



Clinical trial results:

GRASP: Getting it Right: Addressing Shoulder Pain. Clinical and cost effectiveness of progressive exercise compared to best practice advice, with or without corticosteroid injection, for the treatment of rotator cuff disorders: a 2x2 factorial randomised controlled trial

Summary

EudraCT number	2016-002991-28
Trial protocol	GB
Global end of trial date	12 June 2020

Results information

Result version number	v1 (current)
This version publication date	28 June 2021
First version publication date	28 June 2021

Trial information

Trial identification

Sponsor protocol code	N/A
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Additional study identifiers

ISRCTN number	ISRCTN16539266
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1185-3750

Notes:

Sponsors

Sponsor organisation name	University of Oxford
Sponsor organisation address	Old Road, Headington, Oxford, United Kingdom,
Public contact	Dr Sally Hopewell, Oxford Clinical Trials Research Unit, sally.hopewell@csm.ox.ac.uk
Scientific contact	Dr Sally Hopewell, Oxford Clinical Trials Research Unit, sally.hopewell@csm.ox.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 June 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 June 2020
Global end of trial reached?	Yes
Global end of trial date	12 June 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary research objective is to assess whether:

An individually tailored progressive exercise programme, that includes behavioural change strategies, led by a physiotherapist provides greater improvement in shoulder pain and function over 12 months post-randomisation than a best practice advice session with a physiotherapist supported by high quality materials; and whether an injection into the shoulder (a subacromial corticosteroid injection) provides greater improvement in shoulder pain and function over 12 months post-randomisation than no injection.

This will be assessed by the the pain and function levels of each participant over 12 months after entering the trial.

Protection of trial subjects:

A Data Monitoring and Ethics Committee (DMEC) was responsible for monitoring the trial's progress and providing independent advice. It advised the chair of the TSC if, at any time, in its view, the trial should have been be stopped for ethical reasons, including concerns about participant safety. The DMEC was comprised of an independent clinician, health service researchers, a specialist physiotherapist and a statistician.

Background therapy:

Not applicable

Evidence for comparator:

The best practice advice session with a physiotherapist was selected as the comparator because it is consistent with current clinical practice guidelines regarding the self-management advice that should be provided to people with rotator cuff disorders. In addition, we used a no-injection comparison as finding an inert robust placebo is challenging and, given the existing evidence on the short term benefit of corticosteroid injection, we believed that it was unethical and undesirable to progress a placebo arm in a large phase III trial.

Actual start date of recruitment	02 January 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 708
Worldwide total number of subjects	708
EEA total number of subjects	0

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	512
From 65 to 84 years	192
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

708 participants were recruited between 10 March 2017 to 2 May 2019 from 20 UK NHS primary care-based musculoskeletal and related physiotherapy services.

Pre-assignment

Screening details:

A total of 2287 patients were screened and assessed to see whether they met the GRASP trial eligibility criteria (see Table 5) of whom 1284 (56%) were eligible and 708 agreed to participate

Period 1

Period 1 title	DefineOverall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

It was not possible to blind physiotherapists or study participants once treatment allocation was revealed. Where practical, team members were blinded until after data analysis was complete. Trial statisticians had access to treatment assignment during the study for the purposes of data monitoring and safety. Data entry personnel entered data from anonymised questionnaires, which included some details on treatments received.

Arms

Are arms mutually exclusive?	No
Arm title	Progressive Exercise

Arm description:

Progressive exercise programme: individually tailored progressive home exercise programme prescribed and supervised by a physiotherapist involving up to six face-to-face sessions over 16 weeks. Preceded by either corticosteroid injection or no corticosteroid injection depending on randomisation.

Arm type	Experimental
Investigational medicinal product name	Methylprednisolone acetate
Investigational medicinal product code	
Other name	triamcinolone acetonide, as per local treatment protocols.
Pharmaceutical forms	Injection
Routes of administration	Injection

Dosage and administration details:

Single injection of Methylprednisolone acetate (up to 40 mg) or triamcinolone acetonide (up to 40 mg), as per local treatment protocols.

Depo-Medrone 40mg <https://www.medicines.org.uk/emc/product/8957/smpc#gref> or Kenalog Intra-articular / Intramuscular injection <https://www.medicines.org.uk/emc/product/6748/pil#gref>

Arm title	Best Practice Advice
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Arm description:

Best practice advice: one face-to-face session with a physiotherapist and home exercise programme supported by high quality self-management materials. Preceded by either corticosteroid injection or no corticosteroid injection depending on randomisation.

Arm type	Active comparator
Investigational medicinal product name	Methylprednisolone acetate
Investigational medicinal product code	
Other name	triamcinolone acetonide, as per local treatment protocols.
Pharmaceutical forms	Injection
Routes of administration	Injection

Dosage and administration details:

Single injection of Methylprednisolone acetate (up to 40 mg) or triamcinolone acetonide (up to 40 mg), as per local treatment protocols.

Arm title	Corticosteroid Injection
Arm description: Subacromial corticosteroid injection. The corticosteroid injected was either methylprednisolone acetate (up to 40 mg) or triamcinolone acetonide (up to 40 mg), as per local treatment protocols. The local anaesthetic was either 1% lidocaine (up to 5 mL) or 0.5% bupivacaine hydrochloride (up to 10 mL). Followed by either progressive exercise programme or best practice advice depending on randomisation.	
Arm type	Experimental
Investigational medicinal product name	Methylprednisolone acetate
Investigational medicinal product code	
Other name	triamcinolone acetonide, as per local treatment protocols.
Pharmaceutical forms	Injection
Routes of administration	Injection

Dosage and administration details:

Single injection of Methylprednisolone acetate (up to 40 mg) or triamcinolone acetonide (up to 40 mg), as per local treatment protocols.

Depo-Medrone 40mg <https://www.medicines.org.uk/emc/product/8957/smpc#gref> or Kenalog Intra-articular / Intramuscular injection <https://www.medicines.org.uk/emc/product/6748/pil#gref>

Arm title	No Corticosteroid Injection
Arm description: No subacromial corticosteroid injection. Followed by either progressive exercise programme or best practice advice (as described above) depending on randomisation.	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Progressive Exercise	Best Practice Advice	Corticosteroid Injection
Started	356	352	360
Completed	343	339	352
Not completed	13	13	8
Lost to follow-up	13	13	8

Number of subjects in period 1	No Corticosteroid Injection
Started	348
Completed	330
Not completed	18
Lost to follow-up	18

Baseline characteristics

Reporting groups

Reporting group title	Progressive Exercise
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Reporting group description:

Progressive exercise programme: individually tailored progressive home exercise programme prescribed and supervised by a physiotherapist involving up to six face-to-face sessions over 16 weeks. Preceded by either corticosteroid injection or no corticosteroid injection depending on randomisation.

Reporting group title	Best Practice Advice
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Reporting group description:

Best practice advice: one face-to-face session with a physiotherapist and home exercise programme supported by high quality self-management materials. Preceded by either corticosteroid injection or no corticosteroid injection depending on randomisation.

Reporting group title	Corticosteroid Injection
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Reporting group description:

Subacromial corticosteroid injection. The corticosteroid injected was either methylprednisolone acetate (up to 40 mg) or triamcinolone acetonide (up to 40 mg), as per local treatment protocols. The local anaesthetic was either 1% lidocaine (up to 5 mL) or 0.5% bupivacaine hydrochloride (up to 10 mL). Followed by either progressive exercise programme or best practice advice depending on randomisation.

Reporting group title	No Corticosteroid Injection
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Reporting group description:

No subacromial corticosteroid injection. Followed by either progressive exercise programme or best practice advice (as described above) depending on randomisation.

Reporting group values	Progressive Exercise	Best Practice Advice	Corticosteroid Injection
Number of subjects	356	352	360
Age categorical			
Participant age at randomisation			
Units: Subjects			
18-35 years	31	24	30
36 years and above	325	328	330
Age continuous			
Participant age at randomisation (continuous)			
Units: years			
arithmetic mean	56.2	54.7	55.3
standard deviation	± 12.7	± 13.5	± 13.4
Gender categorical			
Units: Subjects			
Female	173	176	178
Male	183	176	182

Reporting group values	No Corticosteroid Injection	Total	
Number of subjects	348	708	
Age categorical			
Participant age at randomisation			
Units: Subjects			
18-35 years	25	55	
36 years and above	323	653	

Age continuous			
Participant age at randomisation (continuous)			
Units: years			
arithmetic mean	55.6		
standard deviation	± 12.8	-	
Gender categorical			
Units: Subjects			
Female	171	349	
Male	177	359	

Subject analysis sets

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Included in the analysis is all participants with at least one follow-up time point SPADI outcome and the baseline variables used in the model (682/total randomised 708)

Reporting group values	ITT		
Number of subjects	708		
Age categorical			
Participant age at randomisation			
Units: Subjects			
18-35 years	52		
36 years and above	630		
Age continuous			
Participant age at randomisation (continuous)			
Units: years			
arithmetic mean	55.8		
standard deviation	± 13.0		
Gender categorical			
Units: Subjects			
Female	330		
Male	352		

End points

End points reporting groups

Reporting group title	Progressive Exercise
Reporting group description: Progressive exercise programme: individually tailored progressive home exercise programme prescribed and supervised by a physiotherapist involving up to six face-to-face sessions over 16 weeks. Preceded by either corticosteroid injection or no corticosteroid injection depending on randomisation.	
Reporting group title	Best Practice Advice
Reporting group description: Best practice advice: one face-to-face session with a physiotherapist and home exercise programme supported by high quality self-management materials. Preceded by either corticosteroid injection or no corticosteroid injection depending on randomisation.	
Reporting group title	Corticosteroid Injection
Reporting group description: Subacromial corticosteroid injection. The corticosteroid injected was either methylprednisolone acetate (up to 40 mg) or triamcinolone acetonide (up to 40 mg), as per local treatment protocols. The local anaesthetic was either 1% lidocaine (up to 5 mL) or 0.5% bupivacaine hydrochloride (up to 10 mL). Followed by either progressive exercise programme or best practice advice depending on randomisation.	
Reporting group title	No Corticosteroid Injection
Reporting group description: No subacromial corticosteroid injection. Followed by either progressive exercise programme or best practice advice (as described above) depending on randomisation.	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description: Included in the analysis is all participants with at least one follow-up time point SPADI outcome and the baseline variables used in the model (682/total randomised 708)	

Primary: SPADI over 12 months

End point title	SPADI over 12 months
End point description:	
End point type	Primary
End point timeframe: over 12 months	

End point values	Progressive Exercise	Best Practice Advice	Corticosteroid Injection	No Corticosteroid Injection
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	343	339	352	330
Units: Adjusted Mean				
arithmetic mean (standard error)	28.8 (± 1.0)	29.4 (± 1.1)	28.5 (± 1.0)	29.6 (± 1.0)

End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	682			

Units: Adjusted Mean				
arithmetic mean (standard error)	29.1 (± 0.7)			

Statistical analyses

Statistical analysis title	Primary analysis for Progressive Exercise
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Statistical analysis description:

The difference in the primary outcome SPADI between the two intervention groups (Progressive Exercise and Best Practice Advice) was estimated over the 12 months period and at each data collection time point using a repeated measures linear mixed effects regression model adjusted for the fixed effects age, sex and baseline SPADI, and random intercepts by centre, physiotherapist and observations within participant.

Comparison groups	Progressive Exercise v Best Practice Advice
Number of subjects included in analysis	682
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.659 ^[1]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.66
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-4.52
upper limit	3.2
Variability estimate	Standard error of the mean

Notes:

[1] - Statistical significance was set at the 1% level and corresponding 99% confidence intervals (CI) for the primary outcome.

Statistical analysis title	Primary analysis for Corticosteroid Injection
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Statistical analysis description:

The difference in the primary outcome SPADI between the two intervention groups (Corticosteroid Injection and No Corticosteroid Injection) was estimated over the 12 months period and at each data collection time point using a repeated measures linear mixed effects regression model adjusted for the fixed effects age, sex and baseline SPADI, and random intercepts by centre, physiotherapist and observations within participant.

Comparison groups	Corticosteroid Injection v No Corticosteroid Injection
Number of subjects included in analysis	682
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.397 ^[2]
Method	Mixed models analysis
Parameter estimate	Median difference (final values)
Point estimate	-1.11
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-4.47
upper limit	2.26

Variability estimate	Standard error of the mean
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Notes:

[2] - Statistical significance was set at the 1% level and corresponding 99% confidence intervals (CI) for the primary outcome.

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

12 months

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	2015
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Frequency threshold for reporting non-serious adverse events: 0 %

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: Foreseeable adverse events occurring as a result of the trial intervention(s) were not planned to be recorded as part of the trial. Instead, participants were provided with information on the potential adverse events resulting from exercise and corticosteroid injection (if applicable) including what they should do if they experience an adverse event, as would happen as part of standard NHS procedures.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Our population was predominantly white British (89.7%), this figure is higher compared with the population in England as a whole (78.7%). The prevalence of rotator cuff disorder in ethnic minority groups is not well known or understood.
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Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/32894159>

<http://www.ncbi.nlm.nih.gov/pubmed/28716796>

<http://www.ncbi.nlm.nih.gov/pubmed/32026827>