Randomized feasibility study of an autologous protein solution versus corticosteroids injection for treating subacromial pain in the primary care setting – the SPiRIT trial

From Oxford University Hospitals NHS Foundation Trust, Oxford, UK

Correspondence should be sent to A. Woods akwoods2@gmail.com

Cite this article:
Bone Jt Open 2024;5(7):
534–542.

DOI: 10.1302/2633-1462.
57.BJO-2023-0180.R1

A. Woods,[1] A. Howard,[2] N. Peckham,[3] I. Rombach,[3] A. Saleh,[3] J. Achten,[4] D. Appelbe,[3] P. Thamattore,[5] S. E. Gwilym[1]

[1]Oxford University Hospitals NHS Foundation Trust, Oxford, UK
[2]Leeds Teaching Hospitals NHS Trust, Leeds, UK
[3]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK
[4]Oxford Trauma and Emergency Care, Nuffield Department of Orthopaedics, Rheumatology & Musculoskeletal Sciences, University of Oxford, Oxford, UK
[5]Healthshare Ltd, London, UK

Aims

The primary aim of this study was to assess the feasibility of recruiting and retaining patients to a patient-blinded randomized controlled trial comparing corticosteroid injection (CSI) to autologous protein solution (APS) injection for the treatment of subacromial shoulder pain in a community care setting. The study focused on recruitment rates and retention of participants throughout, and collected data on the interventions' safety and efficacy.

Methods

Participants were recruited from two community musculoskeletal treatment centres in the UK. Patients were eligible if aged 18 years or older, and had a clinical diagnosis of subacromial impingement syndrome which the treating clinician thought was suitable for treatment with a subacromial injection. Consenting patients were randomly allocated 1:1 to a patient-blinded subacromial injection of CSI (standard care) or APS. The primary outcome measures of this study relate to rates of recruitment, retention, and compliance with intervention and follow-up to determine feasibility. Secondary outcome measures relate to the safety and efficacy of the interventions.

Results

A total of 53 patients were deemed eligible, and 50 patients (94%) recruited between April 2022 and October 2022. Overall, 49 patients (98%) complied with treatment. Outcome data were collected in 100% of participants at three months and 94% at six months. There were no significant adverse events. Both groups demonstrated improvement in patient-reported outcome measures over the six-month period.

Conclusion

Our study shows that it is feasible to recruit to a patient-blinded randomized controlled trial comparing APS and CSI for subacromial pain in terms of clinical outcomes and health-resource use in the UK. Safety and efficacy data are presented.

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Take home message

- We report the results of a multicentre, randomized controlled trial feasibility study recruiting patients to undergo blinded subacromial injections with either autologous protein solution (APS) or corticosteroids (CSI).
- Recruitment was achieved ahead of predicted timelines, and the procedure and postoperative data-gathering protocols were well tolerated.
- We conclude that it is feasible to run a full-scale, definitive trial to detect a meaningful potential difference in clinical outcome between CSI and APS in the management of subacromial pain syndrome.

Introduction

Shoulder pain accounts for 1% to 2% of all adult consultations with a general practitioner.[1] Around 70% is subsequently attributed to pain arising from inflammation and/or degeneration of the rotator cuff.[2] Symptoms may be disabling in terms of the patient's ability to carry out daily activities at home and in the workplace. This poses a substantial burden to the individual and to society.[3–5] Only 59% of patients with subacromial pain, treated in primary care, show a complete recovery within six months.[6]

A mechanical explanation for shoulder pain has previously been favoured, whereby contact occurs between the rotator cuff tendons and the overlying bone. This 'rubbing' process was believed to result in inflammation of the rotator cuff tendons and nearby structures such as the subacromial bursa. Treatments have historically been directed at reducing this inflammation and rubbing, either by injection of corticosteroids (CSI) (to address the inflammation) or surgical intervention to remove some of the bone. Evidence for the efficacy of both surgical and non-surgical treatments of shoulder pain is limited. A publication in 2015 by the British Elbow and Shoulder Society (BESS) and the British Orthopaedic Association (BOA) highlighted the lack of evidence for a number of interventions used to treat subacromial shoulder pain, and the need for research in this area.[7] Given the large numbers of patients who present to primary care with subacromial shoulder pain, any developments in the treatment of this chronically painful condition will improve the care of thousands each year in the UK alone.

Currently, CSI remains the mainstay of initial treatment in most cases of shoulder pain presenting to both primary and secondary care. The efficacy of CSI has been tested in several trials and subsequently through systematic review. These have reported differing conclusions, but the consensus view is that any benefits seen are most likely to be short-term. There remains a significant number of patients who go on to have surgical intervention despite CSI.[8] In addition to the lack of strong evidence towards the efficacy of CSI, there have also been theoretical and lab-based reports of deleterious effects of corticosteroids on tendon biology. CSI might impair the potential for intrinsic tendon repair mechanisms, and it may increase the risk of subsequent tendon tearing.[9]

Contemporary understanding of the biology of shoulder tendons, however, gives potential targets for new pharmaceutical or biological treatments. Examples include injectable platelet-rich plasma (PRP) or autologous protein solution (APS). PRP is a concentrate of platelet-rich plasma protein derived from whole blood, centrifuged to remove red blood cells. Basic science studies have consistently shown the beneficial effects of PRP on tendons, including increased tendon cell proliferation, increased expression of anabolic genes and proteins, and reduced tendon inflammation.[10–12] Unfortunately, these in vitro findings have not translated to reliable clinical application when subject to clinical trial.[13] APS is prepared via a single-use device that produces a cell concentrate from autologous blood. Conceptually, APS and PRP are very similar as they both aim to isolate anti-inflammatory cytokines and anabolic growth factors from a patient's own blood, allowing this to be reintroduced at the site of pain. However, unlike PRP systems, the APS production process preferentially concentrates anti-inflammatory cytokines production by white blood cells, including interleukin (IL)-1 receptor antagonist and tumour necrosis factor (TNF) receptor inhibitor.[14] The use of APS is expanding both in the UK and worldwide, and feasibility studies investigating APS have been conducted in patients with knee arthritis.[15]

It is recognized that robust evidence must be produced before blood-derived therapies are further introduced into orthopaedic clinical practice.[16] No work currently exists to assess the efficacy of APS in treating shoulder pain, and although this is not the licensed indication for APS, its use for this indication has been gaining traction. The best means of evaluating the clinical and cost-effectiveness of APS would be to compare its safety and efficacy against the current standard of care (CSI) through a multicentre randomized controlled trial (RCT). However, uncertainties – specifically regarding willingness of both patients and healthcare professionals to take part in such a study, and whether proposed methods could be adhered to – need to be assessed before undertaking a large-scale RCT, and so the primary aim was to undertake a randomized feasibility trial.

This feasibility study trial aimed to identify the rates of recruitment, retention, and compliance with intervention and follow-up, and to determine feasibility. It also record data on safety and efficacy.

Methods

Trial design summary

This is a feasibility study of a participant-blinded, parallel group RCT. The study protocol has been published elsewhere,[17] and the full protocol is included as Supplementary Material. The trial was conducted in accordance with the UK Policy Framework for Health and Social Care Research,[18] the applicable UK Statutory Instruments (which include the Data Protection Act 2018), and the principles of Good Clinical Practice.[19] The study is funded by the National Institute for Health and Care Research – Research for Patient Benefit (NIHR201473) – and registered under Trial Registration Number ISRCTN12536844.

Recruitment of participants

As part of the usual care for management of shoulder pain, musculoskeletal (MSK)-triage clinicians initially prescribed structured physiotherapy to all patients. In addition to structured physiotherapy, patients were also offered an injection into the subacromial space at a separate appointment. GP referrals to the two MSK centres were triaged, the trial eligibility screening was undertaken, and patients were asked about their willingness to take part in the study.

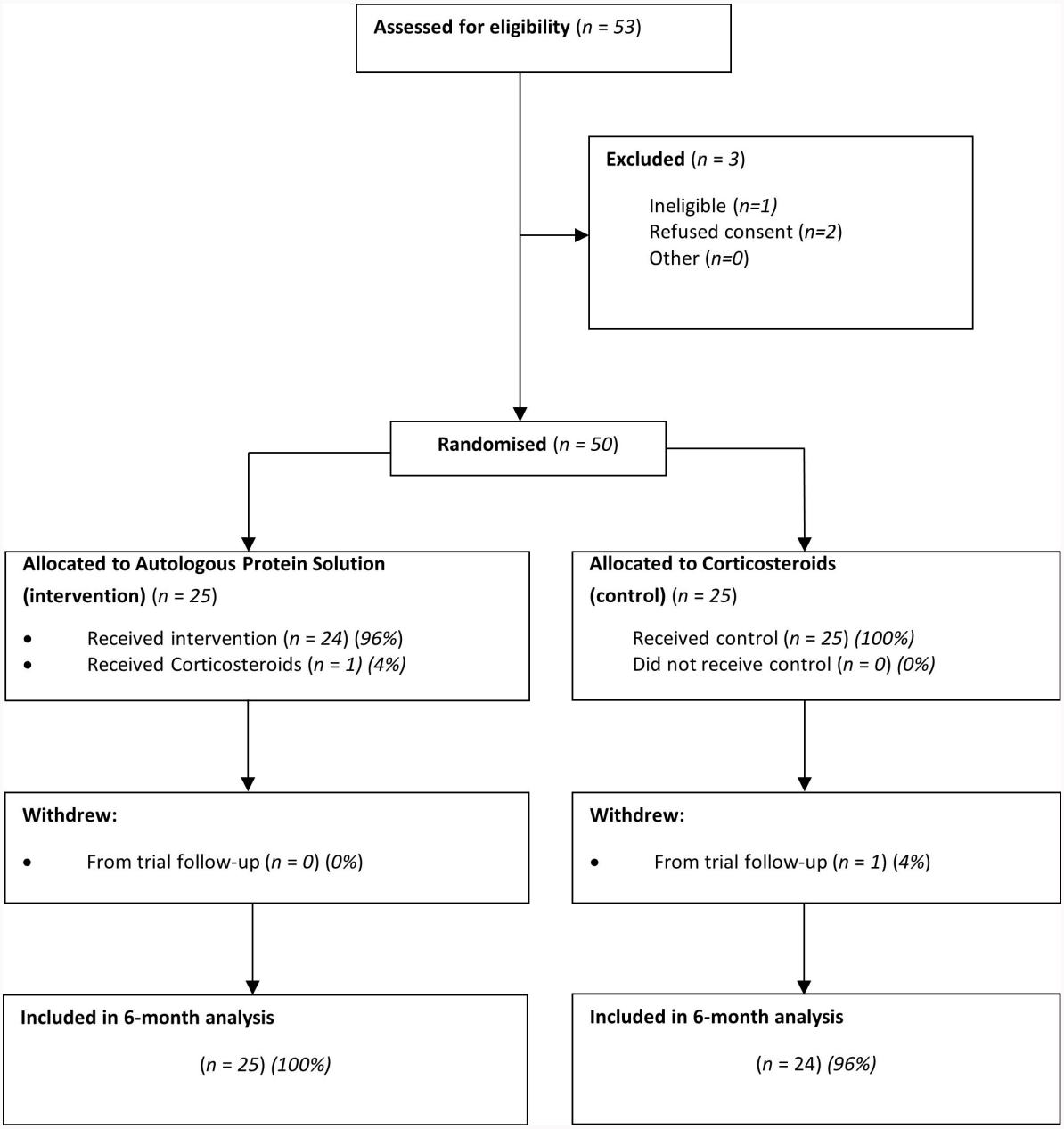

Fig. 1
Consolidated Standards of Reporting Trials (CONSORT) diagram showing participant flow through the trial.

If willing to participate, then these individuals separately received a trial invitation letter and participant information sheet (PIS) from the research team ahead of their appointment. Details on screening and recruitment can be found in Figure 1.

At the next clinic visit, participants who met the eligibility criteria were provided with a verbal explanation of the study (in addition to the written information already received) and given the opportunity to ask any questions. Patients were informed that they could freely withdraw from the trial at any time without it affecting their rights or future care. Patients willing to take part were asked to complete an electronic consent form. Inclusion criteria were as follows: willing and able to give informed consent for participation in the study; male or female, aged 18 years or above; they had a community-based clinician who would offer a CSI into the subacromial space as their standard of care. Exclusion criteria were as follows: a history of considerable shoulder trauma (fracture or dislocation in the last five years); previous shoulder surgery on the affected shoulder; contraindications to APS therapy or CSI; a pre-existing neurodegenerative and/or vascular condition that affects shoulder function; received CSI/APS injection within the two months prior to randomization; unable to follow trial procedures; and/or does not have direct or indirect access to an email account or smartphone.

Randomization and blinding

Recruitment was undertaken from two NHS MSK triage centres (Oxford and Leeds) which receive general practice referrals for patients with shoulder pain. Once informed consent was obtained, eligibility confirmed, and baseline data collected,

Table I. Baseline characteristics of participants.

	Treatment allocation		
Variable	**APS (n = 25)**	**CSI (n = 25)**	**Total (n = 50)**
Mean age, yrs (SD, range)	60 (10, 78 to 46)	59 (14, 85 to 20)	60 (12, 85 to 20)
Centre, n (%)			
Leeds	13 (52)	12 (48)	25 (50)
Oxford	12 (48)	13 (52)	25 (50)
Duration of symptoms, n (%)			
> 6 months	22 (88)	23 (92)	45 (90)
≤ 6 months	3 (12)	2 (8.0)	5 (10)
Shoulder, n (%)			
Left	14 (56)	12 (48)	26 (52)
Right	11 (44)	13 (52)	24 (48)
Diabetic, n (%)			
No	19 (76)	20 (80)	39 (78)
Yes	6 (24)	5 (20)	11 (22)

APS, autologous protein solution; CSI, corticosteroid injections; SD, standard deviation.

Table II. Reported complications.

		After 6 months' follow-up	
Complication	**N**	**APS, n (%)**	**CSI, n (%)**
Septic arthritis	50	0 (0)	0 (0)
Dizziness	50	2 (8.0)	4 (16.0)
Nervousness	50	1 (4.0)	1 (4.0)
Facial flushing	50	1 (4.0)	0 (0)
Insomnia	50	0 (0)	1 (4.0)
Flare-up of pain intensity	50	2 (8.0)	5 (20)
Change in skin pigmentation	50	0 (0)	1 (4.0)
Subcutaneous fat wasting	50	0 (0)	1 (4.0)

APS, autologous protein solution; CSI, corticosteroid injections.

participants were randomized at the level of the individual in a 1:1 basis to either a CSI or an APS injection. Randomization was performed via a secure web-based service provided by the Oxford Clinical Trials Research Unit, and was implemented via a minimization algorithm using a random element and stratified by centre, duration of symptoms (less than or more than 6 months), and baseline patient-reported outcome measurement information system (PROMIS) pain interference scores.

To avoid bias, participants were blinded to the treatment that was allocated. Blinding was achieved by collecting the blood sample required for APS (55 ml) from both groups of patients. In the intervention group, this blood was used for the preparation of the APS; in the control group, this blood was sham-prepared as APS, but subsequently discarded. The injections were then performed using opaque syringes to help prevent the difference in colour of the injectant unblinding the patient.

APS

After the consent and randomization processes, a 55 ml sample of blood was obtained and used for the preparation of the APS injection (nSTRIDE; Zimmer Biomet, USA). The injectable solution was created as per the manufacturer's guidelines. It is a two-step process taking 15 to 20 minutes – first the blood is separated by centrifuging it, after which it is concentrated in specialized tubes. The total volume of the resultant APS is approximately 3 ml. The solution was administered using standard aseptic techniques under ultrasound guidance to provide image confirmation of needle placement into the subacromial space.

Comparator group (CSI)

Participants did not receive any change to the standard care in the CSI group, except the aforementioned 55 ml sample blood taken to maintain patient blinding. The control participants then received Depo-Medrone (40 mg; Pfizer, USA) mixed with 3 ml of 0.5% bupivacaine local anaesthetic, administered using standard aseptic techniques under ultrasound guidance to provide image confirmation of needle placement into the subacromial space.

Intervention

Injections were performed by clinicians (orthopaedic surgeons, AW, SG, AH, or extended scope practitioners with appropriate training in ultrasound-guided injections, PT and EJ) under ultrasound guidance. Injections were perfomed in an identical manner using a 'blinding syringe' (non-transparent sides). Both the APS and the comparator group underwent structured physiotherapy following injection, as per local protocols.

Post-injection follow-up

For both treatments, immediately after the injection the participants received standard post-injection care advice and were advised to resume normal daily activities. If after six to eight weeks no significant benefit (as defined by usual clinical assessment) was reported, the patient would be referred to secondary care to discuss alternative treatment options as per standard care pathways.

Outcomes

The primary outcome measures of this study relate to rates of recruitment, retention, and compliance with intervention and follow-up to determine feasibility.

Secondary outcome measures relate to the safety and efficacy of the interventions and included: safety indicators, collected by patient- and hospital-completed 'complication forms'; and efficacy assessments established through the administration of PROMIS upper limb physical function, PROMIS pain interference,[20] Oxford Shoulder Score

Table III. Analysis of patient-reported outcome measures. All values are presented as means (standard deviations).

	Baseline		Month 3		Month 6	
Outcome	**APS**	**CSI**	**APS**	**CSI**	**APS**	**CSI**
PROMIS PI	65.6 (6.3)	63.3 (5.8)	61.7 (9.5)	58.8 (8.6)	61.0 (8.5)	54.6 (10.1)
PROMIS PF	30.6 (5.1)	31.2 (5.9)	33.0 (6.7)	36.9 (8.4)	33.3 (8.8)	37.4 (10.7)
OSS	23.2 (8.8)	26.6 (8.0)	26.7 (8.9)	32.7 (10.0)	29.0 (11.2)	33.0 (11.4)
EQ-5D-5L Index	0.48 (0.24)	0.63 (0.13)	0.55 (0.22)	0.64 (0.21)	0.56 (0.24)	0.65 (0.23)
EQ-VAS	59.8 (22.7)	65.6 (21.0)	56.6 (20.3)	67.2 (18.6)	57.5 (16.5)	66.3 (23.3)
Pain VAS	62.0 (23.3)	58.6 (22.1)	56.8 (32.6)	39.6 (31.0)	54.3 (29.4)	39.8 (33.1)
WPAI						
Percent work time missed	0.27 (0.44)	0.05 (0.20)	0.12 (0.33)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
Percent impairment while working	0.58 (0.36)	0.45 (0.23)	0.51 (0.29)	0.31 (0.25)	0.29 (0.31)	0.23 (0.27)
Percent overall work impairment	1.02 (0.05)	1.02 (0.06)	1.01 (0.02)	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)
Percent activity impairment	0.62 (0.22)	0.53 (0.19)	0.54 (0.24)	0.35 (0.28)	0.45 (0.28)	0.31 (0.28)

APS, autologous protein solution; CSI, corticosteroid injections; EQ-5D-5L, EuroQol five-dimension five-level questionnaire; EQ-VAS, EuroQol visual analogue scale; OSS, Oxford Shoulder Score; PF, physical function; PI, pain interference; PROMIS, Patient-Reported Outcome Measurement Information System; WPAI, Work Productivity Impairment Questionnaire.

(OSS),[21] Pain visual analogue score, and EuroQol five-dimension five-level (EQ-5D-5L)[22] questionnaires, which all represent patient-reported outcome measures (PROMs) relating to shoulder-specific or general function. There were also questionnaires administered to assess work productivity (Work Productivity Impairment Questionnaire (WPAI))[23] and patient- and hospital-reported resource use including the referral rates for shoulder surgery six months after randomization.

Data collection

Baseline demographic data, patient function, and pain data using the above validated PROM scores were collected after the participant provided initial consent. All cae report forms, including screening, consent, randomization, and baseline assessment, were completed online on the REDCap database.[24–26] At the relevant follow-up timepoints, participants were contacted by the Oxford central study office by automated SMS or email with a personalized link to the REDCap database. Participants received reminder SMS/email messages or phone calls if they did not respond within an appropriate time frame.

Up to week 6 post-randomization, participants were asked once a week to indicate their level of pain in the previous 24 hours, and whether they had any analgesia for their injury. At three and six months post-randomization, they were asked to complete the PROMIS, OSS, EQ-5D-5L, VAS, WPAI, health resource use, and complications questionnaires.

Any patient-reported complications were verified with the local research teams. In addition, at six months post-randomization, local research teams completed a medical notes review for all participants to ensure all expected complications were recorded. Foreseeable adverse events which were recorded as complications include: septic arthritis; dizziness; nervousness; facial flushing; insomnia; flare-up of pain intensity at the injection site; injection site skin pigmentation; and subcutaneous fat atrophy.

Statistical considerations and data analysis

For a small, standardized difference (0.1 to 0.3) and 80% power, a pilot study sample size of 40 participants (20 per arm) would be sufficient to estimate reliable input parameters for the sample size estimation of the definitive trial including a robust estimate of the standard deviation around the PROMIS upper-limb function PROM.[27] The recruitment was set at 50 participants in order to allow for up to 20% loss to follow-up, which represented a recruitment rate of three to four participants per centre per month.

Feasibility and clinical outcome summaries are presented by treatment group using the intention to treat (ITT) population. This study was not powered for formal hypothesis testing (no p-values reported), but mean differences and 95% confidence intervals have been provided for the clinical outcomes. We used the Consolidated Standards of Reporting Trials (CONSORT) guidelines for pilot and feasibility trials (Figure 1).[28]

Results

Between 13 April 2022 and 13 October 2022, a total of 53 patients were screened for eligibility. Of those screened, 94% (n = 50) were recruited between the two sites at roughly one patient per site per week and randomly assigned to the CSI (n = 25) and APS (n = 25) groups. Baseline characteristics of each group are presented in Table I. Overall, 98% of participants received their allocated intervention as per protocol. There was one intervention deviation in the APS group as a result of equipment malfunction, secondary to blood clotting in the syringe. Following review, this was concluded to be a user error, whereby inadequate anticoagulant was used to prime the butterfly needle prior to spinning. The participant subsequently received corticosteroids as per the control group. Levels of participant retention, measured as withdrawals from the trial and compliance with questionnaire returns,

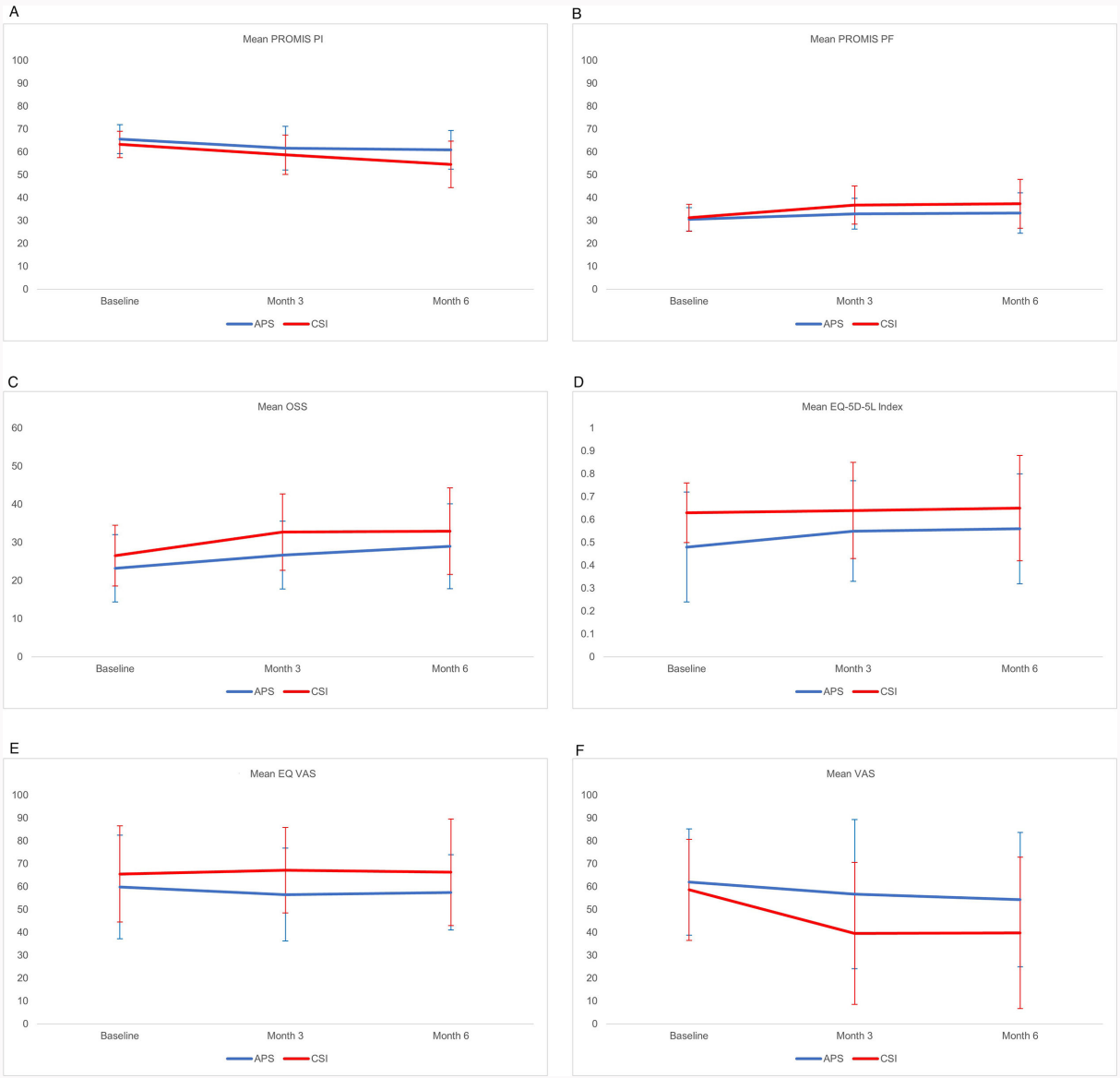

Fig. 2

Mean patient-reported outcome measure scores at baseline, Month 3, and Month 6 with standard deviation error bars. a) Patient-reported outcome measurement information system (PROMIS) pain interference (PI) score (lower result = less pain); b) PROMIS physical function (PF) (higher result = better function); c) Oxford Shoulder Score (OSS) (higher result = better function and less pain); d) EuroQol five-dimension five-level (EQ-5D-5L) Index (higher result = better function); e) EuroQol visual analogue scale (EQ-VAS) (lower result = less pain); and f) VAS (lower result = less pain). APS, autologous protein solution; CSI, corticosteroid injections.

were high, with only one participant failing to complete all trial questionnaires.

Safety (harms)

There were no serious adverse events (SAEs) for this trial. The number of site-reported complications are reported in Table II. On review of the medical notes, the reported complications of dizziness, nervousness, and flushing which had an onset of several months post-injection were investigated within secondary care and diagnosed as anxiety, rather than being attributed to the injection. One patient reported "infection in the shoulder" (APS group) and one reported "septic arthritis" (CSI group) but on review of the medical records these appeared to be misrepresentations of localized warmth and redness. Neither patient required specific treatment for these adverse events.

Efficacy

Table III details the reported PROMs reported by participants over the six-month follow-up. Both groups demonstrated improvement in all PROM scores over the six-month period (Figure 2). Mean improvement in PROMIS PI for APS and CSI was 4.63 and 8.71, respectively, and for PROMIS PF 2.78 and 6.16, respectively. This study was not adequately powered to allow for comparative analysis. Overall, 20% of patients in the trial were referred to see a shoulder surgeon within the six-month follow-up period, with one patient from the CSI group subsequently being listed and undergoing shoulder surgery.

Discussion

The primary aim of this trial was to evaluate the feasibility of conducting a full-scale, adequately powered, prospective

RCT to compare CSI and APS for shoulder pain. The trial proved acceptable to patients with a high acceptance rate for recruitment, with only a single withdrawal from the study and high completion rates of outcome measures.

This was the first RCT to investigate the use of APS as a treatment for patients presenting with shoulder pain that is consistent with subacromial pain syndrome. The study suggests that the treatment was well tolerated, and participants achieved clinical improvements over six months that would meet previously reported minimal clinically important difference (MCID) improvements for VAS and OSS for subacromial shoulder pain.

There is currently no reported MCID for subacromial pain for PROMIS PF scores. However, the MCID for nonoperatively managed partial-thickness cuff tears, a comparable condition, has been reported as 3.95.[29]

The data from this feasibility study suggest a SD for the PROMIS PF scores at six months of 10. Using this estimate for SD, and a MCID of 4, a minimum of 266 participants would be required for a definitive study with 90% power. This would translate to a 'small to medium' effect size of 0.4 based on Cohen's criteria.[30] Allowing for 10% loss to follow-up would give an anticipated target sample size of 296 based on a superiority, parallel, definitive study.

There are limitations to this study. Participants in both groups had an intervention at risk of placebo augmentation, in addition to the pharmacological benefits of the injectate. Complex or invasive medical interventions are known to benefit from clinically significant placebo effects. In this context, the APS group were subject to a necessary process of blood-taking and product production (e.g. centrifuge), while in the CSI group this effect was in addition to routine clinical care. Without the inclusion of a placebo-only group, it is not possible to assess the placebo versus the pharmacological mechanisms of any recorded benefits in either group.

Further, within this study, injections were performed under ultrasound guidance – this impacts the generalizability, as not all injections provided within community MSK centres are performed under ultrasound guidance, but does offer reassurance of injection location for the purposes of this study.

APS has not been validated for simultaneous injection with local anaesthetic and, despite a rigorous patient blinding protocol, it is possible that patients could have become unblinded due to the lack of localized numbness post-injection. Additionally, the transient pain-relieving effect of the CSI injection with local anaesthetic may be contributing to the differences observed between CSI and APS in this study.

A final limitation is that the design of this study was specifically aimed at point of care within community settings for subacromial shoulder pain, regardless of cause. This respects the pragmatic nature of the trial, but it is possible there may be diagnostic heterogeneity within the recruited population.

In any fully powered trial, health resource data would need to be collected. This study suggests that patient self-reported information on service use appears feasible, although patient-reported complications require secondary validation.

In conclusion, we report the successful completion of a multicentre, RCT feasibility study recruiting patients to undergo subacromial injections with either APS or CSI. Recruitment of the planned 50 patients was achieved ahead of predicted timelines, and the procedure and postoperative data-gathering protocols were well tolerated. We conclude that it is feasible to run a full-scale, definitive trial to detect a meaningful potential difference in clinical outcome between CSI and APS in the management of subacromial pain syndrome.

Social media

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Supplementary material

The SPiRIT protocol

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Author information

A. Woods, MA, D.Phil, BMBCH, FRCS (T&O), Senior Clinical Fellow
S. E. Gwilym, MBBS, BSc, DPhil, FRCS (Tr&Orth), Associate Professor & Consultant Orthopaedic Surgeon
Oxford University Hospitals NHS Foundation Trust, Oxford, UK.

A. Howard, LLB (Hons), MBChB, MSc, PhD, NIHR Clinical Fellow, Leeds Teaching Hospitals NHS Trust, Leeds, UK.

N. Peckham, BSc, MSc, OCTRU Senior Medical Statistician
I. Rombach, D.Phil, Senior Medical Statistician
A. Saleh, MSci, PhD, Medical Statistician
D. Appelbe, PhD, Senior Research Information Specialist
Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK.

J. Achten, D.Phil, Research Manager, Oxford Trauma and Emergency Care, Nuffield Department of Orthopaedics, Rheumatology & Musculoskeletal Sciences, University of Oxford, Oxford, UK.

P. Thamattore, MACP, Associate Clinical Director, Healthshare Ltd, London, UK.

Author contributions

A. Woods: Formal analysis, Investigation, Methodology, Writing – original draft, Funding acquisition, Project administration, Writing – review & editing.
A. Howard: Investigation, Methodology, Writing – review & editing, Project administration.
N. Peckham: Formal analysis, Investigation, Methodology, Writing – review & editing.
I. Rombach: Formal analysis, Investigation, Methodology, Writing – review & editing.
A. Saleh: Formal analysis, Investigation, Methodology, Writing – review & editing.
J. Achten: Methodology, Supervision, Writing – review & editing.
D. Appelbe: Formal analysis, Methodology, Supervision, Writing – review & editing.
P. Thamattore: Investigation, Methodology, Project administration, Writing – review & editing.
S. E. Gwilym: Methodology, Supervision, Writing – review & editing.

A. Woods and A. Howard are joint first authors.

Funding statement

The authors disclose receipt of the following financial or material support for the research, authorship, and/or publication of this article: this paper presents independent research funded by the National Institute for Health Research (NIHR) under its Research for Patient Benefit (RfPB) Programme (Grant Reference Number NIHR201473). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health.

ICMJE COI statement

Zimmer Biomet provided nStride APS kits and blinded syringes for the purposes of the trial but had no part in the design, delivery, or reporting of the trial. J. Achten's employer (the University of Oxford) receives research grant funding from the National Institute for Health and Care Research and Wellcome Trust for research into musculoskeletal trauma. D. Appelbe reports NIHR/HTA institutional funding for this study. S. E. Gwilym, A. Howard, I. Rombach, and A. Woods report that the NIHR Research for Patient Benefit (RfPB) funded this study (NIHR201473). S. E. Gwilym has also taught on related topics at educational events run by Zimmer Biomet, after submission of this article.

Data sharing

The data that support the findings for this study are available to other researchers from the corresponding author upon reasonable request.

Acknowledgements

The authors would like to acknowledge Hannah Crook & Kylea Draper for their roles as trial Manager and their team at the Oxford Clinical Trials Unit for their help with managing this trial. Emma Jones for assisting in set up and management of the Leeds Trial site and recruitment of patients. Healthshare Ltd. for providing access and support in setting up the Oxford Trial Site.

Ethical review statement

This study received full Research Ethics Committee (REC) approval. REC Ref: 21/EE/0211; IRAS project ID: 294982.

Open access funding

The open access fee for this article was funded by the National Institute for Health and Care Research (NIHR201473).

Trial registration number

The study is registered within the International Standard Randomised Controlled Trials Number registry (ISRCTN12536844).