing Advisory Committee (2012–16).
Scientific summary

Background

Shoulder pain is very common, with around 70% of cases due to rotator cuff-related shoulder pain. Despite the widespread use of physiotherapy, there is uncertainty regarding which type of exercise therapy is associated with the best outcomes. There is also uncertainty about the long-term benefits and harms of corticosteroid injection therapy, which is often used in addition to physiotherapy.

Objectives

The GRASP (Getting it Right: Addressing Shoulder Pain) trial assessed (1) if an individually tailored progressive home exercise programme prescribed and supervised by a physiotherapist provided greater improvement in shoulder pain and function over 12 months compared with a best-practice advice session with a physiotherapist supported by high-quality self-management materials; and (2) if subacromial corticosteroid injection provided greater improvement in shoulder pain and function over 12 months compared with no injection.

Methods

Design

This was a pragmatic multicentre superiority randomised controlled trial using a 2 × 2 factorial design. Participants and physiotherapists were not blinded to group allocation.

Setting

Participants were recruited from 20 NHS primary care-based musculoskeletal and related physiotherapy services.

Participants

Adults aged ≥ 18 years with a new episode of shoulder pain (i.e. in the previous 6 months) attributable to a rotator cuff disorder (e.g. cuff tendonitis, impingement syndrome, tendinopathy or rotator cuff tear), as per British Elbow & Shoulder Society guidelines, not currently receiving physiotherapy or being considered for surgery.

Interventions

Participants (n = 708) were randomised (March 2017–May 2019) using a centralised computer-generated 1 : 1 : 1 : 1 allocation ratio to one of four interventions: (1) progressive exercise (n = 174) (six or fewer physiotherapy sessions), (2) best-practice advice (n = 174) (one physiotherapy session), (3) corticosteroid injection then progressive exercise (n = 182) (six or fewer physiotherapy sessions) or (4) corticosteroid injection then best-practice advice (n = 178) (one physiotherapy session).

Participants randomised to the progressive exercise intervention received up to six individual face-to-face sessions with a physiotherapist over 16 weeks. Participants were provided with a folder containing an advice booklet, an exercise action planner and diary, and instructions on their exercise programme, which was set up in collaboration with their physiotherapist. A resistance band was issued as required. The progressive exercise programme was highly structured, but could be tailored to the needs and preferences of participants.
Participants randomised to the best-practice advice intervention received a single individual face-to-face session with a physiotherapist. Participants were given an advice booklet. The content of the advice in the booklet was the same as that provided for the progressive exercise group, with the exception of a different exercise programme. Participants were given a simple set of self-guided exercises, at least one level of resistance band and access to an exercise video (available on a website and a digital versatile disc), which could be progressed and regressed, depending on their capability. The exercises were designed using similar concepts to the progressive exercise intervention, such as increased resistance, but these were a simpler range. An exercise diary was provided in addition to an exercise action planner that was simpler than the one provided to those in the progressive exercise group.

### Follow-up

Measurements for the primary and secondary outcomes were collected by postal questionnaires at 8 weeks and at 6 and 12 months after randomisation. Telephone follow-up was used to contact those who did not respond or fully complete the returned questionnaire.

### Clinical outcomes and analysis

The primary outcome was the mean difference in Shoulder Pain and Disability Index (SPADI) total score over 12 months. The scale is from 0 to 100, with higher values representing worse pain. Secondary outcomes were the pain and function SPADI subdomains, health-related quality of life (assessed using the EuroQol-5 Dimensions, five-level version), sleep disturbance, fear avoidance, pain self-efficacy, return to activity, global impression of treatment, health resource use, out-of-pocket expenses and work disability. Prespecified subgroup analyses included age, sex, smoking status, higher baseline SPADI score (≥ 50) and higher baseline pain self-efficacy score (≥ 8). The planned sample size was 704 participants, assuming 20% loss to follow-up at 12 months, and based on 90% power and 1% two-sided statistical significance to detect a minimally clinically important difference of eight points on the SPADI total scale. The primary analysis was intention to treat. The two main effect comparisons for this 2 × 2 factorial trial were (1) progressive exercise compared with best-practice advice to determine the efficacy of progressive exercise and (2) subacromial corticosteroid injection compared with no injection to determine the efficacy of subacromial corticosteroid injection. The presence of an interaction effect was formally investigated before testing their effects on the primary outcome. The difference in SPADI score between the two intervention groups was estimated overall and at each data collection time point using a repeated measures linear mixed-effects regression model adjusted for baseline and other covariates.

### Economic analysis

The cost-utility of interventions was evaluated from an NHS and Personal Social Services perspective, using a within-trial intention-to-treat analysis. Quality-adjusted life-years were estimated from data collected from the EuroQol-5 Dimensions, five-level version, at baseline, 8 weeks and 6 and 12 months. Costs were estimated for each participant over 12 months of follow-up based on patient-reported use of health-care services attributable to their rotator cuff disorder. The cost of delivering each intervention, including physiotherapists’ training, materials, delivery of the progressive exercise and advice sessions, and corticosteroid injections, was also estimated.

### Results

The mean age of participants was 55.5 (standard deviation 13.1) years, 49.3% of participants were female and the mean duration of symptoms was 4 (interquartile range 3–6) months. Intervention groups were well matched in terms of demographic data and clinical and generic health-related quality-of-life measures. Overall, 92% (324/352) of participants randomised to the best-practice advice intervention and 95% (339/356) of participants allocated to progressive exercise either partially or fully completed the intervention. High levels of protocol adherence were achieved across all intervention groups. Follow-up data were obtained for 87% (618/708), 87% (615/708) and 91% (641/708) of participants at 12 months, 6 months and 8 weeks, respectively.
The overall mean baseline SPADI score was 54.1 (standard deviation 18.5), with higher baseline levels of shoulder pain (mean SPADI pain subscale score 63.9; standard deviation 22.1) than impaired function (mean SPADI function subscale score 44.3; standard deviation 22.1). There was an overall improvement in SPADI score in each of the four groups from baseline over time, representing a 32.2-point improvement (standard deviation 23.9 points) on the SPADI scale [with a SPADI score of 21.9 (standard deviation 23.4) at 12 months]. There was no evidence of an interaction effect and so results were analysed for the two main effect comparisons.

Clinical results

Over 12 months, there was no evidence of a difference in the SPADI scores between the progressive exercise intervention and best-practice advice intervention (adjusted mean difference between groups over 12 months –0.66, 99% confidence interval –4.52 to 3.20); nor was there evidence of a difference when analysed at the 8-week and 6- and 12-month time points (adjusted mean difference at 12 months –3.10, 99% confidence interval –7.85 to 1.64). There was also no difference between groups for secondary outcome measures, with the exception of progressive exercise, which resulted in an improvement in patient-reported global impression of treatment over the 12 months (adjusted mean difference over 12 months 0.38, 95% confidence interval 0.10 to 0.66) and at the 6- and 12-month time points.

Over 12 months, there was also no evidence of a difference in SPADI scores between the injection and the no injection groups (adjusted mean difference over 12 months –1.11, 99% confidence interval –4.47 to 2.26). There was a small difference in SPADI scores at 8 weeks (adjusted mean difference at 8 weeks –5.64, 99% confidence interval –9.93 to –1.35) in favour of the injection group, but not at the 6- and 12-month time points (adjusted mean difference at 12 months 1.93, 99% confidence interval –2.41 to 6.27). There was no difference between groups for secondary outcome measures, with the exception of the injection group at 8 weeks, which resulted in a small improvement in shoulder pain, shoulder function, sleep disturbance, return to desired activities and global impression of treatment.

Prespecified subgroup analysis showed that the effect of injection was stronger at 8 weeks in people with a higher baseline SPADI score (adjusted mean difference at 8 weeks –9.67, 99% confidence interval –15.37 to –3.97) than in those who received injections but had a lower baseline SPADI score (adjusted mean difference at 8 weeks –0.36, 95% confidence interval –8.87 to 6.16). No differences were observed for other prespecified subgroup analyses. No serious adverse events were associated with treatment interventions.

Economics results

The base-case cost-effectiveness analysis showed that, over the 12-month period, participants in the best-practice advice treatment group gained, on average, 0.74 quality-adjusted life-years (95% confidence interval 0.710 to 0.763) and an NHS cost of £195. Adding progressive exercise to best-practice advice resulted in a gain of an additional 0.019 quality-adjusted life-years (p = 0.220), compared with best-practice advice alone, at an additional cost of £52 (p = 0.247). Adding corticosteroid injection to best-practice advice resulted in a gain of 0.021 quality-adjusted life-years (p = 0.184), compared with best-practice advice alone, and increased the cost by £10 per participant (p = 0.747). At a £20,000 per quality-adjusted life-year ceiling ratio, best-practice advice plus injection was found to have a 54.93% probability of being best value for money of the four treatments evaluated in the trial. Best-practice advice plus injection cost £475.59 per quality-adjusted life-year gained compared with best-practice advice alone, and strongly dominated progressive exercise alone and progressive exercise plus injection, being less costly and accruing more quality-adjusted life-years. Sensitivity analyses assuming additive effects, taking a societal perspective and varying the cost of training physiotherapists, confirmed the base-case conclusion that best-practice advice plus injection is expected to be best value for money at a ceiling ratio of £20,000 per quality-adjusted life-year, although there was substantial uncertainty around this conclusion in all analyses.
Conclusion

Implications for health care
The GRASP trial shows that the progressive exercise intervention was not superior to a best-practice advice session with a physiotherapist. Subacromial corticosteroid injection improved shoulder pain and function at 8 weeks, but provided modest short-term benefit only, with the greatest benefit being in those with higher levels of pain and functional impairment. Best-practice advice in combination with corticosteroid injection has a 54.93% probability of being the most cost-effective intervention for the NHS.

Recommendations for research
There is a case to extend follow-up to assess long-term outcomes, as some participants still reported ongoing pain and impaired shoulder function at 12 months. There is a need to better understand the natural history of rotator cuff disorders, including whether symptoms resolve over an extended period or persist in the longer term. Longer-term follow-up would also address concerns regarding later surgery and corticosteroid injection, and potential long-term harm due to its possible effects on tendon structure.

Trial registration
This trial is registered as ISRCTN16539266 and EudraCT 2016-002991-28.

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**This report**

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