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	v3 (current)
This version publication date	27 October 2021
First version publication date	28 April 2017
Version creation reason	• Changes to summary attachments Correction of data in line with published analysis amended following journal peer review. No change to overall conclusion. Longitudinal mixed model evaluation remodelled & results updated (primary endpoint mean difference -0.18, p=0.32; previously -0.19, p=0.28) . Endpoints section expanded to include descriptive summaries & statistical analyses for secondary outcomes.

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.			
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 of the primary pain outcome was 84% in the naproxen group and 86% in the colchicine arm at day 7, and 85% and 87% respectively at 4 weeks.

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.			
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	8		
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 of the primary pain outcome was 84% in the naproxen group and 86% in the colchicine arm at day 7, and 85% and 87% respectively at 4 weeks.	

Primary: Pain scores 1-7 days (primary outcome measure)

End point title	Pain scores 1-7 days (primary outcome measure)
End point description:	
As above	
End point type	Primary
End point timeframe:	
The main outcome measure is pain measured on a 0-10 pain intensity numeric rating scale measured over days 0-7. The primary outcome is change in pain from baseline measured across days 1-7.	

End point values	Naproxen	Low dose Colchicine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170[1]	174[2]		
Units: 0-10				
arithmetic mean (standard deviation)				
Day 1	0.6 (± 2.0)	0.5 (± 2.1)		
Day 2	2.3 (± 2.7)	1.8 (± 2.5)		
Day 3	3.3 (± 2.9)	3.1 (± 2.7)		
Day 4	4.4 (± 2.9)	4.1 (± 2.8)		
Day 5	4.9 (± 2.8)	4.6 (± 2.9)		
Day 6	5.3 (± 2.7)	5.0 (± 2.8)		
Day 7	5.7 (± 2.6)	5.4 (± 2.7)		

Notes:

[1] - 170 participants had >=1 follow up data on 1-7 days pain change in the naproxen group

[2] - 174 participants had >=1 follow-up data on 1-7 days pain change in the colchicine group

Attachments (see zip file)	Graphs of Absolute and Change in Pain scores/Graphs -

Statistical analyses

Statistical analysis title	Primary endpoint - Overall 1-7 day pain change
Statistical analysis description:	
By intention to treat (ITT): mean difference (colchicine - naproxen) adjusted for age, sex, baseline pain.	
Comparison groups	Low dose Colchicine v Naproxen
Number of subjects included in analysis	344
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.32
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.53
upper limit	0.17
Variability estimate	Standard error of the mean

Notes:

[3] - For the primary/main 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 -0.18 (95% CI: -0.53, 0.17; p=0.32). This equated to a 'small' effect size (0.09) in favour of naproxen.
Sensitivity analyses between-group mean differences were: (i) Unadjusted -0.24 (95% CI: -0.70, 0.23; p=0.31); (ii) Multiple imputation -0.22 (95% CI: -0.57, 0.13; p=0.22).

Statistical analysis title	Analysis of pain change day 1
Statistical analysis description:	
By intention to treat (ITT): mean difference (colchicine - naproxen) adjusted for age, sex, baseline pain.	
Comparison groups	Low dose Colchicine v Naproxen
Number of subjects included in analysis	344
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.79
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.51
upper limit	0.39
Variability estimate	Standard error of the mean

Statistical analysis title	Analysis of pain change day 2
Statistical analysis description:	
By intention to treat (ITT): mean difference (colchicine - naproxen) adjusted for age, sex, baseline pain.	
Comparison groups	Low dose Colchicine v Naproxen

Number of subjects included in analysis	344
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.047
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	-0.01
Variability estimate	Standard error of the mean

Statistical analysis title	Analysis of pain change day 3
Statistical analysis description:	
By intention to treat (ITT): mean difference (colchicine - naproxen) adjusted for age, sex, baseline pain.	
Comparison groups	Low dose Colchicine v Naproxen
Number of subjects included in analysis	344
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.48
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.61
upper limit	0.28
Variability estimate	Standard error of the mean

Statistical analysis title	Analysis of pain change day 4
Statistical analysis description:	
By intention to treat (ITT): mean difference (colchicine - naproxen) adjusted for age, sex, baseline pain.	
Comparison groups	Low dose Colchicine v Naproxen
Number of subjects included in analysis	344
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.61
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.12

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.56
upper limit	0.33
Variability estimate	Standard error of the mean

Statistical analysis title	Analysis of pain change day 5
Statistical analysis description: By intention to treat (ITT): mean difference (colchicine - naproxen) adjusted for age, sex, baseline pain.	
Comparison groups	Low dose Colchicine v Naproxen
Number of subjects included in analysis	344
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.58
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.57
upper limit	0.32
Variability estimate	Standard error of the mean

Statistical analysis title	Analysis of pain change day 6
Statistical analysis description: By intention to treat (ITT): mean difference (colchicine - naproxen) adjusted for age, sex, baseline pain.	
Comparison groups	Low dose Colchicine v Naproxen
Number of subjects included in analysis	344
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.57
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.57
upper limit	0.31
Variability estimate	Standard error of the mean

Statistical analysis title	Analysis of pain change day 7

Statistical analysis description:

By intention to treat (ITT): mean difference (colchicine - naproxen) adjusted for age, sex, baseline pain.

Comparison groups	Low dose Colchicine v Naproxen
Number of subjects included in analysis	344
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.34
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.65
upper limit	0.22
Variability estimate	Standard error of the mean

Statistical analysis title	Overall 1-7 day pain change - Per protocol [1]

Statistical analysis description:

Per protocol analysis [1] excluding participants with treatment violation by medical record note reporting (i.e. excluding treatment crossover and early cessation of treatment). Subset number analysed: 184 naproxen group; 182 colchicine group. Adjusted mean difference (colchicine group minus naproxen group).

Comparison groups	Low dose Colchicine v Naproxen
Number of subjects included in analysis	344
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.32
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.54
upper limit	0.17
Variability estimate	Standard error of the mean

Statistical analysis title	Overall 1-7 day pain change - Per protocol [2]

Statistical analysis description:

Per protocol analysis [2] excluding participants with treatment violation by medical record note reporting plus at least 1-day use of randomised treatment by self-report. Subset number analysed: 149 naproxen group; 155 colchicine group. Adjusted mean difference (colchicine group minus naproxen group).

Comparison groups	Low dose Colchicine v Naproxen

Number of subjects included in analysis	344
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.14
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.62
upper limit	0.09
Variability estimate	Standard error of the mean

Statistical analysis title	Overall 1-7 day pain change - Per protocol [3]

Statistical analysis description:

Per protocol analysis [3] excluding participants with treatment violation by medical record note reporting plus 7 days (4-7 days) use of randomised treatment naproxen (colchicine) by self-report. Subset number analysed: 118 naproxen group; 134 colchicine group. Adjusted mean difference (colchicine group minus naproxen group).

Comparison groups	Low dose Colchicine v Naproxen
Number of subjects included in analysis	344
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.18
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.67
upper limit	0.13
Variability estimate	Standard error of the mean

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:

Logistic regression models were used to model estimates for between-group comparisons of secondary outcomes (except pain change at 4 weeks): 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. Outcomes 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	175[4]	180[5]		
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		

Notes:

[4] - 175 is the number of participants who responded to at least one of the diary follow ups

[5] - 180 is the number of participants who responded to at least one of the diary follow ups

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 (1-7 days) and between weeks 2-4

End point values	Naproxen	Low dose Colchicine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164[6]	170[7]		
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		

Notes:

[6] - 164 participants completed all diary or week 4 items (n=149 for 1-7 days; n=134 for 2-4 weeks)

[7] - 170 participants completed all diary or week 4 items (n=144 for 1-7 days; n=154 for 2-4 weeks)

Statistical analyses

Statistical analysis title	Paracetamol 1-7 days

Statistical analysis description:

Odds ratio (colchicine relative to naproxen) adjusted for age, sex, baseline score

Comparison groups	Naproxen v Low dose Colchicine

Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.022
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.11
upper limit	3.93
Variability estimate	Standard error of the mean

Statistical analysis title	Paracetamol 2-4 weeks
Statistical analysis description:	
Odds ratio (colchicine relative to naproxen) adjusted for age, sex, baseline score	
Comparison groups	Naproxen v Low dose Colchicine
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.81
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	2.82
Variability estimate	Standard error of the mean

Statistical analysis title	Ibuprofen 1-7 days
Statistical analysis description:	
Odds ratio (colchicine relative to naproxen) adjusted for age, sex, baseline score	
Comparison groups	Naproxen v Low dose Colchicine
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.27
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.54

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	3.29
Variability estimate	Standard error of the mean

Statistical analysis title	Ibuprofen 2-4 weeks
Statistical analysis description:	
Odds ratio (colchicine relative to naproxen) adjusted for age, sex, baseline score	
Comparison groups	Naproxen v Low dose Colchicine
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.026
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.11
upper limit	4.94
Variability estimate	Standard error of the mean

Statistical analysis title	Codeine 1-7 days
Statistical analysis description:	
Odds ratio (colchicine relative to naproxen) adjusted for age, sex, baseline score	
Comparison groups	Naproxen v Low dose Colchicine
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.47
upper limit	8.93
Variability estimate	Standard error of the mean

Statistical analysis title	Codeine 2-4 weeks

Statistical analysis description:

Odds ratio (colchicine relative to naproxen) adjusted for age, sex, baseline score

Comparison groups	Naproxen v Low dose Colchicine
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.32
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.22
upper limit	1.65
Variability estimate	Standard error of the mean

Statistical analysis title	Any analgesic or non-naproxen NSAID 1-7 days

Statistical analysis description:

Odds ratio (colchicine relative to naproxen) where 'Any analgesic or non-naproxen NSAID' refers to paracetamol or codeine or tramadol or ibuprofen or diclofenac or inomethacin.

Comparison groups	Naproxen v Low dose Colchicine
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.35
upper limit	3.66
Variability estimate	Standard error of the mean

Statistical analysis title	Any analgesic or non-naproxen NSAID 2-4 weeks

Statistical analysis description:

Odds ratio (colchicine relative to naproxen) where 'Any analgesic or non-naproxen NSAID' refers to paracetamol or codeine or tramadol or ibuprofen or diclofenac or inomethacin.

Comparison groups	Naproxen v Low dose Colchicine

Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.26
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	2.21
Variability estimate	Standard error of the mean

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	175[8]	180[9]		
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		

Notes:
[8] - 175 is the number of participants who responded to at least one of the diary follow ups
[9] - 180 is the number of participants who responded to at least one of the diary follow ups

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	164[10]	171[11]		
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		

Notes:
[10] - 164 participants completed all diary or week 4 items (n=150 for 1-7 days; n=134 for 2-4 weeks)
[11] - 171 participants completed all diary or week 4 items (n=146 for 1-7 days; n=154 for 2-4 weeks)

Statistical analyses

Statistical analysis title	Nausea and/or vomiting 1-7 days

Statistical analysis description:
Odds ratio (colchicine relative to naproxen) adjusted for age, sex, baseline pain score

Comparison groups	Low dose Colchicine v Naproxen

Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.066
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.96
upper limit	3.46
Variability estimate	Standard error of the mean

Statistical analysis title	Nausea and/or vomiting 2-4 weeks
Statistical analysis description:	
Odds ratio (colchicine relative to naproxen) adjusted for age, sex, baseline pain score	
Comparison groups	Naproxen v Low dose Colchicine
Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.14
upper limit	1.83
Variability estimate	Standard error of the mean

Statistical analysis title	Dyspepsia 1-7 days
Statistical analysis description:	
Odds ratio (colchicine relative to naproxen) adjusted for age, sex, baseline pain score	
Comparison groups	Low dose Colchicine v Naproxen
Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.95
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.89

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	1.9
Variability estimate	Standard error of the mean

Statistical analysis title	Dyspepsia 2-4 weeks
Statistical analysis description:	
Odds ratio (colchicine relative to naproxen) adjusted for age, sex, baseline pain score	
Comparison groups	Low dose Colchicine v Naproxen
Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.094
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.17
upper limit	1.15
Variability estimate	Standard error of the mean

Statistical analysis title	Abdominal pain 1-7 days
Statistical analysis description:	
Odds ratio (colchicine relative to naproxen) adjusted for age, sex, baseline pain score	
Comparison groups	Low dose Colchicine v Naproxen
Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.86
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	2.25
Variability estimate	Standard error of the mean

Statistical analysis title	Abdominal pain 2-4 weeks

Statistical analysis description:	
Odds ratio (colchicine relative to naproxen) adjusted for age, sex, baseline pain score	
Comparison groups	Low dose Colchicine v Naproxen
Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.49
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	5.53
Variability estimate	Standard error of the mean

Statistical analysis title	Headache 1-7 days
Statistical analysis description:	
Odds ratio (colchicine relative to naproxen) adjusted for age, sex, baseline pain score	
Comparison groups	Low dose Colchicine v Naproxen
Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.21
upper limit	4.68
Variability estimate	Standard error of the mean

Statistical analysis title	Headache 2-4 weeks
Statistical analysis description:	
Odds ratio (colchicine relative to naproxen) adjusted for age, sex, baseline pain score	
Comparison groups	Low dose Colchicine v Naproxen
Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.91
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.92

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.22
upper limit	3.86
Variability estimate	Standard error of the mean

Statistical analysis title	Constipation 1-7 days
Statistical analysis description:	
Odds ratio (colchicine relative to naproxen) adjusted for age, sex, baseline pain score	
Comparison groups	Low dose Colchicine v Naproxen
Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.08
upper limit	0.48
Variability estimate	Standard error of the mean

Statistical analysis title	Constipation 2-4 weeks
Statistical analysis description:	
Odds ratio (colchicine relative to naproxen) adjusted for age, sex, baseline pain score	
Comparison groups	Low dose Colchicine v Naproxen
Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.22
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.16
upper limit	1.54
Variability estimate	Standard error of the mean

Statistical analysis title	Diarrhoea 1-7 days

Statistical analysis description:	
Odds ratio (colchicine relative to naproxen) adjusted for age, sex, baseline pain score	
Comparison groups	Low dose Colchicine v Naproxen
Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.1
upper limit	5.99
Variability estimate	Standard error of the mean

Statistical analysis title	Diarrhoea 2-4 weeks
Statistical analysis description:	
Odds ratio (colchicine relative to naproxen) adjusted for age, sex, baseline pain score	
Comparison groups	Low dose Colchicine v Naproxen
Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.32
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	5.26
Variability estimate	Standard error of the mean

Statistical analysis title	Skin rash 1-7 days
Statistical analysis description:	
Odds ratio (colchicine relative to naproxen) adjusted for age, sex, baseline pain score	
Comparison groups	Low dose Colchicine v Naproxen
Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.88
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.13

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.22
upper limit	5.83
Variability estimate	Standard error of the mean

Statistical analysis title	Skin rash 2-4 weeks
Statistical analysis description:	
Odds ratio (colchicine relative to naproxen) adjusted for age, sex, baseline pain score	
Comparison groups	Low dose Colchicine v Naproxen
Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.98
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.19
upper limit	5.09
Variability estimate	Standard error of the mean

Statistical analysis title	Any side effect(s) 1-7 days
Statistical analysis description:	
Odds ratio (colchicine relative to naproxen) adjusted for age, sex, baseline pain score	
Comparison groups	Low dose Colchicine v Naproxen
Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.11
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.92
upper limit	2.43
Variability estimate	Standard error of the mean

Statistical analysis title	Any side effect(s) 2-4 weeks

Statistical analysis description:	
Odds ratio (colchicine relative to naproxen) adjusted for age, sex, baseline pain score	
Comparison groups	Low dose Colchicine v Naproxen
Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.064
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.33
upper limit	1.03
Variability estimate	Standard error of the mean

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	160	152		
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	173	177		
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:

Categories were dichotomised as completely better/ much better and somewhat better/ about the same/ somewhat worse/ much worse

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	160	152		
Units: Number				
Completely/much better now	114	110		
Not completely/much better	46	42		

Statistical analyses

Statistical analysis title	Global change day 7 analysis
Statistical analysis description:	
Odds ratio (colchicine relative to naproxen) adjusted for age, sex, baseline pain score	
Comparison groups	Naproxen v Low dose Colchicine
Number of subjects included in analysis	312
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.69
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.84
Variability estimate	Standard error of the mean

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	173	177		
Units: Number				
Completely/much better now	140	143		
not completely/much better	33	34		

Statistical analyses

Statistical analysis title	Global change week 4 analysis
Statistical analysis description:	
Odds ratio (colchicine relative to naproxen) adjusted for age, sex, baseline score	
Comparison groups	Naproxen v Low dose Colchicine

Number of subjects included in analysis	350
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.64
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	1.52
Variability estimate	Standard error of the mean

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	200	199		
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) Productivity costs (£)	0.4 (± 2.47) 32.16 (± 190.4)	0.35 (± 2.51) 28.44 (± 207.42)		

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

Statistical analyses

Statistical analysis title	GP visits
Statistical analysis description: Mean difference (naproxen - colchicine)	
Comparison groups	Naproxen v Low dose Colchicine
Number of subjects included in analysis	399
Analysis specification	Pre-specified
Analysis type	superiority
Method	Multiple Imputation regression
Parameter estimate	Mean difference (final values)
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.15
upper limit	0.0002
Variability estimate	Standard error of the mean

Statistical analysis title	Nurse visits
Statistical analysis description: Mean difference (naproxen - colchicine)	
Comparison groups	Naproxen v Low dose Colchicine
Number of subjects included in analysis	399
Analysis specification	Pre-specified
Analysis type	superiority
Method	Multiple Imputation regression
Parameter estimate	Mean difference (final values)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	0.03
Variability estimate	Standard error of the mean

Statistical analysis title	Emergency GP visits
Statistical analysis description: Mean difference (naproxen - colchicine)	
Comparison groups	Naproxen v Low dose Colchicine
Number of subjects included in analysis	399
Analysis specification	Pre-specified
Analysis type	superiority
Method	Multiple Imputation regression
Parameter estimate	Mean difference (final values)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.04
Variability estimate	Standard error of the mean

Statistical analysis title	A & E visits
Statistical analysis description: Mean difference (naproxen - colchicine)	
Comparison groups	Naproxen v Low dose Colchicine
Number of subjects included in analysis	399
Analysis specification	Pre-specified
Analysis type	superiority
Method	Multiple Imputation regression
Parameter estimate	Mean difference (final values)
Point estimate	-0.001
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.01
Variability estimate	Standard error of the mean

Statistical analysis title	Drug costs
Statistical analysis description: Mean difference (naproxen - colchicine)	
Comparison groups	Naproxen v Low dose Colchicine
Number of subjects included in analysis	399
Analysis specification	Pre-specified
Analysis type	superiority
Method	Multiple Imputation regression
Parameter estimate	Mean difference (final values)
Point estimate	-0.37

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.78
upper limit	0.02
Variability estimate	Standard error of the mean

Statistical analysis title	GP costs
Statistical analysis description: Mean difference (naproxen - colchicine)	
Comparison groups	Naproxen v Low dose Colchicine
Number of subjects included in analysis	399
Analysis specification	Pre-specified
Analysis type	superiority
Method	Multiple Imputation regression
Parameter estimate	Mean difference (final values)
Point estimate	-2.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.74
upper limit	0.12
Variability estimate	Standard error of the mean

Statistical analysis title	Nurse costs
Statistical analysis description: Mean difference (naproxen - colchicine)	
Comparison groups	Naproxen v Low dose Colchicine
Number of subjects included in analysis	399
Analysis specification	Pre-specified
Analysis type	superiority
Method	Multiple Imputation regression
Parameter estimate	Mean difference (final values)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.68
upper limit	0.31
Variability estimate	Standard error of the mean

Statistical analysis title	Emergency GP costs
Statistical analysis description: Mean difference (naproxen - colchicine)	

Comparison groups	Naproxen v Low dose Colchicine
Number of subjects included in analysis	399
Analysis specification	Pre-specified
Analysis type	superiority
Method	Multiple Imputation regression
Parameter estimate	Mean difference (final values)
Point estimate	0.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.28
upper limit	2.04
Variability estimate	Standard error of the mean

Statistical analysis title	A & E costs
Statistical analysis description: Mean difference (naproxen - colchicine)	
Comparison groups	Naproxen v Low dose Colchicine
Number of subjects included in analysis	399
Analysis specification	Pre-specified
Analysis type	superiority
Method	Multiple Imputation regression
Parameter estimate	Mean difference (final values)
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.21
upper limit	0.95
Variability estimate	Standard error of the mean

Statistical analysis title	Intervention cost
Statistical analysis description: Mean difference (naproxen - colchicine)	
Comparison groups	Naproxen v Low dose Colchicine
Number of subjects included in analysis	399
Analysis specification	Pre-specified
Analysis type	superiority
Method	Multiple Imputation regression
Parameter estimate	Mean difference (final values)
Point estimate	-3.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.17
upper limit	-2.08

Variability estimate	Standard error of the mean

Statistical analysis title	Total cost
Statistical analysis description: Mean difference (naproxen - colchicine)	
Comparison groups	Naproxen v Low dose Colchicine
Number of subjects included in analysis	399
Analysis specification	Pre-specified
Analysis type	superiority
Method	Multiple Imputation regression
Parameter estimate	Mean difference (final values)
Point estimate	-5.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.03
upper limit	-1.64
Variability estimate	Standard error of the mean

Statistical analysis title	EQ5D day 7
Statistical analysis description: Mean difference (naproxen - colchicine)	
Comparison groups	Naproxen v Low dose Colchicine
Number of subjects included in analysis	399
Analysis specification	Pre-specified
Analysis type	superiority
Method	Multiple Imputation regression
Parameter estimate	Mean difference (final values)
Point estimate	0.009
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.03
Variability estimate	Standard error of the mean

Statistical analysis title	EQ5D week 4
Statistical analysis description: Mean difference (naproxen - colchicine)	
Comparison groups	Naproxen v Low dose Colchicine

Number of subjects included in analysis	399
Analysis specification	Pre-specified
Analysis type	superiority
Method	Multiple Imputation regression
Parameter estimate	Mean difference (final values)
Point estimate	0.006
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.03
Variability estimate	Standard error of the mean

Statistical analysis title	QALYs
Statistical analysis description: Mean difference (naproxen - colchicine)	
Comparison groups	Naproxen v Low dose Colchicine
Number of subjects included in analysis	399
Analysis specification	Pre-specified
Analysis type	superiority
Method	Multiple Imputation regression
Parameter estimate	Mean difference (final values)
Point estimate	0.0006
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.001
upper limit	0.002
Variability estimate	Standard error of the mean

Statistical analysis title	Time off work (days)
Statistical analysis description: Mean difference (naproxen - colchicine)	
Comparison groups	Naproxen v Low dose Colchicine
Number of subjects included in analysis	399
Analysis specification	Pre-specified
Analysis type	superiority
Method	Multiple Imputation regression
Parameter estimate	Mean difference (final values)
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.42
upper limit	0.53

Variability estimate	Standard error of the mean

Statistical analysis title	Productivity cost (£)
Statistical analysis description:	
Mean difference (naproxen - colchicine)	
Comparison groups	Naproxen v Low dose Colchicine
Number of subjects included in analysis	399
Analysis specification	Pre-specified
Analysis type	superiority
Method	Multiple Imputation regression
Parameter estimate	Mean difference (final values)
Point estimate	3.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-34.27
upper limit	40.73
Variability estimate	Standard error of the mean

Secondary: Recurrence of gout flare during 4-week follow up	
End point title	Recurrence of gout flare during 4-week 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	133	154		
Units: count				
No	93	100		
Yes	40	54		

Statistical analyses

Statistical analysis title	Recurrence of gout
Statistical analysis description:	
Odds ratio (colchicine relative to naproxen) adjusted for age, sex, baseline score	
Comparison groups	Naproxen v Low dose Colchicine

Number of subjects included in analysis	287
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.33
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	2.13
Variability estimate	Standard error of the mean

Secondary: Pain change 4 weeks

End point title	Pain change 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	170	174		
Units: 0-10 numerical rating scale				
arithmetic mean (standard deviation)	5.9 (± 2.9)	5.7 (± 2.8)		

Statistical analyses

Statistical analysis title	Pain change 4 weeks

Statistical analysis description:

Analysed through linear mixed model. Mean difference (colchicine - naproxen) adjusted for age, sex, baseline score.

Comparison groups	Naproxen v Low dose Colchicine
Number of subjects included in analysis	344
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.68
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.09

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.53
upper limit	0.35
Variability estimate	Standard error of the mean

Statistical analysis title	Pain change 4 weeks - Per protocol analysis [1]

Statistical analysis description:

Analysed through linear mixed model. Mean difference (colchicine - naproxen) adjusted for age, sex, baseline score.
Per protocol subset [1]: Excludes participants with treatment violation by medical record note reporting (i.e. treatment crossovers and eraly cessation of treatment). Subset number analysed: 184 naproxen group and 182 colchicine group.

Comparison groups	Naproxen v Low dose Colchicine
Number of subjects included in analysis	344
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.29
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.68
upper limit	0.2
Variability estimate	Standard error of the mean

Statistical analysis title	Pain change 4 weeks - Per protocol analysis [2]

Statistical analysis description:

Analysed through linear mixed model. Mean difference (colchicine - naproxen) adjusted for age, sex, baseline score.
Per protocol subset [2]: No treatment violation by medical record note reporting plus at least 1-day use of randomised treatment by self-report. Subset number analysed: 149 naproxen group and 155 colchicine group.

Comparison groups	Naproxen v Low dose Colchicine
Number of subjects included in analysis	344
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.038
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.94
upper limit	-0.03

Variability estimate	Standard error of the mean

Statistical analysis title	Pain change 4 weeks - Per protocol analysis [3]

Statistical analysis description:

Analysed through linear mixed model. Mean difference (colchicine - naproxen) adjusted for age, sex, baseline score.
Per protocol subset [3]: No treatment violation by medical record note reporting plus 7 days (4-7 days) use of randomised treatment naproxen (colchicine) by self-report. Subset number analysed: 118 naproxen group and 134 colchicine group.

Comparison groups	Naproxen v Low dose Colchicine
Number of subjects included in analysis	344
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.025
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.07
upper limit	-0.07
Variability estimate	Standard error of the mean

Secondary: Pain resolution 7 days

End point title	Pain resolution 7 days

End point description:

Classified as resolution = 0-1 score; no resolution = 2-10 score

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	171	173		
Units: count				
No	56	57		
Yes	115	116		

Statistical analyses

Statistical analysis title	Pain resolution 7 days
Statistical analysis description:	
Mean difference (colchicine - naproxen) adjusted for age, sex, baseline score	
Comparison groups	Naproxen v Low dose Colchicine
Number of subjects included in analysis	344
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.87
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.54
Variability estimate	Standard error of the mean

Secondary: Pain resolution 4 weeks	
End point title	Pain resolution 4 weeks
End point description:	
Classified as: resolution 0-1 score; no resolution 2-10 score	
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	173	177		
Units: count				
No	43	47		
Yes	130	130		

Statistical analyses

Statistical analysis title	Pain resolution 4 weeks
Statistical analysis description:	
Mean difference (colchicine - naproxen) adjusted for age, sex, baseline score	
Comparison groups	Naproxen v Low dose Colchicine

Number of subjects included in analysis	350
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.46
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	1.36
Variability estimate	Standard error of the mean

Secondary: Re-consultation with health professional within 4 weeks

End point title	Re-consultation with health professional 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	133	154		
Units: count				
No	103	113		
Yes	30	41		

Statistical analyses

Statistical analysis title	Re-consultation with health professional 4 weeks
Statistical analysis description:	
Odds ratio (colchicine relative to naproxen) adjusted for age, sex, baseline score	
Comparison groups	Naproxen v Low dose Colchicine
Number of subjects included in analysis	287
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.21
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.43

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	2.51
Variability estimate	Standard error of the mean

Secondary: Re-consultation with GP within 4 weeks

End point title	Re-consultation with GP 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	134	154		
Units: count				
No	108	115		
Yes	26	39		

Statistical analyses

Statistical analysis title	Re-consultation with GP 4 weeks
Statistical analysis description:	
Odds ratio (colchicine relative to naproxen) adjusted for age, sex, baseline score	
Comparison groups	Naproxen v Low dose Colchicine
Number of subjects included in analysis	288
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.083
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.93
upper limit	3.05
Variability estimate	Standard error of the mean

Secondary: Re-consultation with Practice nurse within 4 weeks	
End point title	Re-consultation with Practice nurse 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	132	152		
Units: count				
No	125	142		
Yes	7	10		

Statistical analyses

Statistical analysis title	Re-consultation with Practice nurse 4 weeks
Statistical analysis description:	
Odds ratio (colchicine relative to naproxen) adjusted for age, sex, baseline score	
Comparison groups	Naproxen v Low dose Colchicine
Number of subjects included in analysis	284
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.61
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	3.64
Variability estimate	Standard error of the mean

Secondary: Re-consultation with emergency GP within 4 weeks	
End point title	Re-consultation with emergency GP 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	134	152		
Units: count				
No	128	146		
Yes	6	6		

Statistical analyses

Statistical analysis title	Re-consultation with emergency GP 4 weeks
Comparison groups	Naproxen v Low dose Colchicine
Number of subjects included in analysis	286
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.77
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.26
upper limit	2.68
Variability estimate	Standard error of the mean

Secondary: Re-consultation with emergency department within 4 weeks	
End point title	Re-consultation with emergency department 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	133	152		
Units: count				
No	132	151		
Yes	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Time off work by 4 weeks

End point title	Time off work by 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	128	151		
Units: count				
No	117	143		
Yes	11	8		

Statistical analyses

Statistical analysis title	Time off work

Statistical analysis description:

Odds ratio (colchicine relative to naproxen) adjusted for age, sex, baseline score

Comparison groups	Naproxen v Low dose Colchicine
Number of subjects included in analysis	279
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.33
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.61

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.22
upper limit	1.64
Variability estimate	Standard error of the mean

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: Adverse events were a specified secondary endpoint are therefore reported under end-points.

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

None reported