Clinical trial results:
A randomised, multi-centre, open-label, active-comparator, pragmatic clinical trial of low-dose colchicine versus naproxen in patients with acute gout.

Summary

EudraCT number	2013-001354-95
Trial protocol	GB
Global end of trial date	31 March 2016

Results information

Result version number	v2
This version publication date	22 June 2019
First version publication date	28 April 2017
Version creation reason	• Correction of full data set Administrative error in reporting

Trial information

Trial identification

Sponsor protocol code	149/11

Additional study identifiers

ISRCTN number	ISRCTN69836939
ClinicalTrials.gov id (NCT number)	NCT01994226
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Keele University
Sponsor organisation address	Keele University , Staffordshire, United Kingdom, ST5 5BG
Public contact	Dr Clark Crawford , Keele University, 01782 734714, research.governance@keele.ac.uk
Scientific contact	Dr Clark Crawford , Keele University, 01782 734714, research.governance@keele.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	31 March 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 March 2016
Global end of trial reached?	Yes
Global end of trial date	31 March 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The principal research objective is to compare the effectiveness of two licensed drugs, which are frequently prescribed within primary care, to reduce pain from acute gout; namely low-dose Colchicine and Naproxen.

Protection of trial subjects:

The trial was performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 52nd World Medical Association General Assembly, Edinburgh, Scotland. Informed written consent was obtained from the participants prior to randomisation into the trial. The right of a participant to refuse participation without giving reasons was respected.

The trial was submitted to and approved by a main Research Ethics Committee (main REC) and the appropriate Site Specific Assessor for each participating centre prior to entering participants into the trial.

All information collected during the course of the trial is kept strictly confidential. Keele CTU comply with all aspects of the 1998 Data Protection Act.

Background therapy:

None.

Evidence for comparator:

The numerous previous trials of NSAIDs for acute gout have either compared NSAID to placebo or, more commonly, involved head-to-head comparisons of one NSAID against corticosteroids, or another NSAID or a COX-2 selective inhibitor . To date, oral NSAIDs have not been directly compared to low-dose colchicine. This randomised trial will be the first direct head-to-head comparison of the effectiveness of naproxen, a commonly used NSAID, with low-dose colchicine for the management of acute gout. It will also directly compare the side-effect profiles of these two treatments, which has important implications for patient safety in view of the increasing prevalence of gout with age, considerable associated comorbidity, and the frequent need to provide repeat prescriptions for recurrent attacks of acute gout. Both naproxen and colchicine have a licence to treat acute gout. Evidence-based guidelines for the management of acute gout state that there is no evidence of superiority of any one NSAID over another and, where use of a NSAID is considered appropriate, recommend the use of any fast-acting NSAID. We have chosen to use naproxen in this trial because it is of comparable effectiveness to oral prednisolone for the treatment of acute gout, is thought to be safer from a cardiovascular perspective than other commonly used NSAIDs such as diclofenac and indomethacin, and is inexpensive. Cardiovascular risk is an important consideration as gout has been shown to be an independent risk factor for coronary heart disease. This trial is needed to establish the effectiveness, safety and cost-effectiveness of low-dose colchicine as a viable alternative to NSAIDs for the first-line treatment of acute gout in primary care.

Actual start date of recruitment	29 January 2014
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: 399
Worldwide total number of subjects	399
EEA total number of subjects	399

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)	240
From 65 to 84 years	154
85 years and over	5

Subject disposition

Recruitment

Recruitment details:

Participants with acute gout were recruited at a consultation with their general practitioner

Pre-assignment

Screening details:

Prior to randomisation the following was completed:
- Eligibility assessment
- Informed Consent form
- Baseline Questionnaire

Period 1

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

Blinding implementation details:

The statistician was blind to participant's treatment allocation during the trial.

Arms

Are arms mutually exclusive?	Yes
Arm title	Naproxen

Arm description:

750 mg immediately followed by 250 mg every eight hours for up to 7 days

Arm type	Active comparator
Investigational medicinal product name	Naproxen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Naproxen (oral use): Single initial dose of 750mg (three tablets) followed by 250mg (one tablet) every eight hours up to seven days.

Arm title	Low dose Colchicine

Arm description:

500 mcg every eight hours for four days

Arm type	Active comparator
Investigational medicinal product name	Colchicine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Low-dose colchicine (oral use): 500mcg (one tablet) every eight hours for four days.

Number of subjects in period 1	Naproxen	Low dose Colchicine
Started	200	199
Completed	179	180
Not completed	21	19
Early Cessation of treatment	7	3
Protocol deviation	14	16

Baseline characteristics

Reporting groups	
Reporting group title	Naproxen
Reporting group description:	
750 mg immediately followed by 250 mg every eight hours for up to 7 days	
Reporting group title	Low dose Colchicine
Reporting group description:	
500 mcg every eight hours for four days	

Reporting group values	Naproxen	Low dose Colchicine	Total
Number of subjects	200	199	399
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	58.7	60	
standard deviation	± 14.4	± 13.4	-
Gender categorical Units: Subjects			
Female	27	25	52
Male	173	174	347
Site of Recruitment			
Baseline characteristics are summarized for the two treatment groups using appropriate descriptive statistics: mean (SD) for normally distributed numerical variables; median (inter-quartile range) for skewed numerical variables; frequency counts for categorical variables. Crude descriptive summary values for outcomes are also presented: mean absolute and change (pain) scores at each follow up time point with standard deviations (SD); other outcome measures are mostly categorical and are summarised through frequency counts (percent).			
Units: Subjects			
Keele	55	52	107
Southampton	88	101	189
Nottingham	16	15	31
Oxford	41	31	72
Preferred mode of contact Units: Subjects			
Electronic	59	63	122
Postal	141	136	277
First instance of Gout Units: Subjects			
Yes	35	51	86
No	161	144	305
Missing Data	4	4	8
Number of body parts affecred Units: Subjects			
One	139	145	284
Two	34	27	61
Three	13	9	22
Four	6	13	19

more than or equal to 5	4	1	5
Missing data	4	4	8
Body Part affected - Shoulder Units: Subjects			
Shoulder Yes	2	1	3
Shoulder No	194	194	388
Shoulder missing	4	4	8
Body Part affected - Elbow Units: Subjects			
Elbow Yes	4	11	15
Elbow No	192	184	376
Elbow missing	4	4	8
Body Part affected - Wrist Units: Subjects			
Wrist Yes	8	7	15
Wrist No	188	188	376
Wrist missing	4	4	8
Body part affected - Thumb Base Units: Subjects			
Thumb base - Yes	5	9	14
Thumb Base - No	191	186	377
Thumb base - missing data	4	4	8
Body Part affected - Small finger joints Units: Subjects			
Small finger joints yes	11	8	19
Small finger joints no	185	187	372
small finger joints - missing data	4	4	8
Body Part affected - Hip Units: Subjects			
Hip - Yes	2	1	3
Hip - No	194	194	388
hip - missing data	4	4	8
Body part affected - Knee Units: Subjects			
Knee - Yes	17	19	36
Knee - No	179	176	355
Knee - missing data	4	4	8
Body part affected - Ankle Units: Subjects			
Ankle- Yes	31	33	64
Ankle - No	165	162	327
Ankle - missing data	4	4	8
Body part affected - Mid-foot Units: Subjects			
Mid Foot- Yes	41	32	73
Mid Foot - No	155	163	318
mid foot - missing data	4	4	8
Body part affected - Big Toe Bunion Joint Units: Subjects			
Big Toe Bunion Joint - Yes	142	135	277

Big Toe Bunion Joint - No	54	60	114
Big toe bunion joint - missing data	4	4	8
Body Part affected - other toes Units: Subjects			
Other Toes - Yes	28	28	56
Other Toes - No	168	167	335
other toes missing data	4	4	8
Body Part affected - missing data Units: Subjects			
Missing data - Yes	4	4	8
Missing data - No	196	195	391
Pain NRS Units: 0-10			
arithmetic mean	7.1	6.9	
standard deviation	± 2.1	± 2.2	-
EQ5D-5L Units: EQ5D units			
arithmetic mean	0.665	0.666	
standard deviation	± 0.21	± 0.225	-
Age when diagnosed Units: Age			
arithmetic mean	52.1	53.4	
standard deviation	± 15.2	± 14.6	-

Subject analysis sets

Subject analysis set title	Main Analysis
Subject analysis set type	Full analysis

Subject analysis set description:

Main analysis was by ITT with evaluation of randomized participants as per allocation assignment. 399 participants were randomised between 02/2014-12/2015; follow up response was 86% in the naproxen group and 89% in the colchicine arm at days 7 and 4 weeks. Average pain scores dropped sharply in both treatment arms over the first 7 days from 7.1 and 6.9 at baseline to 1.4 and 1.5 at day 7 for naproxen and colchicine groups, respectively. For the primary endpoint analysis of between-group difference in average pain-change scores over 7 days through linear mixed model analysis adjusted for baseline pain score, age and gender: the mean difference was -0.19 (95% CI: -0.55, 0.16; p=0.283) This equated to a 'small' effect size (0.09) in favour of naproxen. The largest between-group mean difference was at day 2, which was -0.48 (95% CI: -0.86, -0.09; p=0.015) in favour of naproxen. Sensitivity analyses showed similar overall results as did per-protocol evaluation of treatment compliers.

Reporting group values	Main Analysis		
Number of subjects	399		
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	59.4		
standard deviation	± 13.9		
Gender categorical Units: Subjects			
Female	52		
Male	347		

Site of Recruitment			
Baseline characteristics are summarized for the two treatment groups using appropriate descriptive statistics: mean (SD) for normally distributed numerical variables; median (inter-quartile range) for skewed numerical variables; frequency counts for categorical variables. Crude descriptive summary values for outcomes are also presented: mean absolute and change (pain) scores at each follow up time point with standard deviations (SD); other outcome measures are mostly categorical and are summarised through frequency counts (percent).			
Units: Subjects			
Keele	107		
Southampton	189		
Nottingham	31		
Oxford	72		
Preferred mode of contact Units: Subjects			
Electronic	122		
Postal	277		
First instance of Gout Units: Subjects			
Yes	86		
No	305		
Missing Data	8		
Number of body parts affecred Units: Subjects			
One	284		
Two	61		
Three	22		
Four	19		
more than or equal to 5	5		
Missing data	8		
Body Part affected - Shoulder Units: Subjects			
Shoulder Yes	3		
Shoulder No	388		
Shoulder missing	4		
Body Part affected - Elbow Units: Subjects			
Elbow Yes	15		
Elbow No	376		
Elbow missing	8		
Body Part affected - Wrist Units: Subjects			
Wrist Yes	15		
Wrist No	376		
Wrist missing	8		
Body part affected - Thumb Base Units: Subjects			
Thumb base - Yes	14		
Thumb Base - No	377		
Thumb base - missing data	8		
Body Part affected - Small finger joints Units: Subjects			
Small finger joints yes	19		
Small finger joints no	372		

small finger joints - missing data	8		
Body Part affected - Hip Units: Subjects			
Hip - Yes	3		
Hip - No	388		
hip - missing data	8		
Body part affected - Knee Units: Subjects			
Knee - Yes	36		
Knee - No	355		
Knee - missing data	8		
Body part affected - Ankle Units: Subjects			
Ankle- Yes	64		
Ankle - No	327		
Ankle - missing data	8		
Body part affected - Mid-foot Units: Subjects			
Mid Foot- Yes	73		
Mid Foot - No	318		
mid foot - missing data	8		
Body part affected - Big Toe Bunion Joint Units: Subjects			
Big Toe Bunion Joint - Yes	277		
Big Toe Bunion Joint - No	114		
Big toe bunion joint - missing data	8		
Body Part affected - other toes Units: Subjects			
Other Toes - Yes	56		
Other Toes - No	335		
other toes missing data	8		
Body Part affected - missing data Units: Subjects			
Missing data - Yes	8		
Missing data - No	391		
Pain NRS Units: 0-10			
arithmetic mean	7		
standard deviation	± 2.1		
EQ5D-5L Units: EQ5D units			
arithmetic mean	0.666		
standard deviation	± 0.217		
Age when diagnosed Units: Age			
arithmetic mean	52.8		
standard deviation	± 14.9		

End points

End points reporting groups

Reporting group title	Naproxen
Reporting group description:	
750 mg immediately followed by 250 mg every eight hours for up to 7 days	
Reporting group title	Low dose Colchicine
Reporting group description:	
500 mcg every eight hours for four days	
Subject analysis set title	Main Analysis
Subject analysis set type	Full analysis
Subject analysis set description:	
Main analysis was by ITT with evaluation of randomized participants as per allocation assignment. 399 participants were randomised between 02/2014-12/2015; follow up response was 86% in the naproxen group and 89% in the colchicine arm at days 7 and 4 weeks. Average pain scores dropped sharply in both treatment arms over the first 7 days from 7.1 and 6.9 at baseline to 1.4 and 1.5 at day 7 for naproxen and colchicine groups, respectively. For the primary endpoint analysis of between-group difference in average pain-change scores over 7 days through linear mixed model analysis adjusted for baseline pain score, age and gender: the mean difference was -0.19 (95% CI: -0.55, 0.16; p=0.283) This equated to a 'small' effect size (0.09) in favour of naproxen. The largest between-group mean difference was at day 2, which was -0.48 (95% CI: -0.86, -0.09; p=0.015) in favour of naproxen. Sensitivity analyses showed similar overall results as did per-protocol evaluation of treatment compliers.	

Primary: Comparison of pain scores at follow up (primary outcome) ITT analysis

End point title	Comparison of pain scores at follow up (primary outcome) ITT analysis
End point description:	
As above	
End point type	Primary
End point timeframe:	
The primary endpoint measure will be pain measured on a 0-10 pain intensity numeric rating scale measured over days 0-7.	

End point values	Naproxen	Low dose Colchicine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	194		
Units: 0-10				
arithmetic mean (standard deviation)				
Day 1	6.7 (± 2.1)	6.5 (± 2.4)		
Day 2	4.9 (± 2.4)	5.2 (± 2.4)		
Day 3	3.8 (± 2.5)	3.9 (± 2.4)		
Day 4	2.8 (± 2.3)	2.8 (± 2.3)		
Day 5	2.3 (± 2.4)	2.3 (± 2.2)		
Day 6	1.8 (± 2.2)	2 (± 2.1)		
Day 7	1.4 (± 2)	1.5 (± 2.0)		

Attachments (see zip file)	Comparison of pain scores primary outcome

Statistical analyses

Statistical analysis title	Main Analysis

Statistical analysis description:

Main analysis was by intention to treat (ITT) with evaluation of randomized participants as per allocation assignment.

Comparison groups	Low dose Colchicine v Naproxen
Number of subjects included in analysis	387
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.283
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.55
upper limit	0.16
Variability estimate	Standard error of the mean

Notes:

[1] - For the primary endpoint analysis of between-group difference in average pain-change scores over 7 days through linear mixed model analysis adjusted for baseline pain score, age and gender: the mean difference was -0.19 (95% CI: -0.55, 0.16; p=0.283) This equated to a 'small' effect size (0.09) in favour of naproxen.

Secondary: Daily Medication use within the first week of follow up

End point title	Daily Medication use within the first week of follow up

End point description:

Generalised linear models (binary or ordinal logistic models) were used to model estimates for between-group comparisons of secondary outcomes: global assessment of response to treatment, another attack of gout, contact with health professionals (GP in the GP Practice, Practice nurse, emergency GP, Accident & Emergency), use of other medications for pain relief, and side effects. These analyses were based on complete data (crude analysis) and the MI dataset (for all patients randomised to align with full-ITT evaluation) and the between-group associations are shown as odds ratios (ORs) with 95% confidence intervals.

Statistical analysis was performed only when all participants had completed 4 week follow-up; The main (ITT) primary outcome evaluation as well as secondary outcomes (except per protocol evaluation and HE evaluation) were carried out blind to treatment. All statistical estimates include 95% confidence intervals; p-values <0.05 (two-sided) denote statistical significance

End point type	Secondary

End point timeframe:

Days 1-7

End point values	Naproxen	Low dose Colchicine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	194		
Units: Number				
Naproxen Day 1	155	0		
Naproxen Day 2	157	0		
Naproxen Day 3	157	0		
Naproxen Day 4	147	1		
Naproxen Day 5	145	3		
Naproxen Day 6	137	7		
Naproxen Day 7	136	7		
Colchicine Day 1	0	159		
Colchicine Day 2	1	160		
Colchicine Day 3	2	157		
Colchicine Day 4	4	143		
Colchicine Day 5	4	67		
Colchicine Day 6	3	47		
Colchicine Day 7	4	44		
Paracetamol Day 1	15	25		
Paracetamol Day 2	13	19		
Paracetamol Day 3	10	16		
Paracetamol Day 4	10	13		
Paracetamol Day 5	10	18		
Paracetamol Day 6	10	11		
Paracetamol Day 7	8	14		
Tramadol Day 1	1	1		
Tramadol Day 2	1	1		
Tramadol Day 3	1	1		
Tramadol Day 4	1	1		
Tramadol Day 5	1	1		
Tramadol Day 6	1	0		
Tramadol day 7	1	0		
Codeine Day 1	4	19		
Codeine Day 2	3	16		
Codeine Day 3	5	12		
Codeine Day 4	3	8		
Codeine Day 5	5	8		
Codeine Day 6	4	7		
Codeine Day 7	2	10		
Ibuprofen Day 1	9	15		
Ibuprofen Day 2	5	11		
Ibuprofen Day 3	5	10		
Ibuprofen Day 4	4	9		
Ibuprofen Day 5	5	10		
Ibuprofen Day 6	5	9		
Ibuprofen Day 7	6	10		
Diclofenac Day 1	1	1		
Diclofenac Day 2	0	2		
Diclofenac Day 3	0	3		
Diclofenac Day 4	0	3		
Diclofenac Day 5	0	4		

Diclofenac Day 6	0	3		
Diclofenac Day 7	1	3		
Indomethacin Day 1	1	0		
Indomethacin Day 2	0	0		
Indomethacin Day 3	0	0		
Indomethacin Day 4	0	0		
Indomethacin Day 5	0	0		
Indomethacin Day 6	0	0		
Indomethacin Day 7	0	0		
Prednisolone Day 1	0	0		
Prednisolone Day 2	0	0		
Prednisolone Day 3	1	1		
Prednisolone Day 4	1	1		
Prednisolone Day 5	1	1		
Prednisolone Day 6	2	1		
Prednisolone Day 7	2	3		
Any 'other' analgesia Day 1	20	42		
Any 'other' analgesia Day 2	17	32		
Any 'other' analgesia Day 3	16	26		
Any 'other' analgesia Day 4	14	20		
Any 'other' analgesia Day 5	16	25		
Any 'other' analgesia Day 6	15	17		
Any 'other' analgesia Day 7	11	20		
Any 'other' NSAIDS Day 1	10	16		
Any 'other' NSAIDS Day 2	5	13		
Any 'other' NSAIDS Day 3	5	13		
Any 'other' NSAIDS Day 4	4	11		
Any 'other' NSAIDS Day 5	5	14		
Any 'other' NSAIDS Day 6	5	12		
Any 'other' NSAIDS Day 7	6	13		
Any 'other' medication Day 1	28	52		
Any 'other' medication Day 2	21	40		
Any 'other' medication Day 3	20	35		
Any 'other' medication Day 4	18	30		
Any 'other' medication Day 5	20	37		
Any 'other' medication Day 6	20	28		
Any 'other' medication Day 7	16	29		

Statistical analyses

No statistical analyses for this end point

Secondary: Medication use over the first week and between weeks 2-4

End point title	Medication use over the first week and between weeks 2-4

End point description:

End point type	Secondary

End point timeframe:

Medication use over the first week and between weeks 2-4

End point values	Naproxen	Low dose Colchicine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	194		
Units: Number				
Naproxen Days 1 -7	148	6		
Naproxen Weeks 2-4	69	26		
Colchicine Days 1-7	6	142		
Colchicine Weeks 2-4	7	52		
Paracetamol Days 1-7	20	34		
Paracetamol Weeks 2-4	10	11		
Ibruprofen Days 1-7	16	20		
Ibruprofen Weeks 2-4	12	27		
Diclofenac Days 1-7	2	4		
Diclofenac Weeks 2-4	4	6		
Indomethacin Days 1-7	1	0		
Indomethacin Weeks 2-4	2	5		
Tramadol Days 1-7	1	0		
Tramadol Week 2-4	1	2		
Codeine Days 1-7	7	21		
Codeine Weeks 2 -4	12	8		
Prednisolone Days 1-7	3	2		
Prednisolone Weeks 2-4	2	1		
'other' analgesia days 1-7	26	49		
'other' analgesia week 2-4	22	19		
'other' NSAIDS days 1-7	17	23		
'other' NSAIDS week 2-4	18	37		
'other' medication days 1-7	37	61		
'other' medication weeks 2-4	37	52		

Statistical analyses

No statistical analyses for this end point

Secondary: Daily side effects within the first week of follow up

End point title	Daily side effects within the first week of follow up

End point description:

End point type	Secondary

End point timeframe:

Days 1-7

End point values	Naproxen	Low dose Colchicine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	194		
Units: Number				
Feeling Sick Day 1	17	15		
Feeling Sick Day 2	11	16		
Feeling Sick Day 3	7	17		
Feeling Sick Day 4	6	11		
Feeling Sick Day 5	6	6		
Feeling Sick Day 6	2	6		
Feeling Sick Day 7	3	5		
Being Sick Day 1	3	1		
Being Sick Day 2	2	1		
Being Sick Day 3	1	1		
Being Sick Day 4	0	0		
Being Sick Day 5	0	0		
Being Sick Day 6	0	1		
Being Sick Day 7	0	0		
Feeling/being Sick Day 1	19	16		
Feeling/being Sick Day 2	12	17		
Feeling/being Sick Day 3	7	18		
Feeling/being Sick Day 4	6	11		
Feeling/being Sick Day 5	6	6		
Feeling/being Sick Day 6	2	7		
Feeling/being Sick Day 7	3	5		
Indigestion Day 1	10	13		
Indigestion Day 2	11	11		
Indigestion Day 3	11	14		
Indigestion Day 4	9	11		
Indigestion Day 5	5	7		
Indigestion Day 6	6	6		
Indigestion Day 7	4	6		
Stomach Pain Day 1	5	7		
Stomach Pain Day 2	6	8		
Stomach Pain Day 3	7	8		
Stomach Pain Day 4	7	8		
Stomach Pain Day 5	3	9		
Stomach Pain Day 6	2	6		
Stomach Pain Day 7	4	6		
Headache Day 1	9	16		
Headache Day 2	10	12		
Headache Day 3	3	13		
Headache Day 4	3	13		
Headache Day 5	5	10		
Headache Day 6	4	5		
Headache Day 7	3	4		
Constipation Day 1	8	1		
Constipation Day 2	15	2		
Constipation Day 3	16	5		
Constipation Day 4	8	4		
Constipation Day 5	6	3		

Constipation Day 6	6	2		
Constipation Day 7	5	3		
Diarrhoea Day 1	7	20		
Diarrhoea Day 2	7	28		
Diarrhoea Day 3	12	40		
Diarrhoea Day 4	10	52		
Diarrhoea Day 5	3	34		
Diarrhoea Day 6	7	18		
Diarrhoea Day 7	5	13		
Skin Day 1	2	3		
Skin Day 2	2	2		
Skin Day 3	0	1		
Skin Day 4	0	1		
Skin Day 5	1	1		
Skin Day 6	0	1		
Skin Day 7	0	2		
Any side effects Day 1	54	54		
Any side effects Day 2	50	64		
Any side effects Day 3	52	76		
Any side effects Day 4	45	78		
Any side effects Day 5	38	52		
Any side effects Day 6	35	36		
Any side effects Day 7	26	32		

Statistical analyses

No statistical analyses for this end point

Secondary: Side effects over the first week and between weeks 2-4

End point title	Side effects over the first week and between weeks 2-4
End point description:	
End point type	Secondary
End point timeframe:	
7 days and 4 week follow up	

End point values	Naproxen	Low dose Colchicine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	194		
Units: Number				
Nausea Days 1-7	21	30		
Nausea Week 2-4	7	5		
Indigestion Days 1-7	20	20		
Indigestion Week 2-4	13	8		
Stomach Pain Days 1-7	16	16		
Stomach Pain Weeks 2-4	4	8		

Headache Days 1-7	16	30		
Headache Week 2-4	4	4		
Constipation Days 1-7	29	7		
Constipation Week 2-4	9	6		
Diarrhoea Day 1-7	30	67		
Diarrhoea Week 2-4	5	10		
Skin Problems Day 1-7	3	3		
Skin Problems Week 2-4	3	3		
Any side effects days 1-7	91	101		
Any side effects week 2-4	37	28		

Statistical analyses

No statistical analyses for this end point

Secondary: Global Change 7 days

End point title	Global Change 7 days

End point description:

End point type	Secondary

End point timeframe:

After 7 days

End point values	Naproxen	Low dose Colchicine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	194		
Units: Number				
Completely better now	52	43		
Much better now	62	67		
Somewhat better now	35	27		
About the same	9	13		
Somewhat worse now	2	0		
Much worse now	0	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Global Change 4 weeks

End point title	Global Change 4 weeks

End point description:

End point type	Secondary

End point timeframe:
4 weeks follow up

End point values	Naproxen	Low dose Colchicine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	194		
Units: Number				
Completely better now	70	81		
Much better now	70	62		
Somewhat better now	19	20		
About the same	11	12		
Somewhat worse now	2	2		
Much worse now	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Global Change Dichotomised 7 days

End point title	Global Change Dichotomised 7 days

End point description:

End point type	Secondary

End point timeframe:
7 days

End point values	Naproxen	Low dose Colchicine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	194		
Units: Number				
Completely/much better now	114	110		
Not completely/much better	46	42		

Statistical analyses

No statistical analyses for this end point

Secondary: Global Change Dichotomised 4 weeks

End point title	Global Change Dichotomised 4 weeks

End point description:

End point type	Secondary

End point timeframe:

4 weeks

End point values	Naproxen	Low dose Colchicine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	194		
Units: Number				
Completely/much better now	140	143		
not completely/much better	33	34		

Statistical analyses

No statistical analyses for this end point

Secondary: Another attack of gout within 4 weeks

End point title	Another attack of gout within 4 weeks

End point description:

End point type	Secondary

End point timeframe:

4 weeks

End point values	Naproxen	Low dose Colchicine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	194		
Units: Number				
Another attack of Gout within 4 week follow up	40	54		

Statistical analyses

No statistical analyses for this end point

Secondary: Further contact with health professional during 4 weeks follow up

End point title	Further contact with health professional during 4 weeks follow up

End point description:	
Health professional: GP, practice nurse, emergency GP and A&E	
End point type	Secondary
End point timeframe:	
4 weeks	

End point values	Naproxen	Low dose Colchicine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	194		
Units: Number				
Further contact with health professional 4 week	30	41		

Statistical analyses

No statistical analyses for this end point

Secondary: Re consulted GP for gout problem within 4 weeks

End point title	Re consulted GP for gout problem within 4 weeks
End point description:	
End point type	Secondary
End point timeframe:	
4 weeks	

End point values	Naproxen	Low dose Colchicine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	194		
Units: Number				
One	14	27		
Two	8	10		
Three	2	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Consulted practice nurse for Gout problem within 4 weeks

End point title	Consulted practice nurse for Gout problem within 4 weeks

End point description:

End point type	Secondary

End point timeframe:

4 weeks

End point values	Naproxen	Low dose Colchicine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	194		
Units: Number				
One	5	9		
Two	1	1		
Three	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Consulted emergency GP for gout problem within 4 weeks

End point title	Consulted emergency GP for gout problem within 4 weeks

End point description:

End point type	Secondary

End point timeframe:

4 weeks

End point values	Naproxen	Low dose Colchicine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	194		
Units: Number				
Consulted Emergency GP within 4 weeks	6	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Attended A&E for gout problem within 4 weeks

End point title	Attended A&E for gout problem within 4 weeks

End point description:

End point type	Secondary

End point timeframe:

4 weeks

End point values	Naproxen	Low dose Colchicine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	194		
Units: Number				
Attended A&E for gout problem within 4 weeks	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Taken time off work because of gout problem within 4 weeks

End point title	Taken time off work because of gout problem within 4 weeks

End point description:

End point type	Secondary

End point timeframe:

4 weeks

End point values	Naproxen	Low dose Colchicine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	194		
Units: Number				
Taken time off work because of gout problem within Number of days (Median)	11 4	8 3		

Statistical analyses

No statistical analyses for this end point

Secondary: Resource use, costs and outcomes per participant over 4 weeks follow up

End point title	Resource use, costs and outcomes per participant over 4 weeks follow up

End point description:

End point type	Secondary

End point timeframe:

4 weeks

End point values	Naproxen	Low dose Colchicine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	194		
Units: Mean (SD)				
arithmetic mean (standard deviation)				
GP visits	0.19 (± 0.34)	0.27 (± 0.4)		
Nurse Visits	0.05 (± 0.19)	0.07 (± 0.22)		
Emergency GP visits	0.05 (± 0.17)	0.04 (± 0.18)		
A&E visits	0.006 (± 0.07)	0.007 (± 0.07)		
Drug Costs	0.83 (± 2)	1.2 (± 2.22)		
GP costs	6.44 (± 11.16)	8.8 (± 13.16)		
Nurse Costs	0.66 (± 2.26)	0.86 (± 2.71)		
Emergency GP costs	2.45 (± 8.54)	2.14 (± 8.68)		
A&E costs	0.41 (± 5.1)	0.48 (± 5.15)		
Intervention costs	6.77 (± 4.56)	9.83 (± 6.32)		
Total Costs	17.57 (± 20.38)	23.31 (± 23.46)		
Baseline EQ-5D	0.665 (± 0.21)	0.663 (± 0.22)		
Day 7 EQ-5D	0.882 (± 0.13)	0.873 (± 0.14)		
Week 4 EQ-5D	0.9 (± 0.11)	0.894 (± 0.15)		
QALYS	0.0663 (± 0.008)	0.0657 (± 0.01)		
Adjusted QALYS*	0.0662 (± 0)	0.0658 (± 0)		
Time off work (days)	0.4 (± 2.47)	0.35 (± 2.51)		
Productivity costs (£)	32.16 (± 190.4)	28.44 (± 207.42)		

Attachments (see zip file)	Cost-effectiveness plane Naproxen v Colchicine/Cost.docx Cost-effectiveness acceptability curve/Cost1.docx

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

4 weeks

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	Naproxen
Reporting group description: -	
Reporting group title	Colchicine
Reporting group description: -	

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: There are no non-serious adverse events recorded for these results

Serious adverse events	Naproxen	Colchicine	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 200 (1.00%)	1 / 199 (0.50%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
General disorders and administration site conditions			
None cardiac chest pain	Additional description: Non cardiac chest pain		
subjects affected / exposed	1 / 200 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Osteomyelitis	Additional description: Osteomyelitis		
subjects affected / exposed	0 / 200 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complication of transcatheter aortic valve implantation procedure	Additional description: Complication of transcatheter aortic valve implantation procedure, patient re-admitted with Hospital acquired Pneumonia.		
subjects affected / exposed	1 / 200 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Naproxen	Colchicine	
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 200 (0.00%)	0 / 199 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 September 2013	The trial data will be held on a database hosted on a secure server by the Primary Care Clinical Research and Trials Unit (PC-CRTU) at University of Birmingham. Previously this data was to be held on a secure server at Keele University. Provision of appropriate client server links/permissions will be given to authorised members of the trial team at Keele Clinical Trials Unit (CTU).
14 November 2013	Addition of sites
20 December 2013	Addition of sites
27 February 2014	Addition of sites
28 March 2014	Addition of sites
22 May 2014	Addition of sites
21 July 2014	Substantial - Change of protocol from Version 3.0 to Version 4.0 and change of 7 day pain diary to add an extra question at Day 1 of the 7 day pain diary. Also Letter of invitation and reminder letter of invitation updated from version 2.0 to version 3.0. Addition of 5 new sites . On advice of the TSC, an additional question to day 1 of the 7 day pain diary was added. It is often stated that Colchicine is less effective if first taken greater than 24 hours after symptom onset, although there is little research evidence to support this. The additional question asked about the time that had elapsed between the onset of symptoms and taking the trial medication. By comparing this between the two treatment groups, we were able to explore whether the elapsed time has an influence on the effectiveness of treatment. We also received phone calls from participants who has received a letter of invitation but were not clear on what they needed to do to enter the trial and whether any immediate action was needed. The letters of invitation were amended to provide clearer instructions about what action was required. This change was submitted to REC on 21/07/2014, however it was not submitted to the MHRA. On Inspection, the MHRA subsequently classified this as a substantial amendment which should have been notified to the MHRA. As the trial had ended recruitment, we could not submit a retrospective substantial amendment to the MHRA. Instead, the sponsor was advised to include this information as part of the update to this database at the end of the study.
16 September 2014	Addition of sites
19 November 2014	Addition of sites
26 November 2014	Addition of sites
04 December 2014	Addition of sites
15 January 2015	Addition of sites

05 February 2015	Addition of sites
27 February 2015	Change of protocol from Version 4.0_27_06_14 to Version 5.0_13_02_15 to remove 'expressed at study entry' for decision on self report data collection (either electronic or postal)
27 February 2015	Addition of sites
09 March 2015	Addition of sites
18 March 2015	Addition of sites
15 May 2015	Addition of sites
22 May 2015	Addition of sites
16 June 2015	Removal of 2 existing sites
16 October 2015	Closure of some sites
10 December 2015	Closure of some sites
24 March 2016	Update to protocol from version 5.0_13_02_2015 to version 6.0_24_Mar_2016 and Generation of participant letter to inform participants of the move of the CONTACT database from the University of Birmingham to Keele University

Notes:

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.

This trial has not yet been published therefore results are confidential.

Notes: