Clinical trial results:
A multicentre double-blind randomised controlled trial to assess the clinical- and cost-effectiveness of facet-joint injections in selected patients with non-specific low back pain: a feasibility study

Summary

EudraCT number	2014-003187-20
Trial protocol	GB
Global end of trial date	31 March 2017

Results information

Result version number	v1 (current)
This version publication date	29 March 2019
First version publication date	29 March 2019

Trial information

Trial identification

Sponsor protocol code	008021 BLT

Additional study identifiers

ISRCTN number	ISRCTN12191542
ClinicalTrials.gov id (NCT number)	NCT03339362
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Barts Health NHS Trust
Sponsor organisation address	3rd Floor, 1 St. Martin's Le- Grand, London, United Kingdom, EC1A 4NP
Public contact	Dr Vivek Mehta, Barts Health NHS Trust, 44 07740950868, vivek.mehta@bartshealth.nhs.uk
Scientific contact	Dr Vivek Mehta, Barts Health NHS Trust, 44 07740950868, vivek.mehta@bartshealth.nhs.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	31 March 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 March 2017
Global end of trial reached?	Yes
Global end of trial date	31 March 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the feasibility of conducting a definitive study to evaluate the clinical- and cost-effectiveness of facet-joint injections compared to a sham procedure, in patients with non-specific low back pain of more than three months' duration.

The definitive trial will be deemed feasible if we are successful in standardisation of the method of injection and the test-run of the sham procedure, and if we are able to recruit and retain patients to the proposed trial design.

Protection of trial subjects:

Potential participants will initially be given a copy of the participant information sheet and given a verbal explanation of its contents. This will include details on the nature of the study, the implications and constraints of the study protocol, and any known side effects and risks involved in taking part in the study. Participants will be told that they are free to withdraw from the study at any time for any reason, without prejudice to future care or obligation to give the reason for withdrawal. They will be given as much time as they wish to consider the information, and to ask questions.

A medically qualified and experienced investigator (Principal Investigator or a medically qualified person within the research team with authority given by the site Principal Investigator, documented on the site delegation log) will obtain written informed consent. Participants will be expected to sign and date the form to indicate their consent. The original signed form will be retained at the study site, and a copy given to the participant and a copy in the site medical records.

Prior to any study-specific procedures being carried out, participants will sign and date the latest approved version of the informed consent form.

Background therapy:

This study seeks to examine the feasibility of undertaking a fully powered double-blind randomised controlled trial ('definitive trial') to evaluate the clinical- and cost-effectiveness of facet-joint injections compared to a sham procedure, in patients with non-specific low back pain of more than three months' duration.

The definitive trial will be deemed feasible if we can demonstrate successful standardisation of the method of injection and the test-run of the sham procedure that the proposed study design is deemed acceptable by patients and clinicians, and we are able to recruit and retain sufficient patients.

Evidence for comparator:

Diagnostic tests: Medial branch nerve blocks were carried out at each painful level with X-ray guidance, using a spinal needle to inject 0.5ml 1% lidocaine per level. A positive response is defined as a 50% or greater pain reduction (measured using a pain intensity numerical rating scale) assessed in the standing position, lasting for over 30 minutes (i.e. the duration of action of lidocaine).

Patients who received a 50% pain reduction after diagnostic tests were then enrolled on the study. These patients were randomised to receive either active arm or sham arm.
A spinal needle was placed within the facet-joint under X-ray guidance, and 0.5ml 0.5% bupivacaine with 20mg methylprednisolone (active) or 0.5ml normal saline (placebo) was injected per joint. Four facet-joints were injected, at two bilateral lumbar levels.

Following interventions, both groups (active vs sham) completed a 12 weeks of combined physical and

psychological programme with trained specialist physiotherapists as recommended by NICE guidelines.

As this was a feasibility study, we do not propose to formally inferentially test differences in outcomes or costs between or within the groups. Recruitment and attrition rates were calculated with 95% confidence intervals. The mean and standard deviations for primary and secondary outcomes were reported for the two groups at baseline and all follow-up visits.

Treatment Groups:
Active: Bupivacaine and Methylprednisolone
Placebo: Normal Saline

All three drugs are licensed for use by the MHRA and were used as licensed. Patients were randomized to one treatment group following positive response of diagnostic test.

Actual start date of recruitment	01 July 2015
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: 16
Worldwide total number of subjects	16
EEA total number of subjects	16

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)	16
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The following patients were recruited from one investigator site from Jan 2016- Dec 2016. Actual number of patients recruited:

- 16 patient consented, 4 withdrawn
- 12 patients passed diagnostic tests, 2 failed diagnostic tests
- 9 patients randomised
- 8 patients completed trial, 1 loss to follow up.

Pre-assignment

Screening details:

A total of 693 patients were screened during Jan 2016-Dec 2016. 16 recruited. Inclusion:
1.18 to 70 years
2.Low back pain of three months or greater duration.
3.Average pain score 4/10 or more 7 days before recruitment
4. Dominantly paraspinal tenderness
5. Completed at least 2 conservative treatments

Period 1

Period 1 title	Enrolment
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Patients must meet the inclusion criteria and pass the diagnostic test to proceed in the trial.

Arms

Arm title	Diagnostic Test

Arm description:

Patients were screened for eligibility to enter the study. Patients who passed the diagnostic test were then randomised.

Arm type	screening test
Investigational medicinal product name	Lidocaine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Perineural use

Dosage and administration details:

Diagnostic medial branch nerve blocks will be carried out at each painful level with X-ray guidance, using a spinal needle to inject 0.5ml 1% lidocaine per level. A positive response is defined as a 50% or greater pain reduction (measured using a pain intensity numerical rating scale) assessed in the standing position, lasting for over 30 minutes (i.e. the duration of action of lidocaine).

Number of subjects in period 1	Diagnostic Test
Started	16
Completed	11
Not completed	5
Physician decision	5

Period 2

Period 2 title	Randomisation
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst

Blinding implementation details:

Eligible and consented participants will be individually randomised in a 1:1 ratio to receive either the facet-joint injection (intervention group) or a sham (placebo injection) procedure (control group).

Arms

Are arms mutually exclusive?	No
Arm title	Sham

Arm description:

Sodium chloride 0.9% intravenous infusion BP ('normal saline')

Arm type	Placebo
Investigational medicinal product name	Sodium chloride 0.9% intravenous infusion BP ('normal saline')
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Periarticular use

Dosage and administration details:

The sham group will receive normal saline 0.9% 0.5ml.

Arm title	Intervention

Arm description:

The active group will receive methylprednisolone acetate (Depo-Medrone) 20mg per joint. A maximum of four joints will be injected i.e. a maximum total dose of 80mg Depo-Medrone.

The active group will additionally receive 0.5ml 0.5% bupivacaine per joint. A maximum of four joints will be injected i.e. a maximum of 2ml 0.5% bupivacaine.

Arm type	Experimental
Investigational medicinal product name	Methylprednisolone acetate BP 40mg/ml,
Investigational medicinal product code	
Other name	Depo-Medrone 40mg/ml
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intraarticular use

Dosage and administration details:

The active group will receive methylprednisolone acetate (Depo-Medrone) 20mg per joint. A maximum of four joints will be injected i.e. a maximum total dose of 80mg Depo-Medrone.

Investigational medicinal product name	Bupivacaine hydrochloride BP 0.5%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for suspension for injection
Routes of administration	Intraarticular use

Dosage and administration details:

The active group will additionally receive 0.5ml 0.5% bupivacaine per joint. A maximum of four joints will be injected i.e. a maximum of 2ml 0.5% bupivacaine.

Number of subjects in period 2	Sham	Intervention
Started	4	5
Completed	4	4
Not completed	0	1
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Diagnostic Test
Reporting group description:	
Patients were screened for eligibility to enter the study. Patients who passed the diagnostic test were then randomised.	

Reporting group values	Diagnostic Test	Total	
Number of subjects	16	16	
Age categorical			
Patients aged 18 to 70 years attending pain clinics identified during routine clinical assessment of non-specific low back pain			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	16	16	
From 65-84 years	0	0	
85 years and over	0	0	
18-70 years	0	0	
Age range	0	0	
Age continuous			
age 18- 70 years			
Units: years			
median	39		
full range (min-max)	18 to 70	-	
Gender categorical			
Patients are suitable for the facet-joint injections and with negative pregnancy test			
Units: Subjects			
Female	9	9	
Male	7	7	

End points

End points reporting groups

Reporting group title	Diagnostic Test
Reporting group description:	
Patients were screened for eligibility to enter the study. Patients who passed the diagnostic test were then randomised.	
Reporting group title	Sham
Reporting group description:	
Sodium chloride 0.9% intravenous infusion BP (‘normal saline’)	
Reporting group title	Intervention
Reporting group description:	
The active group will receive methylprednisolone acetate (Depo-Medrone) 20mg per joint. A maximum of four joints will be injected i.e. a maximum total dose of 80mg Depo-Medrone. The active group will additionally receive 0.5ml 0.5% bupivacaine per joint. A maximum of four joints will be injected i.e. a maximum of 2ml 0.5% bupivacaine.	

Primary: Numerical rating pain score

End point title	Numerical rating pain score
End point description:	
End point type	Primary
End point timeframe:	
Baseline and 6 months follow up	

End point values	Sham	Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: pain scores				
arithmetic mean (standard deviation)				
baseline	9.5 (± 1.0)	8.4 (± 1.5)		
follow up	7.5 (± 1.9)	7.0 (± 1.6)		

Statistical analyses

Statistical analysis title	Analysis
Statistical analysis description:	
As this is a feasibility study, we do not propose to formally inferentially test differences in outcomes or costs between or within the groups. We shall report mean and standard deviations for primary and secondary outcomes for the two groups at baseline and all follow-up visits.	
Comparison groups	Sham v Intervention

Number of subjects included in analysis	9
Analysis specification	Post-hoc
Analysis type	other[1]
P-value	< 0.05
Method	mean and SD
Parameter estimate	not reported
Point estimate	5
Confidence interval	
level	95 %
sides	1-sided
lower limit	2
Variability estimate	Standard deviation
Dispersion value	0

Notes:

[1] - Mean and standard deviations.

Secondary: Brief Pain Inventory

End point title	Brief Pain Inventory

End point description:

Pain intensity and characteristics: Brief Pain Inventory (BPI) (Short Form) Modified, with its 11-point NRS Short Form McGill Pain Questionnaire. As movement could potentially influence the intervention (lumbar facet-joint injections or sham), all numerical rating scores were assessed in the standing position

End point type	Secondary

End point timeframe:

Baseline and 6 months follow up

End point values	Sham	Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: scores				
arithmetic mean (standard deviation)				
Baseline average pain	7.5 (± 1.9)	7.0 (± 1.0)		
Follow up Average pain	5.3 (± 4.5)	5.6 (± 2.6)		
baseline least pain	6.0 (± 2.7)	6.0 (± 3.5)		
follow up least pain	5.3 (± 2.2)	5.0 (± 2.8)		
baseline worst pain	9.3 (± 1.5)	7.2 (± 2.2)		
follow up worst pain	6.3 (± 4.7)	6.0 (± 3.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Oswestry Disability Index, mean

End point title	Oswestry Disability Index, mean

End point description:

End point type	Secondary

End point timeframe:
Baseline and 6 months follow up

End point values	Sham	Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: mean points				
arithmetic mean (standard deviation)				
Baseline	48.8 (± 19.9)	43.0 (± 15.0)		
follow up	42.6 (± 34.0)	39.9 (± 26.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: McGill Pain Questionnaire, mean

End point title	McGill Pain Questionnaire, mean

End point description:

End point type	Secondary

End point timeframe:
Baseline and 6 months follow up

End point values	Sham	Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: mean scores				
arithmetic mean (standard deviation)				
baseline	3.3 (± 2.0)	4.5 (± 2.0)		
Follow up	3.5 (± 2.9)	3.4 (± 2.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pain Self Efficacy Questionnaire

End point title	Pain Self Efficacy Questionnaire

End point description:

End point type	Secondary

End point timeframe:

Baseline and 6 months follow up

End point values	Sham	Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: mean scores				
arithmetic mean (standard deviation)				
baseline	27.0 (± 7.7)	22.6 (± 12.2)		
follow up	28.3 (± 21.7)	33.2 (± 19.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: SF-12

End point title	SF-12

End point description:

End point type	Secondary

End point timeframe:

Baseline and follow up (6, 12 and 24 weeks)

End point values	Sham	Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: mean scores				
arithmetic mean (standard deviation)				
Baseline MCS	43.4 (± 10.0)	30.4 (± 4.6)		
Baseline PCS	32.7 (± 6.0)	33.1 (± 6.7)		
Follow up MCS	47.2 (± 22.1)	38.1 (± 13.5)		
Follow up PCS	34.4 (± 12.5)	39.5 (± 13.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Hospital Anxiety and Depression Score, mean

End point title	Hospital Anxiety and Depression Score, mean

End point description:

End point type	Secondary

End point timeframe:

Baseline and 6 months follow ups

End point values	Sham	Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: mean				
arithmetic mean (standard deviation)				
Baseline Anxiety	7.5 (± 3.4)	12.0 (± 1.2)		
Baseline Depression	6.8 (± 3.9)	10.4 (± 3.4)		
Follow up Anxiety	6.7 (± 5.7)	10.0 (± 3.9)		
Follow up Depression	7.7 (± 8.1)	8.7 (± 7.1)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Patients will be asked if they experience any adverse events at every visit after signing the consent form (visits: diagnostic test, randomisation, 4, 6, 12 and 24 weeks post intervention).

Adverse event reporting additional description:

Patients will be asked if they experience any Adverse events (AE) at every visit after consent. Any study related serious adverse events (SAEs) will be recorded in the subjects' notes, the CRF, the Sponsor SAE form and reported to the sponsor within 24 hours of the PI or co-investigators becoming aware of the event.

Assessment type	Non-systematic

Dictionary used

Dictionary name	SNOMED CT
Dictionary version	1

Reporting groups

Reporting group title	randomisation

Reporting group description:

patients experienced adverse event after randomised injections.

Serious adverse events	randomisation		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 9 (11.11%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Skin and subcutaneous tissue disorders			
Swelling at injection site	Additional description: Patient experienced swelling at site of injection after diagnostic injections		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
urinary incontinence	Additional description: Urine incontinence. Patient visited Clinical Department in emergency dept. regarding urine incontinence		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	randomisation		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 9 (44.44%)		
Psychiatric disorders			
Depression postoperative	Additional description: Patient experienced severe depression as a result of his back pain and medication. He visited his GP to have his medication changed. He has reported it has helped.		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Flare up	Additional description: Patient experienced flare up following injections		
subjects affected / exposed	4 / 9 (44.44%)		
occurrences (all)	4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 January 2016	Information updated for patient safety section: "what happens if something happens?" (REC approval required only for NHS permission) -minor amendment for protocol: TSC and DMC details updated (REC approval required to include minor amendment re:16 Sep 2015)
17 June 2016	-Patients can be recruited from spinal, pain and orthopaedic clinics. -CPP information made clearer. -Lidocaine removed as IMP and now a non-IMP -Storage of IMP -Change of CI and PI at coordinating centre.
12 December 2016	End of recruitment. 1/3 sites opened for recruitment only. Now single centre

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
12 December 2016	End of recruitment for all three centres. The study was designed to be a multi-centre study but became a single centre study. We were unable to receive NHS permission to recruit and perform the study at the other two sites. Thus limiting our population type and unable to reach our target population size for the study.	-

Notes:

Limitations and caveats

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

- population type- many patients had previous injections or back surgery
- unable to recruit from other sites
- delays receiving approvals to start the study

Notes: