Colchicine Or Naproxen Treatment for ACute gouT

Protocol

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1. TRIAL SUMMARY

Gout is the most prevalent inflammatory arthritis. It is largely managed in primary care but treatment is often suboptimal. Acute gout causes attacks of excruciating joint pain requiring rapid treatment. In primary care, treatment is most frequently with non-steroidal anti-inflammatory drugs (NSAIDs) which are effective but have frequent gastrointestinal, cardiovascular and renal side-effects, particularly in the elderly. Oral colchicine has been used to treat acute gout for many years although high-doses can cause intolerable gastrointestinal side-effects. Low-dose colchicine is thought to be as effective and better-tolerated and is now recommended by the British National Formulary. However, there has been no direct comparison of NSAID and low-dose colchicine for acute gout.

This pragmatic randomised trial will compare the effectiveness of low-dose colchicine (500 mcg three times every eight hours) and naproxen (750 mg immediately followed by 250 mg every eight hours) for reducing pain in adults aged 18 years and over consulting their GP with acute gout, recruited from up to 100 general practices. People experiencing their first attack of gout or a recurrent attack will be eligible to participate. However, all patients registered with each participating practice who have consulted with gout in the preceding two years will be mailed a letter of invitation and Participant Information Sheet informing them that the trial is taking place and encouraging them to consult their GP if they experience an attack of acute gout. Eligibility assessment, informed consent, randomisation, baseline data collection and prescription will be performed when the patient consults in primary care with acute gout. Outcome measures will be collected via self-complete questionnaires at days 1-7 (daily diary), and 4 weeks. The primary outcome measure will be change in worst pain intensity in the previous 24 hours measured daily over days 0-7. Secondary outcome measures include side-effects, time to treatment response, patient global assessment of response to treatment, adherence to treatment, use of other medications for pain relief, and cost. A sample size of 200 patients per treatment arm provides 90% power to detect a minimum clinically important treatment effect of a small standardised effect size of 0.3 between the treatment groups.

2. GLOSSARY OF TERMS AND DEFINITIONS

Term/ Abbreviation	Definition
4wk	4 week
A&E	Accident and Emergency
AE	Adverse Event
AR	Adverse Reaction
BL	Baseline
BNF	British National Formulary
BSR	British Society for Rheumatology
CI	Chief Investigator
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTU	Clinical Trials Unit
DMC	Data monitoring Committee
EULAR	European League Against Rheumatism
GCP	Good Clinical Practice
GEE	Generalized estimating equations
GLM	Generalized linear modelling
GP	General Practitioner
ICMJE	International Committee of Medical Journal Editors
IMP	Investigational Medicinal Product
mcg	microgram
mg	milligram
MHRA	Medicines and Healthcare Products Regulatory Agency
NHS	National Health Service
NSAID	Non-steroidal anti-inflammatory drug
OMERACT	Outcome Measures in Rheumatology
PCRN	Primary Care Research Network
PI	Principal Investigator
PMC	PubMed Central
QALY	Quality adjusted life years
Read code	Standard medical diagnosis coding system used in General Practice
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TSC	Trial Steering Committee
UK	United Kingdom
UKPMC	United Kingdom PubMed Central

3. BACKGROUND AND RATIONALE

Gout is the most common inflammatory arthritis affecting approximately 600,000 people in the UK which equates to a prevalence of 1.4%, rising to over 7% in men aged over 75 years [1,2]. Most patients with gout are managed in primary care, with the average practice having 40 patients per 10,000 registered population consulting per year with this condition [3]. There are two treatment issues for primary care: (i) effective and efficient management of the acute attack and (ii) prevention of recurrent attacks and the long-term consequences of the condition. Establishing safe, efficient and effective management of acute attacks is a crucial component of this and this trial addresses an important gap in the evidence-base on which primary care can base care of the acute attack of gout. There have been few primary care-based trials of interventions for the management of gout [4].

Acute gout is characterised by sudden attacks of excruciating pain, swelling and exquisite tenderness to touch. It usually affects a single peripheral joint most commonly the first metatarsophalangeal joint of the big toe. Effective treatment options to rapidly reduce pain, swelling and inflammation associated with acute gout include non-steroidal anti-inflammatory drugs (NSAIDs), low-dose colchicine and corticosteroids [5,6]. Our previous research has shown that primary care management of gout, including treatment of acute attacks, is frequently suboptimal [7,8]. NSAIDs are the most commonly used drugs in all age-groups including the elderly who are at the greatest risk of significant potentially life-threatening side-effects such as gastrointestinal bleeding, renal failure and cardiovascular disease; colchicine is prescribed infrequently but at high-dose risking diarrhoea and vomiting; and, remarkably for such a painful condition, one in eight people receive only simple analgesics or no prescription at all [8]. Diclofenac and indomethacin, two of the more potentially toxic NSAIDs [9], account for 73% of NSAID prescriptions for acute gout in primary care [8]. Furthermore, although attacks of gout usually require only short duration of treatment, suggesting that the overall risk of such side-effects when treating acute gout might be small, patients often experience recurrent attacks. Following their first attack of gout, 60% of gout sufferers will experience a second attack within 12 months [10]. In one observational study in primary care, one-third of patients experienced two or more attacks of gout over one year [7], illustrating the potential for side-effects, especially given the higher frequency of the condition in older people. Worryingly, clinical experience suggests that NSAIDs for acute gout are often prescribed for patients with relative contraindications to their use such as renal and cardiovascular comorbidity.

Rheumatologists have long advocated the use of low-dose colchicine which is effective and well-tolerated [5,6,11]. However, low-dose colchicine is infrequently prescribed by GPs [8] possibly because of their experiences of prescribing colchicine in higher doses for acute gout, for example 1 mg immediately followed by 500 mcg every 2-3 hours until the pain resolves or the patient experiences side-effects. Although such high-dose regimes are effective, they are almost always complicated by severe diarrhoea and vomiting, deterring many prescribers and patients from using high-dose colchicine. In a randomised trial comparing high-dose colchicine to placebo, all participants in the colchicine arm experienced diarrhoea and/or vomiting [12]. In 2008, the dose of colchicine recommended in the British National Formulary (BNF) was changed from high-dose to a low-dose regime (500 mcg two to four times daily). A more recent randomised controlled trial suggests that lower doses of colchicine are as effective as higher doses but better tolerated [13] although the trial was undertaken in secondary care in the United States and used a different dosing regime than that currently advocated in the BNF. The findings of this trial are promising therefore, but may not be directly applicable to gout management in primary care in the UK and could potentially lead to further confusion over dosing.

Short courses of oral prednisolone are an alternative to NSAIDs and low-dose colchicine. Oral prednisolone is an effective treatment for acute gout and was shown to be equally effective to naproxen in a recent randomised equivalence trial [4]. However, oral corticosteroids are associated with a number of significant undesirable side-effects including hyperglycaemia, hypertension, fluid retention, adrenal suppression and osteoporosis which may be of particular significance in the elderly and those with co-morbidity. The cumulative risk of such side-effects may also increase by the use of repeated short courses of oral prednisolone to treat recurrent attacks of acute gout.

Evidence-based guidelines for the management of acute gout currently recommend NSAIDs and low-dose colchicine as treatment options, with corticosteroids reserved for those in whom NSAIDs and low-dose colchicine are not tolerated or contra-indicated [5,6]. However, they differ in their advice regarding which should be considered first-line. The European League Against Rheumatism (EULAR) recommendations state that either oral NSAIDs or low-dose colchicine should be considered as first-line agents [5] whereas the British Society for Rheumatology (BSR) guidelines recommend oral NSAIDs as the first drug of choice for acute gout [6]. The BSR guidelines also state that colchicine is slower to work than oral NSAIDs, but acknowledges that this is based on anecdote and expert consensus [6].

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 [4,14,15]. 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 [1,2], considerable associated comorbidity [1,2,16], and the frequent need to provide repeat prescriptions for recurrent attacks of acute gout [7,10]. 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 [5,6]. We have chosen to use naproxen in this trial because it is of comparable effectiveness to oral prednisolone for the treatment of acute gout [4], is thought to be safer from a cardiovascular perspective than other commonly used NSAIDs such as diclofenac and indomethacin [9], and is inexpensive. Cardiovascular risk is an important consideration as gout has been shown to be an independent risk factor for coronary heart disease [17,18]. 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. This will offer choice to both patients and practitioners, depending on the profile of the individual patient. In addition to investigating whether low-dose colchicine is an effective and safe drug for the management of acute gout in primary care, this trial has high potential for important implications for the treatment of acute gout in the elderly and other high-risk groups, in whom NSAIDs are frequently poorly tolerated or contra-indicated, increasing primary care treatment options and informing future clinical guidelines.

4. AIMS AND OBJECTIVES

4.1 PRIMARY OBJECTIVE

The primary objective is to directly compare the effectiveness of low-dose colchicine and naproxen at reducing pain from adults presenting with acute gout in primary care.

4.2 SECONDARY OBJECTIVES

The secondary objectives are:

- To compare the side-effect profiles of low-dose colchicine and naproxen when used to treat acute gout in primary care
- To compare the cost-effectiveness of low-dose colchicine and naproxen for the treatment of acute gout in primary care
- To compare the adherence to treatment with each drug
- To compare the time taken for low-dose colchicine and naproxen to reduce pain in patients with acute gout.

5. DESIGN

The trial is a randomised, multi-centre, open-label, active-comparator, pragmatic clinical trial of low-dose colchicine versus naproxen in patients with acute gout.

5.1 SETTING

A total of 400 patients with acute gout will be recruited from GP practices, primary care out-of-hours services and walk-in centres and will be randomised on an equal basis to either low dose colchicine or naproxen. Observational data from our local primary care network indicates that 40 patients per 10,000 registered patients will consult their GP with gout in a one-year period [3]. If 20% of these are both eligible and provide consent to participate in the trial, we will need to recruit from 50-100 large practices in order to recruit our required sample size (400 participants) over a 12-month period. Participants will be followed up for a period of 4 weeks.

5.2 ELIGIBILITY

The study population will consist of consecutive patients consulting in primary care with an attack of acute gout. Diagnosis will be made clinically by the GP based on clinical history and examination findings.

These patients will be assessed for eligibility by the GP based on the inclusion / exclusion criteria outlined below.

The eligibility criteria are designed to select a relatively homogenous group of patients with acute gout, suitable to receive treatment with either low-dose colchicine or naproxen.

5.3 INCLUSION CRITERIA

Factors, both medical and non-medical, should be taken into account including whether a patient will be able to participate in the trial.

- Adults aged 18 years and over
- Consultation with their GP, primary care out-of-hours service or walk-in-centre that is approved for the trial.
- Current attack of acute gout (first attack or recurrent). The diagnosis of gout will be made on clinical grounds and will not require joint aspiration, blood tests, imaging or clinical criteria.
- Patient has capacity and willingness, in the view of the recruiting clinician, to give consent and complete the trial paperwork, including the symptom diary.

5.4 EXCLUSION CRITERIA

Patients with the following characteristics are ineligible for this trial:

- Known unstable medical conditions (such as ischaemic heart disease, impaired liver function)
- Known stage 4/5 kidney disease (eGFR/creatinine clearance <30ml/min)
- Recent surgery or gastrointestinal bleed
- History of gastric ulcer
- Current anticoagulant use
- Allergy to aspirin/NSAID
- Previous inability to tolerate naproxen or low-dose colchicine
- Other contraindication to either study drug in accordance with the Summary of Product Characteristics (SPC) supplied in the Investigator Site File
- Prescription of naproxen or colchicine in the previous 24 hours
- Pregnant or lactating females
- Potentially vulnerable (see section 6.2 below)
- Previous participation in the CONTACT trial during a previous acute attack of gout.
- Involvement in another clinical trial of an investigational medicinal product in the last 90 days or any other research within the last 30 days

6. RECRUITMENT PROCESS

6.1 RECRUITMENT SETTING

Participants will be recruited at multiple centres throughout England. It is anticipated that 400 participants (200 in each arm) will be recruited over a 12 month period from up to 100 GP practices.

Research centres must have obtained local management approval and undertaken a site initiation meeting with one of the collaborating sites (Keele University, Oxford University, Southampton University or Nottingham University) prior to the start of recruitment into the trial.

6.2 INITIAL CONTACT

Acute gout is a medical emergency and requires rapid treatment to relieve pain and inflammation. In view of the need for urgent treatment for acute gout, we will forgo the traditional "cool-off" period prior to entering the trial on the grounds that it would be unethical to delay treatment. However, all patients registered with each participating practice who have consulted with gout in the preceding two years will be mailed a letter of invitation from their general practitioner (on general practice headed notepaper) and a Participant Information Sheet before the study commences and at three-monthly intervals during the recruitment period informing them that the trial is taking place and encouraging them to consult their GP if they experience an attack of acute gout. This information will also include a postcard which patients will be asked to take with them when they consult the GP to remind the GP about the trial. Practice lists will be screened prior to mailing to ensure that recent deaths and departures are excluded, as are patients who may have previously said they did not wish to be contacted about research. The lead general practitioner (GP) at each practice will be invited to identify potentially vulnerable patients to be excluded (e.g. recent bereavement or severe mental distress). Posters will also be displayed in practice waiting rooms.

Patients who consult a GP about gout for the first time and have not therefore been mailed the letter of invitation and Participant Information Sheet as described above, will also have the opportunity to participate in the trial when they consult. Such patients will be provided with a different version of the Participant Information Sheet, specifically for patients who have not consulted previously, at their appointment. Patients will be given time to consider the information prior to agreeing to take part.

6.3 CONSULTATION IN PRIMARY CARE / RECRUITMENT SCREENING

Patients with acute gout will consult in primary care in the usual way according to normal NHS clinical attendance procedures. However, we will work closely with practice staff including receptionists to ensure that patients contacting the practice about acute gout are offered a same day appointment. The GP will undertake the clinical consultation according to usual practice. In those practices in which it is feasible, an electronic on-screen "pop-up" reminder will be installed in practice computer systems which will remind GPs about the study and eligibility criteria when a gout Read code is entered. Eligibility for the trial will be assessed by the GP. Patients who fulfil trial eligibility criteria will be asked by the GP if they wish to be considered for trial participation. Patients who do not wish to take part will receive normal clinical care delivered by the GP according to usual practice.

6.4 INFORMED CONSENT

Patients who are interested in trial participation will be seen by a member of the primary care clinical team who has received specific training to administer trial procedures, received training in relevant aspects of GCP and is authorised on the delegation log to perform such activities. According to the preferences of individual practices, this primary care healthcare professional could be the GP or practice nurse. The primary care healthcare professional will explain the trial in full. Patients will be able to ask questions about trial involvement. Patients who then do not wish to participate in the trial will resume normal clinical care delivered by the GP according to usual practice. The right of the participant to refuse consent without giving reasons will be respected. Further, the participant will remain free to withdraw from the trial at any time without giving reasons and without prejudicing any further treatment.

Eligible patients who remain interested in the trial will be asked by the primary care healthcare professional to provide written informed consent including permission for medical record review.

A record of the consent process detailing the date of consent and all those present will be kept in the participant healthcare records. The original consent form will be retained in the investigator site file, a copy of the consent form will be given to the participant, a second copy filed in the healthcare records (as per local practice) and a third copy will be returned to Keele CTU via mail, secure fax or nhs.net e-mail. Where an out-of-hours service or walk-in centre has taken informed consent, the copy for the healthcare records needs to be returned to the participant's GP to be filed in the healthcare records.

NOTE: Informed consent must be obtained prior to the participant undergoing procedures that are specifically for the purpose of the study (including the collection of identifiable participant data).

6.4.1 RESPONSIBILITIES

The local Principal Investigator (PI) retains overall responsibility for the informed consent of participants at their centre and must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki 1996.

6.5 LOSS OF CAPACITY FOLLOWING INFORMED CONSENT

Where valid, informed consent is obtained from the participant and the participant subsequently becomes unable to provide on-going informed consent by virtue of physical or mental incapacity, the consent previously given when capable remains legally valid. Participants who lose capacity after informed consent has been obtained and are unable to complete follow-up questionnaires will be excluded from active follow-up but will remain in the trial according to the principle of intention-to-treat. On-going collection of safety data will continue via the clinical care team for inclusion in the trial analysis in order to preserve the integrity of the trial's intention-to-treat analysis and fulfil regulatory requirements specifically for Pharmacovigilance purposes.

Any further treatment/follow-up of the trial participant will be in consultation with the local Principal Investigator and participant's carer / family with the participant's best interests foremost in the decision-making process.

6.6 BASELINE DATA COLLECTION

The participant will be assisted to self-complete a paper baseline questionnaire including the primary outcome measure (worst pain intensity in the previous 24 hours) prior to randomisation (Table 1).

Table 1 – Data collection

Data to be collected	Time-point
Worst pain in last 24 hours	All
First attack of gout	BL
Age at gout diagnosis	BL
Which joint(s) affected?	BL
Time elapsed between symptom onset and starting trial medication	Diary (day 1)
Side-effects	Diary, 4wk
Patient global assessment of response to treatment	Diary (day 7), 4wk
Other medications used for pain relief	Diary, 4wk
Adherence to naproxen/low-dose colchicine	Diary
Relapse/recurrence of acute gout	4wk
EQ-5D 5-L	BL, diary (day 7), 4wk
Re-attendance at GP, A&E, primary care out-of-hours	4wk
Time off work/education	4wk

Definitions; BL – Baseline, 4wk – 4 week

6.7 RANDOMISATION

Prior to randomisation, the following must be completed:

- Eligibility assessment
- Informed Consent form
- Baseline Questionnaire

Randomisation will be undertaken by the primary care healthcare professional at the trial site using web access to a secure remote allocation system. Authorised personnel will be allocated personalised log in details, by Keele CTU, in order to access the randomisation system.

The primary care healthcare professional will enter the following information onto the randomisation system:

- Participant details, including name, gender, date of birth, address, telephone number and e-mail address (if applicable)
- Name of person undertaking randomisation
- Name of the treating clinician
- Confirmation of eligibility
- Confirmation of written informed consent and date
- Confirmation of completion of baseline questionnaire

Following completion of all the required information, the treatment allocation will be confirmed. Allocation will be made at the level of the individual, in a 1:1 ratio to receive either naproxen or low dose colchicine.

If, during office hours, the randomisation system is online but the site network is down, the site will be instructed to call the Keele Clinical Trials Unit (CTU) and the CTU will perform the randomisation on the site's behalf. Authorised staff at the CTU will access the randomisation tool to perform randomisation and inform the healthcare professional of the allocation.

If the site is unable to access the randomisation system outside of office hours or the site network is down and Keele CTU cannot access the database, the healthcare professional will call Aberdeen Health Services Research Unit (HSRU) who will provide an emergency 24/7 telephone randomisation service. Aberdeen HSRU will perform the randomisation on their behalf. The healthcare professional will be provided with a random allocation of treatment. To ensure that only patients registered with approved practices are randomised, Aberdeen HSRU will be provided with a list of participant ID numbers that can be used.

7. INVESTIGATIONAL MEDICINAL PRODUCTS AND INTERVENTIONS

7.1 INVESTIGATIONAL MEDICINAL PRODUCTS

Within the trial, the following are classed as Investigational Medicinal Products (IMPs):

7.1.1 LOW DOSE COLCHICINE

Composition: Supplied as Colchicine 500 micrograms Tablets

Supplier details: This is an 'off the shelf' product, has a marketing authorisation in the UK and is being used within the conditions of the SPC. Please refer to the trial supplied Summary of Product Characteristics (SPC).

Route of Administration: Tablet – Oral Use

Dose: 500 mcg (one tablet) every eight hours for four days

PLEASE NOTE: Participants who are already prescribed a statin and who are randomised to receive low-dose colchicine will be advised to omit the statin for the duration of treatment with colchicine, reflecting usual clinical practice.

7.1.2 NAPROXEN

Composition: Supplied as Naproxen Tablets BP 250 mg

Supplier details: This is an 'off the shelf' product, has a marketing authorisation in the UK and is being used within the conditions of the SPC. Please refer to the trial supplied Summary of Product Characteristics (SPC).

Route of Administration: Tablet – Oral Use

Dose: Single initial dose of 750 mg (three tablets) followed by 250 mg (one tablet) every eight hours for up to seven days

PLEASE NOTE: Co-prescription of a proton-pump inhibitor will be at the discretion of the treating GP e.g. age greater than 65 years and co-prescription with either an antiplatelet or selective serotonin reuptake inhibitor (SSRI).

As outlined above, both drugs will be used within their licensed indication at doses recommended for acute gout in the British National Formulary [19].

7.2 INVESTIGATIONAL MEDICINAL PRODUCT PREPARATION, LABELLING AND HANDLING

As participants will be issued with a prescription from the healthcare professional for either of the trial drugs, for them to collect from a pharmacy (as per standard care), there is no special requirements for the storage, labelling, accountability, destruction and disposal of the trial drugs at the trial sites. Either of the trial drugs will be labelled by the issuing pharmacist as per standard care.

7.3 INTERVENTION

Participants will be randomised during their consultation to receive either a 4 day course of colchicine (500 mcg every eight hours) as per BNF guidance or up to a 7 day course of Naproxen (single initial dose of 750 mg followed by 250 mg every eight hours). The GP will issue a prescription to the participant for the trial drug that they have been randomised to receive. The participant will collect this from the pharmacy (as per standard care). Patients will be provided with a pre-paid envelope in their study pack for return of the receipt to Keele CTU so that any prescription charge can be reimbursed.

In this pragmatic trial, where treatment for an acutely painful condition will be delivered rapidly and in real-time, we will not issue placebo tablets, and neither participants nor the treating GP will be blind to treatment allocation. This approach is in line with the recent Consort statement extension relating specifically to pragmatic trials [20] and will maximise the applicability of the trial's results to usual clinical care by replicating as closely as possible the delivery of these interventions in normal practice and by setting broad eligibility criteria which encourage a wide range of participants. One potential source of bias in the trial may relate to GPs' and patients' prior beliefs about the two medications. In order to address this we will provide trial-specific training for participating GPs and a drug-specific advice leaflets for patients which will also include general advice about non-pharmacological treatment including rest and application of topical ice to the affected joint.

7.4 CROSS OVER BETWEEN TRIAL ARMS

Participants cannot be crossed-over from one arm of the trial to the other. If the intervention needs to be discontinued, participants will remain in the trial according the principle of intention-to-treat unless the participant wishes to withdraw.

8. FOLLOW-UP AND OUTCOME ASSESSMENT

Outcome measures will be collected before randomisation (in the GP surgery by completion of the baseline questionnaire), by daily diary (days 1-7) and by a follow-up questionnaire at week 4 (see Table 1 and Appendix 1).

Study participants will be asked to keep a daily diary of worst pain (primary outcome), side-effects, adherence to treatment and use of other analgesic drugs (secondary outcomes) for the first 7 days after randomisation. On study entry, participants will be asked to choose their preferred mode of diary/questionnaire completion: paper questionnaire (postal return) or web-based questionnaires. Instructions for completion will be provided at the time of recruitment.

Participants preferring a paper diary will be given this in their study pack along with first class pre-paid return envelope. Participants will be mailed a reminder postcard during week 1 to optimise completion of the pain diary and will be asked to return the pain diary to the trial co-ordinator at the Keele CTU.

Participants preferring to complete a web-based diary/questionnaire will receive a daily e-mail reminder during days 1-7 containing a web-link to the secure data collection web-page. If diary data has not been received by day 10, participants will be contacted by telephone by the Research Nurse to try and capture key outcome data.

The week 4 questionnaire will also be available either as a paper or web-based questionnaire according to the participant's preference. Participants requesting a paper questionnaire will be sent this with a cover letter and pre-paid return envelope 4 weeks after randomisation. Non-responders to the 4-week follow-up questionnaire will be sent a reminder postcard after two weeks. Those who do not respond to the reminder postcard will be sent a repeat questionnaire and Participant Information Sheet with a further covering letter and pre-paid return envelope four weeks after the initial mailing. Participants will be asked to return their follow-up questionnaire to the trial co-ordinator at Keele CTU. This follow-up procedure has been used successfully in our previous trials at the Keele CTU.

Participants preferring to complete a web-based questionnaire will receive an e-mail inviting them to complete the 4-week questionnaire which contains a web-link to the secure data collection web-page. Non-responders to the 4-week follow-up questionnaire will be sent a reminder e-mail after two weeks. Those who do not respond to the reminder e-mail will be sent a further reminder e-mail four weeks after the initial mailing.

Those who do not respond to the second reminder (postal or electronic) regarding the 4-week questionnaire will be telephoned by the Research Nurse (who will remain blind to group allocation), in order to try to capture the key outcome data (worst pain intensity, patient global assessment of response, and side-effects) to minimise the effect of missing data. However, if after 5 phone-call attempts or if 2 weeks have lapsed, then a minimum data collection form will be mailed to the participant, asking them to complete the form and to return it to Keele CTU. Non-responders to the mailed minimum data collection form will not be contacted again.

The primary outcome measure will be the change in pain intensity from baseline measured over the first 7 days (1 week), as endorsed by the Outcome Measures in Rheumatology (OMERACT) group [21] (Table 1). Participants will be asked to rate the intensity of the worst pain experienced in the last 24 hours using a validated 0-10 numeric rating scale.

Secondary outcome measures will include (Table 1):

- the proportion of participants in each group reporting complete resolution of pain and time to treatment effect.
- self-reported side-effects (nausea, vomiting, dyspepsia, diarrhoea and abdominal pain)
- patient global assessment of response to treatment
- use of other medications for pain relief (for example, steroids, paracetamol, opiates)
- adherence to naproxen/low-dose colchicine
- relapse/recurrence of acute gout
- EQ-5D 5-L, healthcare utilisation (re-attendance at GP/accident and emergency/primary care out-of-hours service), time off work/education

Participants will be required to provide consent for their medical records over the 4-week study period to be reviewed in order to capture adverse events and health-care utilisation.

8.1 SCHEDULE OF EVENTS

The timings of interventions and assessment are summarised in table 2 below. Participants will be followed up for a period of 4 weeks overall.

Table 2: Timings of interventions/ assessments

Intervention / follow up activity	Prior to start of recruitment	Day 0 (consultation)	Days 1 – 6 (pain diary)	Day 7 (pain diary)	4-week questionnaire
Intervention					
Patient records screened for acute gout Read code	X				
Patients mailed Patient Information Sheet (with covering letter and drug information) informing them of trial	X				
Patient consults GP (eligibility screen)		X			
Informed Consent to participate (if patient eligible and willing)		X			
Assessments					
Worst pain in last 24 hours		X	X	X	X
First Attack of Gout?		X			
Age at Gout diagnosis		X			
Which joint(s) affected?		X			
Time elapsed between symptom onset and starting trial medication			X (day 1 only)		
Side-effects			X	X	X
Patient global assessment of response to treatment				X	X
Other medications used for pain relief			X	X	X
Adherence to naproxen/low-dose colchicine			X	X	
Relapse/recurrence of acute gout					X
EQ-5D 5-L		X		X	X
Re-attendance at GP, A&E, primary care out-of-hours					X
Time off work/education					X
Follow up					
Web-based randomisation		X			

Intervention / follow up activity	Prior to start of recruitment	Day 0 (consultation)	Days 1 – 6 (pain diary)	Day 7 (pain diary)	4-week questionnaire
Web based data collection (see section 6.7)		X			
Administration of study intervention		X			
GP SAE/SUSAR/ withdrawal/death reporting [1]			X	X	X
Medical record review [2]					

[1] ongoing throughout follow-up period; [2] completed after follow-up period

Definitions; CRF – Case Report Form, SAE – Serious Adverse Events, SUSAR – Suspected Unexpected Serious Adverse Reaction

8.2 DISCONTINUATION OF TRIAL INTERVENTION / WITHDRAWAL OF CONSENT

In line with usual clinical care, cessation or alteration of the intervention at any time will be at the discretion of the local Investigator or the participants themselves. All participants who discontinue a trial intervention, or prescribed alternative or additional treatment, will continue to be followed up, unless unwilling to do so, therefore, questionnaires will continue to be completed and returned to Keele CTU.

The PI should make every effort to ensure that the specific wishes of any participant who wishes to withdraw consent for further involvement in the trial are defined and documented using the withdrawal CRF in order that the correct processes are followed by Keele CTU and the trial site following the withdrawal of consent.
It should be made clear to any participant specifically withdrawing consent for further data collection that data pertaining to safety will continue to be collected for regulatory reporting purposes and will be included in any safety analysis. In addition, it is suggested that the participant is made aware of the fact that if any significant new information becomes available in regard to the treatment they have received in the trial it may be necessary to contact them in the future.

9. ASSESSMENTS AND DATA COLLECTION

Participating centres will be expected to maintain a file of essential trial documentation (Investigator Site File), which will be provided by Keele CTU. Copies of all completed Case Report Forms (CRFs) for the trial will also be kept in this file.

9.1 CASE REPORT FORMS

Trial data will be recorded by research staff on trial-specific CRFs.

If a participant withdraws consent for their data to be used, no further follow-up information will be collected from the patient's healthcare records except data pertaining to safety for regulatory reporting purposes. However, all information collected prior to the date of withdrawal will be included in the trial analyses.

Please refer to section 17 for details of the trial archiving requirements.

9.2 END OF TRIAL INTERVENTION

If the participant discontinues from trial intervention for any reason, an early cessation of trial treatment CRF must be completed within 7 days of the site research team becoming aware of this.

9.3 MONITORING OF ADVERSE AND SERIOUS ADVERSE EVENTS

Both naproxen and colchicine have a licence to treat acute gout and will be used within their licensed indication at doses recommended for acute gout in the British National Formulary [19]. Adverse events (AEs) will be monitored via a number of methods:

- self-reported side-effects will be collected from days 1-7 in the daily diary and at week 4 in the follow-up questionnaire. These AEs will be recorded on the web-based data collection database either by the participant or by Keele CTU.

- GPs will be asked to report all serious adverse events (SAEs) to Keele CTU within 24 hours of the research staff at the participating site becoming aware of them (see section 10).

- AEs will also be identified by review of medical records once recruitment and follow-up are complete.

9.4 DEATHS

All deaths occurring up to 4 weeks after randomisation must be notified to Keele CTU within 24 hours (see section 10 for further details). Keele CTU will forward the appropriate CRF for completion, which should be returned to Keele CTU within a further 24 hours. Deaths which in the opinion of the local investigator are related to trial treatment occurring at any time during the participant's time in the study will be processed as a SUSAR

Deaths occurring after 4 weeks post-randomisation will not be collected unless related to trial treatment.

9.5 END OF TRIAL

The end of the trial is defined as the last participants' last data item.

10. PHARMACOVIGILANCE

10.1 GENERAL DEFINITIONS

10.1.1 ADVERSE EVENTS (AE)

An adverse event (AE) is any untoward medical occurrence in a patient or clinical trial participant which does not necessarily have a causal relationship with this treatment and can include:

- Any unintentional, unfavourable clinical sign or symptom

- Any new illness or disease or the deterioration of existing disease or illness
- Any clinically relevant deterioration in any laboratory assessments or clinical tests
- Requires medical or surgical intervention to prevent permanent impairment of function or permanent damage to body structure.

10.1.2 ADVERSE REACTION (AR)

All untoward and unintended responses to an investigational medicinal product related to any dose administered. This definition implies a reasonable possibility of a causal relationship which is supported by facts, evidence or arguments to suggest a causal relationship. This definition includes medication errors and uses outside what is foreseen in the protocol (i.e. if an AR occurs as a result of a medication error).

10.1.3 SERIOUS ADVERSE EVENTS (SAE)

A Serious Adverse Event (SAE) is defined in general as “any untoward medical occurrence or effect that:

- Results in death
- Is life-threatening*
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- May jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above

* the term life-threatening refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.

Where an SAE is deemed to have been related to the IMP used within the trial, the event is termed as a Serious Adverse Reaction (SAR).

Medical judgement should be exercised in deciding whether an AE or AR is serious in other situations. Important AE/ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one or the other outcomes listed in the definition above, should also be considered serious.

10.1.4 SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS (SUSARS)

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is a Serious Adverse Reaction which also demonstrates the characteristic of being unexpected, the nature and severity of which is not consistent with the information about the medicinal product as set out in the Reference Safety Information (Summary of Product Characteristics). The term ‘severity’ is used to describe the intensity of a specific event. This should be distinguished from the term ‘serious’.

10.2 OPERATIONAL DEFINITION OF ADVERSE EVENTS

AEs will be recorded from the commencement of trial intervention up until completion of the 4 week questionnaire.

Information about AEs volunteered by the participant will be collected and recorded in the 7 day pain diary and at week 4 in the follow-up questionnaire. AEs will also be collected during review of participant's medical records once recruitment and follow-up are complete.

10.2.1 RECORDING AND REPORTING ADVERSE EVENTS AND REACTIONS

All AEs, both related and unrelated to acute gout and its treatment, will be collected for all participants.

10.3 OPERATIONAL DEFINITION OF SAEs

It is considered that there are minimal risks to patients associated with their participation in this study as interventions are to be applied in accordance with usual clinical care. Both colchicine and naproxen are being used within the terms of their marketing authorisation. Therefore, it is not expected that there will be many SAEs in this study.

10.3.1 EVENTS NOT CLASSED AS SAEs

The following events **will** be recorded but **will not** be reported as SAEs within this trial:

Hospitalisation for:

- Routine treatment or monitoring of acute gout associated with any deterioration in condition
- Treatment which was elective and pre-planned, for a pre-existing condition not associated with any deterioration in condition
- Prolongation of hospitalisation not associated with an adverse event
- Admission to hospital or other institution for general care, not associated with any deterioration in condition
- Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions for serious as given above and not resulting in hospital admission

Such events should be recorded by the site trial team in the participant's healthcare records in accordance with local standard practice.

Deaths not attributable to the trial intervention beyond the end of the 4 week treatment period will not be considered as SAEs.

10.3.2 EXPECTED SAEs

Table 3 lists example events which will be classed as expected SAEs within this trial and will not be considered as SUSARs unless the severity or outcome of the event is considered to be unexpected. This is not intended to be an exhaustive list, therefore when determining whether an SAE is expected or not, trial approved Reference Safety Information (Summary of Product Characteristics) for either low-dose colchicine or naproxen (whichever treatment the participant has been allocated) will be used.

Table 3: Examples of expected SAEs in the CONTACT Trial

Examples of expected SAEs related to acute gout
• Hospitalisation for acute gout
Examples of expected SAEs related to low-dose colchicine:
• nausea, vomiting, abdominal pain, diarrhoea, gastrointestinal haemorrhage, renal failure, skin rashes, peripheral neuropathy, myopathy, rhabdomyolysis, bone marrow suppression fulfilling SAE definition given in section 10.1.3
Examples of expected SAEs related to naproxen:
• Gastro-intestinal haemorrhage/perforation, hypersensitivity reaction/anaphylaxis, myocardial infarction, stroke, cardiac failure, acute renal failure, liver function abnormalities, hepatitis, jaundice, bone marrow suppression, Stevens-Johnson syndrome fulfilling SAE definition given in section 10.1.3

10.4 RECORDING AND REPORTING SAEs AND SUSARs

In the first instance, all events must be reviewed and classed by the local PI or another medically qualified member of the clinical team approved by the local PI.

All SAEs occurring from the point when participants are registered on the trial must be notified to Keele CTU via telephone within 24 hours of the research staff at the participating site becoming aware of the event. Keele CTU will then provide the appropriate Case Report Form, which must be completed and returned (via fax or secure e-mail) within 24hours of receipt. Any follow-up information should be sent to the Keele CTU as it is available. Events will be followed up until the event has been resolved or a final outcome has been reached.

For each SAE, the following information will be collected:

- Full details in medical terms with a diagnosis, if possible
- Duration (start and stop dates if applicable)
- Action taken
- Outcome
- Causality* (i.e. relatedness to the trial drug/investigation), in the opinion of the local PI (or authorised delegate)

**** Assessment of causality must be made by an authorised medical doctor. If an authorised medical doctor is unavailable, initial reports without causality assessment should be submitted to Keele CTU within 24 hours, but must be followed up with assessment by an authorised medical doctor as soon as possible thereafter.***

Only one event will be reported on each SAE CRF (details of multiple symptoms should be listed if they relate to the same event).

10.4.1 EXPECTEDNESS ASSESSMENT

SAEs which are reported to Keele CTU as related to trial treatment, will be formally assessed by the CI (or their delegate) for expectedness. The protocol and trial approved Reference Safety Information (Summary of Product Characteristics) for either low-dose colchicine or naproxen (whichever treatment the participant has been allocated) will be used to determine whether an SAE is expected.

10.4.2 SUSARs

All SAEs assigned by the CI or their delegate as both suspected to be related to IMP treatment and unexpected will be classified as SUSARs and will be subject to a request for additional information from the local PI (or their delegate) which must be returned to Keele CTU within 24 hours of request.

SUSARs will be subject to expedited reporting to the MHRA and main REC. Keele CTU will inform the MHRA and the main REC of any SUSARs within the required expedited reporting timelines, and will notify the Sponsor in accordance with their requirements.

10.5 PREGNANCIES

If a patient becomes pregnant whilst involved in the trial, it is not considered to be an SAE or an AE. However, it is an event that requires monitoring and follow up to outcome. If a patient becomes pregnant, Keele CTU must be informed within 7 days.

The local PI (or delegate) must follow up the pregnancy until delivery. Any outcome that could be considered to be a SAE must be reported to Keele CTU.

10.6 RESPONSIBILITIES

10.6.1 Local Principal Investigator (participating centre)

1. Reporting SAEs to Keele CTU

2. Medical judgement in assigning:

    - Seriousness
    - Causality
    - Expectedness in accordance with the protocol

3. Ensuring all SAEs are recorded and reported to Keele CTU within 24 hours of becoming aware and to provide further follow-up information as soon as available.

4. Reporting SAEs to local committees in line with local arrangements.

10.6.2 Chief Investigator (or nominated individual in CI's absence)

1. Assigning causality of SAEs where it has not been possible to obtain local assessment.
2. Assigning expected nature of related SAEs
3. Undertaking cumulative SAE review.
4. Reviewing any events reported to Keele CTU as SUSARs by a local PI (or authorised delegate). In the event of disagreement between local assessment and the Chief Investigator, local assessment will not be downgraded but the Chief Investigator may add comments prior to reporting to MHRA and main REC.
5. Assigning a body system code to all SAEs suspected to be related to trial treatment prior to submission of annual safety reports.

10.6.3 Keele CTU

1. Expedited reporting of SUSARs to the MHRA, main REC, DMC and Sponsor within required timelines.

2. Preparing annual safety reports in collaboration with appropriate members of the Trial Management Team to the MHRA and main REC, periodic safety reports to the Trial Steering Committee and Data Monitoring Committee as appropriate and reports required by the sponsor.

3. Notifying Investigators of SUSARs that occur within the trial and any updates to relevant Summary of Product Characteristics.

10.6.4 Trial Steering Committee (TSC)

In accordance with the Trial Terms of Reference for the TSC, periodically reviewing safety data and liaising with the DMC regarding safety issues.

10.6.5 Data Monitoring Committee (DMC)

1. In accordance with the Trial Terms of Reference for the DMC, periodically reviewing unblinded overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

2. Reporting to TSC chair, Sponsor and/or CI as appropriate

11. ENDPOINTS

11.1 PRIMARY ENDPOINT

The primary endpoint measure will be pain measured on a 0-10 pain intensity numeric rating scale measured over days 0-7.

11.2 SECONDARY ENDPOINTS

Secondary endpoint measures will include the following and will be measured over 4 weeks:

- the proportion of participants in each group reporting complete resolution of pain and time to treatment effect.
- side-effects (e.g. nausea, vomiting, dyspepsia, diarrhoea and abdominal pain) via a self-reported drug side-effect questionnaire
- patient global assessment of response to treatment
- use of other medications for pain relief (for example, steroids, paracetamol, opiates)
- adherence to naproxen/low-dose colchicine
- relapse/recurrence of acute gout
- EQ-5D 5-L, healthcare utilisation (re-attendance at GP/accident and emergency/primary care out-of-hours service), time off work/education

12. STATISTICAL CONSIDERATIONS

12.1 SAMPLE SIZE

The required sample size is based upon a conservative estimate of a small standardised effect size of 0.3 [27], obtained as the difference in mean score between the two treatment groups divided by the pooled standard deviation. The desired power of approximately 90% was set to detect a between-group difference and two-sided type one error fixed at 0.05. Taking repeated measures structure into account (with assumed correlation of 0.6), and allowing approximately 20% loss to follow-up, the estimated sample size is 200 participants per treatment arm (total 400 participants) assuming a 1-1 random allocation ratio. Statistical power is increased by analysis of repeated measures, the primary outcome being assessed at baseline (day 0) and then daily from day 1 through to day 7 (see Statistical Analysis section below) [28].

12.2 RECRUITMENT RATE

Observational data from our local primary care network indicates that 40 patients per 10,000 registered patients will consult their GP with gout in a one-year period [3]. If 20% of these are both eligible and provide consent to participate in the trial, we will need to recruit from 50-100 large practices in order to recruit our required sample size (400 participants) over a 12-month period.

12.3 STATISTICAL ANALYSIS

Statistical analysis is the responsibility of Keele CTU Statisticians. The analysis plan outlined in this section will be reviewed and a final statistical analysis plan written before any analysis is undertaken. The analysis plan will be written in accordance with current Keele CTU standard operating procedures and will be finalised and agreed by the following people: the Statistician, the Chief Investigator and the Keele CTU Principal Investigator. Any changes to the finalised analysis plan, and reasons for changes, will be documented.

The primary outcome to be analysed is the change in 0-10 pain intensity numeric rating scale. Crude mean scores with standard deviations (SD) will be presented at baseline and at each follow-up time point (days 1 through to 7) and compared between the two treatments. Mean change (with 95% confidence intervals) from baseline to each follow-up time point and from baseline to day 7 will be calculated for each treatment group

and between-group comparisons made using generalized linear modelling (GLM) and generalized estimating equations (GEE). Model assumptions will be tested throughout.

We will subsequently perform repeated measures analysis via linear mixed model, taking the dependent variable as the change in units in the scores on the numeric rating scale between baseline and each of the 7 follow-up time points, thus we will have 7 measures per patient. The focus will then be placed on the average change in score during the first 7 days. All statistical analyses will be performed before and after adjustment for baseline covariates, including age, gender and baseline pain score. The primary analysis approach will be intention-to-treat with between-group evaluation of all patients as randomised. A secondary analysis will compare treatment groups treated as per protocol. All statistical analysis will be performed using STATA 12. Statistical estimates will be accompanied with associated 95% confidence intervals and all *p* values <0.05 considered statistically significant.

12.4 FREQUENCY AND TIMING OF ANALYSIS

Outcome data will be analysed once only, at final analysis. A Data Monitoring Committee (DMC) will be set up to meet at least annually to independently review interim safety, recruitment data and follow up response in strict confidence. No formal statistical interim analyses are planned. This committee, in light of the interim data, and of any other advice or evidence they wish to request, will advise the TSC if there are any concerns with the trial. At any point in the trial, the DMC may advise the TSC to request, in writing to the CI, unblinded outcome analysis if the interim safety data suggest issues with one or both of the treatments. Based on this unblinded analysis, the DMC and TSC can stipulate an early termination of the trial. Final analysis will take place when each participant has completed 4 week follow-up.

13. HEALTH ECONOMICS

An economic evaluation will be undertaken alongside the trial, in the form of a cost-utility analysis. The base-case analysis will be from a health care perspective, with exploration of productivity costs due to time off work in a sensitivity analysis. Quality of life will be measured using the 5 level EQ-5D (EQ-5D 5L) at baseline, day 7 and 4 weeks in order to calculate quality adjusted life years (QALYs) over the trial period. The 5-level version will be used rather than the 3-level version as it is expected to demonstrate greater sensitivity, which is of importance in a study over a short-time period of 4 weeks. Resource use will concentrate on the cost of the interventions and health care costs related to the treatment of gout and any treatment-related side effects. Data will be collected on the use of primary and secondary care services and other prescribed medications. In addition, information on employment status and time off work will be sought to calculate productivity losses related to gout and its treatment. An incremental analysis will be performed to determine the most cost-effective intervention in terms of the cost per additional QALY gained. The robustness of the results will be explored using sensitivity analysis. This will explore uncertainties in the trial data itself, the methods employed to analyse the data and the generalisability of the results to other settings. Uncertainty in the confidence to be placed on the results of the economic analysis will be explored using probabilistic sensitivity analysis to estimate cost effectiveness acceptability curves.

14. MONITORING

14.1 DATA MONITORING COMMITTEE

An independent Data Monitoring Committee (DMC) will review the safety and ethics of the trial. Detailed blinded reports will be prepared by Keele CTU for the DMC after the first 6 months of participant recruitment and then at approximately 6 monthly intervals.

The DMC will be provided with detailed blinded reports containing the following information:

- Rates of occurrences of SAEs, SARs and SUSARs
- Rates of adverse events
- Deaths

14.2 DATA MONITORING

Data will be centrally monitored for quality and completeness by Keele CTU. Missing data will be chased until it is received, confirmed as not available, or the trial is at analysis. Keele CTU/Sponsor will reserve the right to intermittently conduct source data verification exercises on a sample of participants, which will be carried out by staff authorised by Keele CTU/Sponsor. Source data verification may involve direct access to participant healthcare records at the participating centres and the on-going central collection of copies of consent forms and other relevant investigation reports. A Trial Monitoring Plan will be defined and agreed by the Trial Management Group.

14.3 CLINICAL GOVERNANCE ISSUES

To ensure responsibility and accountability for the overall quality of care received by participants during the study period, clinical governance issues pertaining to all aspects of routine management will be brought to the attention of the Trial Steering Committee and, where applicable, to individual participating Centres or NHS Trusts.

15. QUALITY ASSURANCE AND ETHICAL CONSIDERATIONS

15.1 QUALITY ASSURANCE

The trial will be conducted in accordance with the principles of Good Clinical Practice (GCP) in clinical trials, as applicable under UK regulations, the NHS Research Governance Framework and Scottish Executive Health Department Research Governance Framework for Health and Social Care 2006.

15.1.1 SERIOUS BREACHES OF THE PROTOCOL AND GCP

Keele CTU have systems in place to ensure that serious breaches of GCP of the trial protocol are picked up and reported. Investigators are required to notify Keele CTU **immediately** of a serious breach as defined in Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 [Statutory Instrument 2004/1031], as amended by Statutory Instrument 2006/1928 that they become aware of. A “serious breach” is a breach which is likely to effect to a significant degree:

a) The safety or physical or mental integrity of the participants of the trial; or
b) The scientific value of the trial.

In the event of doubt, or for further information or guidance, the investigator should contact the Study Co-ordinator or Principal Investigator at Keele CTU.

15.2 ETHICAL CONSIDERATIONS

The trial will be 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 will be obtained from the participants prior to randomisation into the trial. The right of a participant to refuse participation without giving reasons must be respected. The participant must remain free to withdraw at any time from the trial without giving reasons and without prejudicing his/her further treatment. The trial will be 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. Keele CTU will provide the main REC with a copy of the final protocol, patient information sheets, consent forms and all other relevant study documentation.

16. CONFIDENTIALITY

All information collected during the course of the trial will be kept strictly confidential. Information will be held securely on paper and managed electronically by Keele University through Keele CTU. Keele CTU will comply with all aspects of the 1998 Data Protection Act and operationally this will include:

- Consent from participants to record personal details including name, date of birth, NHS number, address, telephone number.
- Appropriate storage, restricted access and disposal arrangements for participant personal and clinical details
- Consent from participants for access to their healthcare records by responsible individuals from the research staff or from regulatory authorities, where it is relevant to trial participation
- Consent from participants for the data collected for the trial to be used to evaluate safety and develop new research
- All data collection forms that are transferred to and from Keele CTU will be coded with a study ID number and will include two further participant identifiers, usually the participants gender and/or initials and date of birth
- Where anonymisation of documentation is required, participating centres are responsible for ensuring only the instructed identifiers are present before sending to Keele CTU

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. Provision of appropriate client server links/permissions will be given to authorised members of the trial team at Keele CTU. At the end of the study, all trial data will be moved from the secure server at the University of Birmingham to a secure server at Keele University under a data migration plan.

All data will be stored securely and in line with the Data Protection Act 1998 at all times. At this time, all participants will be notified of this planned move and will be given the opportunity to raise any queries or concerns that have regarding the move of this data.

Following the move of the data, the data will go through a series of data cleaning stages, prior to the final dataset being locked down for analysis prior to the data being archived.

If a participant withdraws consent from further trial intervention and/or further collection of data their data will remain on file and will be included in the final study analysis.

17. ARCHIVING

At the end of the trial, data will be securely archived in line with the Sponsor's procedures for a minimum of 15 years. Data held by Keele CTU will be archived in the designated Keele CTU archive facility and site data and documents will be archived at the participating sites. Following authorisation from the Sponsor, arrangements for confidential destruction will then be made.

18. STATEMENT OF INDEMNITY

This trial is sponsored by Keele University and therefore Keele University will be liable for negligent harm caused by the design of the trial.

The NHS has a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and the NHS organisation remains liable for clinical negligence and other negligent harm to patients under this duty of care.

As this is an investigator-led trial, there are no arrangements for no-fault compensation.

19. STUDY ORGANISATIONAL STRUCTURE

19.1 INDIVIDUALS AND INDIVIDUAL ORGANISATIONS

Trial Sponsor: The Sponsor is responsible for trial initiation management and financing of the trial as defined by Directive 2001/20/EC. These responsibilities are delegated to the Keele CTU as detailed in the trial contract.

Chief Investigator (CI): The CI is involved in the design, conduct, co-ordination and management of the trial. The CI has overall responsibility for the scientific quality and delivery of the study, the investigational drug supply and pharmacovigilance within the trial.

Keele CTU: Keele CTU has responsibility for conduct of the trial as delegated by the Sponsor in accordance with relevant GCP standards and Keele CTU SOPs. Keele CTU will provide set-up and monitoring of trial conduct to Keele CTU SOPs, and the GCP Conditions and Principles as detailed in the UK Medicines for Human Use (Clinical Trials) Regulations 2006 including, randomisation design and service, database development and provision, protocol development, CRF design, trial design, monitoring schedule and statistical analysis for the trial. In addition Keele CTU will support main REC, Clinical Trial Authorisation application, Site Specific Assessment and NHS Permissions submissions and clinical set-up, ongoing management including training, monitoring reports and promotion of the trial. Keele CTU will be responsible for the overall day-to-day running of the trial including trial administration, database administrative functions, data management, safety reporting and all statistical analyses.

National Primary Care Research Network (PCRN): The PCRN will coordinate the local implementation and study set up into primary care sites and report progress to the study team. The relevant research network (PCRN or Comprehensive Local Research Network (CLRN)) will provide funding or staff resource to secure the additional clinical time associated with service support to embed the study into primary care sites to allow identification of suitable and potentially eligible participants.

Local Principal Investigator (PI): The local PI is responsible for the conduct and leadership of the trial at their site as detailed in the applicable Sponsor-Site Agreement available in the Investigator Site File and ensuring the trial is run at their site in accordance with the GCP Conditions and Principles as detailed in the UK Medicines for Human Use (Clinical Trials) Regulations 2006. This includes (but is not limited to) informed consent of trial participants, eligibility, collection of baseline questionnaires, completion of relevant clinical CRFs, randomisation, delivery of intervention, safety reporting.

Other collaborating sites: Nottingham, Oxford and Southampton will have responsibility for conduct of the trial as delegated by the Sponsor in accordance with relevant GCP standards. All sites will be responsible for GP Practice set up, training and ongoing management of the study including training, monitoring reports, promotion of the trial and overall day-to-day running of the trial for their areas.

19.2 OVERSIGHT / TRIAL MONITORING GROUPS

Trial Management Team: the Trial Management Team comprising the Chief Investigator, the Keele CTU team, other key internal and external members of staff involved in the trial have responsibility for the clinical set-up, ongoing management, promotion of the trial, and for the interpretation of results. Specifically the Trial Management Team will be responsible for (i) protocol completion, (ii) CRF development, (iii) obtaining approval from the main REC and supporting applications for Site Specific Assessments, (iv) submitting a CTA application and obtaining approval from the MHRA, (v) completing cost estimates and project initiation, (vi) nominating members and facilitating the TSC and DMC, (vii) reporting of serious adverse events, (viii) monitoring of screening, recruitment, treatment and follow-up procedures, (ix) auditing consent procedures, data collection, trial end-point validation and database development. The group will meet on a regular basis throughout the trial.

Trial Steering Committee (TSC): the TSC will provide overall supervision of the trial, in particular trial progress, adherence to protocol, participant safety and consideration of new information. The TSC comprises a rheumatologist, general practitioner, independent statistician and two consumer representatives in addition to the Chief Investigator, trial co-ordinator and trial statistician. The Committee will meet every six-months as a minimum.

Data Monitoring Committee (DMC): the DMC will review the safety and ethics of the trial by reviewing interim data during recruitment. The Committee will meet annually as a minimum.

20. PUBLICATION POLICY

The trial will be registered with an authorised registry, according to the International Committee of Medical Journal Editors (ICMJE) Guidelines, prior to the start of recruitment.

The results will be disseminated through oral and poster presentations at Conferences along with publications in peer review journals and other media.

The success of the trial depends upon the collaboration of all participants. For this reason, credit for the main results will be given to all those who have collaborated in the trial, through authorship and contributorship. Uniform requirements, for authorship for manuscripts submitted to medical journals will guide authorship decisions. These state that authorship credit should be based only on substantial contribution to:

- Conception and design, or acquisition of data, or analysis and interpretation of data
- Drafting the article or revising it critically for important intellectual content
- Final approval of the version to be published
- All these conditions must be met (www.icmje.org).

Any additional contributors to the trial will be acknowledged in the main trial publication, giving details of roles in planning, conducting and reporting the trial.

To maintain the scientific integrity of the trial, data will not be released prior to the first publication of the analysis of the primary endpoint, either for trial publication or oral presentation purposes, without the permission of the Trial Steering Committee.

In addition, individual collaborators must not publish data concerning their participants which is directly relevant to the questions posed in the trial until the first publication of the analysis of the primary endpoint.

Publications relating to this study will be Open Access. Articles will be archived in UK PubMed Central or PubMed Central open access archives as soon as possible (maximum 6 months) after publication.

21. REFERENCES

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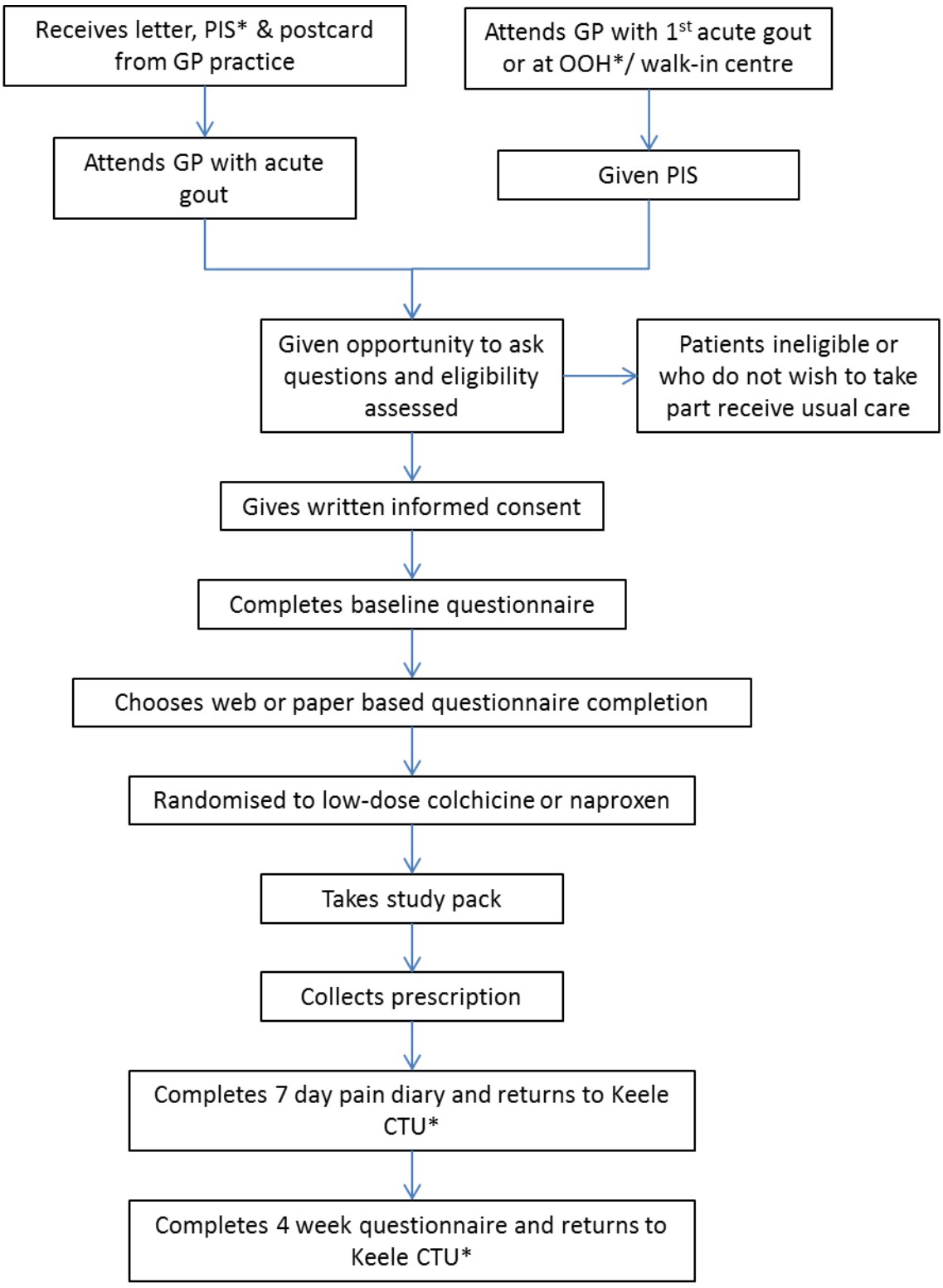
Appendix 1
Patient Pathway



* PIS = Patient Information Sheet, OOH = Primary Care Out of hours service, CTU = Clinical Trials Unit