

OCCUR

A pragmatic randomised trial comparing **O**ral **C**orticosteroids and **C**olchicine for the treatment of go**U**t fla**R**es in people with relative contraindications to non-steroidal anti-inflammatory drugs.

Protocol version number and date: V2.0 02/Dec/2025

- **This protocol has regard for the HRA guidance**

RESEARCH REFERENCE NUMBERS

IRAS Number:	1011829
ISRCTN Number:	ISRCTN12564318
SPONSORS Number:	RG-0367-23
FUNDERS Number:	NIHR160813

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:

Signature: Date:

Name

Position:

Chief Investigator:

Signature: Date:

Name:

Position:

Statistician:

Signature: Date:

Name:

Position:

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ii. LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
AE	Adverse Event
AI	Associate Investigator
AR	Adverse Reaction
BSR	British Society for Rheumatology
BNF	British National Formulary
CA	Competent Authority
CI	Chief Investigator
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
CTU	Clinical Trials Unit
DERA	Deep End Research Alliance
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
eGFR	Estimated Glomerular Filtration Rate
EULAR	European Alliance of Associations for Rheumatology
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HRA	Health Research Authority
HSCR	Health and Social Care Research
IAU	Impact Accelerator Unit
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
IMP	Investigational Medicinal Product
ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials Number
MA	Marketing Authorisation

MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NRS	Numerical Rating Scale
NSAIDs	Non-steroidal anti-inflammatory drugs
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
PPIE	Public and Patient Involvement and Engagement
QA	Quality Assurance
QALYs	Quality-adjusted life years
QC	Quality Control
QMS	Quality Management System
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SMS	Short message service
SNOMED CT	Systematized Nomenclature of Medicine Clinical Terms
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
URL	Uniform Resource Locator (web link)

iii. TRIAL SUMMARY

Research question: What is the clinical and cost-effectiveness of oral prednisolone versus colchicine in people currently experiencing a gout flare who have relative contraindications to non-steroidal anti-inflammatory drugs (NSAIDs)?

Background: Gout is the most prevalent inflammatory arthritis, affecting 2.5% of adults in the UK, and causes significant pain, disability and impaired health-related quality of life. It is largely managed in primary care, where gout flares are most frequently treated with NSAIDs. However, relative contraindications to NSAIDs such as older age, chronic kidney disease and/or cardiovascular disease are prevalent in people with gout. When gout flares occur in people with such contraindications, alternative treatments to NSAIDs, such as colchicine and corticosteroids, are needed.

Objectives: to compare (1) the effectiveness of oral prednisolone and colchicine at reducing pain in people with a gout flare and relative contraindications to NSAIDs; (2) the effect of oral prednisolone and colchicine on time to resolution of pain, joint swelling and tenderness, adverse effects, physical function, quality of life, participant global assessment of treatment response, flare relapse/recurrence; sleep, use of walking aids, work/education absence, treatment adherence and satisfaction; and (3) the cost-effectiveness of oral prednisolone and colchicine.

Methods: A multicentre pragmatic randomised open-label two-arm parallel group superiority trial with 12-month internal pilot and health economic evaluation. 280 people aged ≥18 years with relative contraindications to NSAIDs and currently experiencing a gout flare will be recruited from approximately 100 general practices across the UK. Participants will be randomised individually in a 1:1 ratio to oral prednisolone 30mg once daily or colchicine 0.5mg three times daily (0.5mg twice daily if aged >70 years or known estimated glomerular filtration rate <30) via a secure centralised web-based, automated computer-generated randomisation system. The primary outcome (change in pain intensity from baseline over days 1-7) will be collected twice daily during week 1 and then also as a secondary analysis at weeks 2, 3 and 4. Secondary outcomes will include time to resolution of joint pain; joint swelling and tenderness; treatment side effects, adherence and satisfaction; analgesic use; physical function; quality of life; global assessment of treatment response; flare relapse/recurrence; sleep; use of walking aids; health care utilisation and work/education absence.

Timelines for delivery: 40 months. Months 0-9: set-up; months 10-33: participant screening & recruitment (months 10-22: internal pilot); month 34: complete follow-up and reminders; months 35-40: data analyses, report and dissemination.

Anticipated impact and dissemination: New evidence will be provided about the relative effectiveness and safety of oral prednisolone and colchicine for gout flares in people who have relative contraindications to NSAIDs, which will inform treatment decisions. If cost-effective, these simple interventions will be easily implemented across clinical services. As well as publishing in high impact journals and presenting at scientific meetings, we will work closely with our networks, professional bodies, specialist societies, charities, and the National Institute for Health and Care Excellence (NICE) to ensure wide dissemination and implementation, supported by our Patient and Public Involvement and Engagement (PPIE) group and Keele University's Impact Accelerator Unit.

Trial Title	A pragmatic randomised trial comparing Oral Corticosteroids and Colchicine for the treatment of goUt flaRes in people with relative contraindications to non-steroidal anti-inflammatory drugs (OCCUR)	
Internal ref. no. (or short title)	OCCUR	
Clinical Phase	Phase IV	
IMP Risk Category	Type A	
Trial Design	Multicentre pragmatic randomised open-label two-arm parallel group superiority trial.	
Trial Participants	People aged ≥18 years with relative contraindications to NSAIDs having a gout flare.	
Planned Sample Size	N = 280 (140 participants per arm).	
Treatment duration	Oral prednisolone - five days Oral colchicine - four days	
Follow up duration	4 weeks	
Planned Trial Period	Start Date: 01/01/2025 (funding) End Date: 30/04/2028 (funding) Duration: 40 months	
	Objectives	Outcome Measures
Primary	To compare the effectiveness of oral prednisolone and oral colchicine at reducing pain in people with a gout flare and relative contraindications to NSAIDs in primary care.	Change in self-reported pain intensity from baseline over days 1-7. Participants will rate worst pain intensity experienced in the last 12 hours (0-10 NRS) twice daily.
Secondary	To compare the effect of oral prednisolone and colchicine on: - time to resolution of pain - joint swelling - joint tenderness - treatment side effects - treatment adherence - treatment satisfaction - physical function - quality of life	- change in self-reported pain intensity from baseline - joint swelling - joint tenderness - treatment side-effects - treatment adherence - treatment satisfaction - physical function (Health Assessment Questionnaire-Disability Index [37] - quality of life (EQ-5D-5-L [38])

	- global assessment of treatment response - flare relapse/recurrence - sleep - use of walking aids - analgesic use - health care utilisation - work/education absence - cost-effectiveness of oral prednisolone and colchicine.	- global assessment of treatment response - flare relapse/recurrence (defined as recurrence after 48 hours without a flare) - sleep - use of walking aids - analgesic use - healthcare utilisation - work/education absence
Investigational Medicinal Products	Oral prednisolone Oral colchicine	
Formulation, Dose, Route of Administration	Oral prednisolone 30mg once daily (six 5mg tablets once daily) for five days Oral colchicine 0.5mg three times daily for four days (twice daily if aged≥70 years or known eGFR 15-29)	

iv. FUNDING AND SUPPORT IN KIND

FUNDER	**FINANCIAL AND NON-FINANCIAL SUPPORT GIVEN**
National Institute for Health and Care Research: Health Technology Assessment (Ref: NIHR160813)	£2,061,658.51

v. ROLE OF TRIAL SPONSOR AND FUNDER

The Sponsor (Keele University) is responsible for the initiation, management and financing of the trial as defined by The Medicines for Human Use (Clinical Trials) Regulations 2004 and any subsequent amendments. Trial management is delegated to the CI and to Keele CTU as detailed below and in Keele University Health and Social Care Research (HSCR) QMS (Quality Management System) and TEM03 CTIMP Delegation of Sponsorship Functions agreement.

vi. ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITTEES/GROUPS & INDIVIDUALS

Chief Investigator (CI): The CI takes primary responsibility for 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. The Associate Investigator (AI) assists the CI, by delegation, where appropriate. Professor Edward Roddy was awarded the grant and was

Chief Investigator from 1st January 2025 until 11th April 2025, when Professor Roddy was succeeded by Professor Mark Lambie. Professor Roddy remains as a Co-Investigator, supporting the CI.

Trial Management Group (TMG): the TMG, comprising the CI, Keele CTU team, other key internal members of staff and external collaborators 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 TMG is responsible for:

- review progress against pre-agreed timelines and milestones (e.g. obtaining regulatory approvals; study set-up; recruitment and retention of participants in the trial)
- receive and discuss reports from the trial statistician
- discuss and agree any trial amendments required
- discuss and monitor any non-compliance and agree any required corrective and preventative actions
- monitor and report any Adverse or Serious Adverse Events
- discuss any issues related to staffing and delivery of research
- ensure clear communication between collaborators
- plan meetings with the TSC and DMC
- ensure timely preparation of progress reports
- discuss and monitor spending plans together with the Finance Manager from Keele University
- discuss action plans for disseminating and implementing research outputs.

Trial Steering Committee (TSC): the TSC will provide independent supervision of the trial, in particular trial progress, adherence to protocol, participant safety and consideration of new information. It will include an Independent Chair and not less than two other independent members. The CI and other members of the TMG may attend the TSC meetings and present and report progress. The TSC will meet at least annually as a minimum.

Data Monitoring Committee (DMC): the DMC is an independent group who will review the safety of the trial by reviewing interim data during recruitment. The DMC will convene on a regular basis throughout the trial and in advance of the TSC meetings. Reports from this committee will be fed into the TSC.

Keele Clinical Trials Unit (CTU): The trial is fully supported by Keele CTU, a UKCRC registered CTU. An experienced Trials Manager at Keele CTU will be responsible for day-to-day trial management, supported by a CTU Senior Trials Manager, a data management team and affiliated statisticians. Keele CTU will be responsible for trial management as detailed in TEM03 CTIMP Delegation of Sponsorship Functions agreement.

Regional Research Delivery Networks (RRDNs): The lead Regional Research Delivery Network (RRDN) for the delivery of the trial will be West Midlands (WM). Their remit along with the other RRDNs will involve the identification of participating sites and associated activities involved in site set-up and the recruitment of eligible participants. All RRDNs involved in the trial will provide funding for staff resources to secure the additional clinical time associated with service support to embed the study into general practice sites to allow identification of suitable and potentially eligible participants.

Our experience of working with RRDNs, includes receiving valuable advice and feedback on the feasibility of planned recruitment methods, and on efficient ways of securing Network infrastructure and service support. To secure timely delivery of research, RRDN representatives will also be invited to attend relevant TMG meetings.

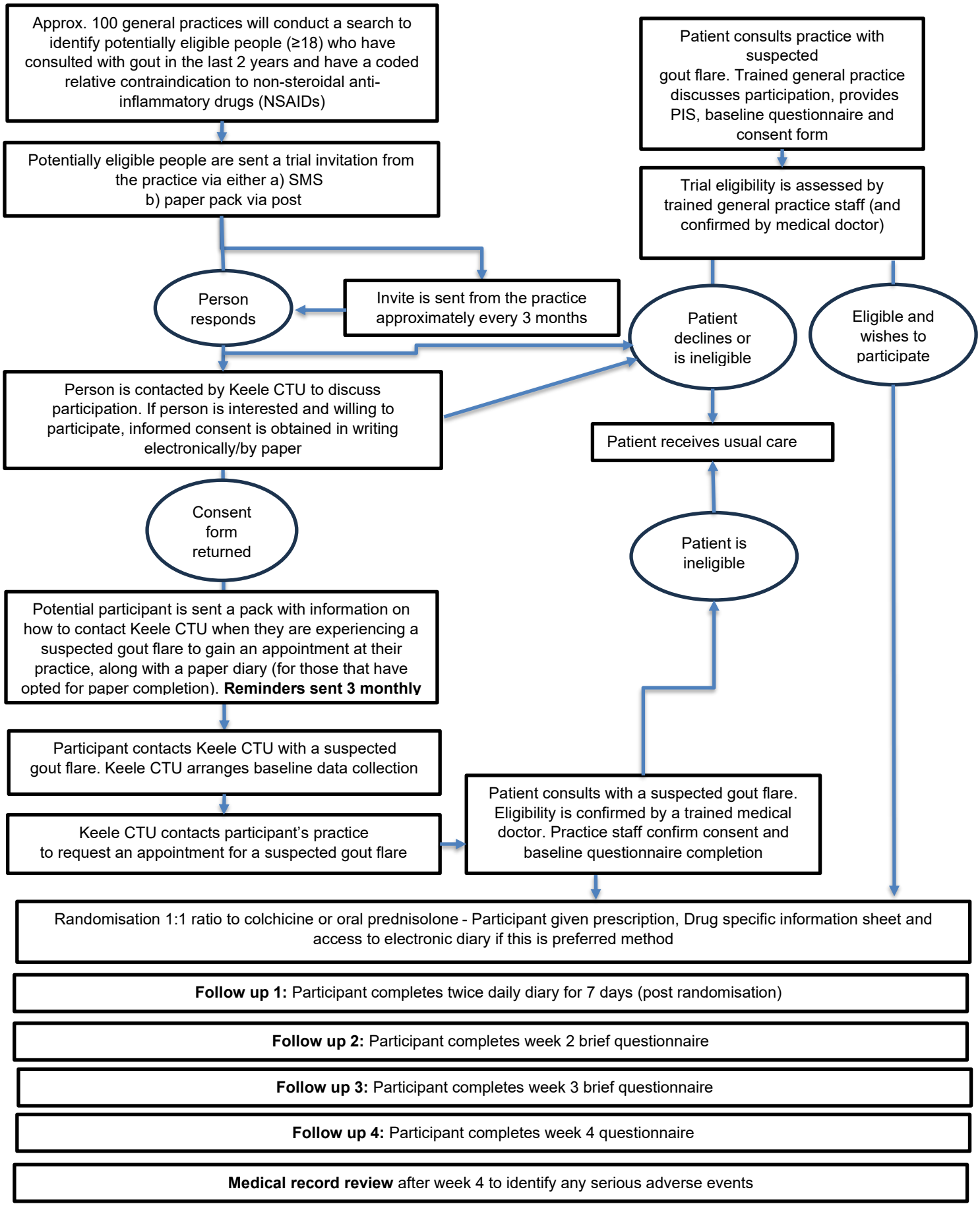
Local Principal Investigator (PI): The local PI is responsible for the conduct and leadership of the trial at their site as detailed in the applicable Sponsor-Site Agreement available in the Investigator Site File and ensuring the trial is run at their site in accordance with the GCP principles as detailed in the UK Medicines for Human Use (Clinical Trials) Regulations 2004 and any subsequent amendments. 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 and safety reporting.

Other collaborators: University of Nottingham, University of Southampton and Midlands Partnership University NHS Foundation Trust, will have responsibilities as described in the Collaboration agreement and in accordance with relevant GCP standards.

vii. KEY WORDS:

Gout, primary care, clinical trial, flares, colchicine, prednisolone

x. TRIAL FLOW CHART



1 BACKGROUND

Gout affects 2.5% of adults in the UK and causes significant pain, disability and impaired health-related quality of life.[1,2] Its prevalence and incidence are rising and it associates with significant comorbidity.[3] It places a significant burden on healthcare resources, causing >250,000 general practice (GP) consultations in England and Wales in 2007.[4] Hospital admissions for gout in England rose by 59% from 2006 to 2017 (7.9 to 12.5/100,000 population).[5]

Gout pathogenesis is well-understood. Elevated serum urate (hyperuricaemia) causes formation of monosodium urate crystals in and around joints. Crystals provoke an intense inflammatory response, manifesting as recurrent flares of excruciating joint pain and swelling, most commonly affecting the big toe. People with gout liken the severity of pain to childbirth or myocardial infarction.[6] Flares require rapid treatment with non-steroidal anti-inflammatory drugs (NSAIDs), colchicine or corticosteroids, typically resolving over 1-2 weeks.[7,8] Existing randomised controlled trials (RCTs), including our NIHR-funded CONTACT trial, show comparable effectiveness of NSAIDs to colchicine [9,10] and oral corticosteroids [11-14] for gout flares. However, there is no direct comparison of the effectiveness and safety of colchicine and corticosteroids.

Our CONTACT trial did not find a difference in pain reduction between naproxen and colchicine for managing gout flares in an unselected population, although colchicine use even for a short period was associated with a high incidence of diarrhoea.(10) NSAIDs are the most frequently used treatment for gout flares,[15] however, relative contraindications to NSAIDs such as older age, chronic kidney disease (CKD), taking anticoagulants, asthma, peptic ulcer disease, hypertension, cardiovascular disease, heart failure, or cerebrovascular disease [16] are common in people with gout. The prevalences of hypertension, CKD stage ≥3, coronary heart disease, and heart failure in people with gout in our recent primary care cohort study were 40%, 30%, 15% and 5% respectively.[3] Serious and potentially life-threatening harms from NSAIDs are frequent but they remain commonly used in high-risk people.[17] They account for 30% of hospital admissions for adverse drug reactions,[18] doubling the risk of acute kidney injury in people aged over 65 years and heart failure and increasing risk of cardiovascular events.[19,20]

Since NSAIDs are widely available, including over the counter, they are commonly used as a reasonable first-line treatment option for gout flares in those without contraindications.[15] Given the high prevalence of contraindications to NSAIDs such as CKD in people with gout [16], the high incidence of diarrhoea following colchicine treatment [21], and the lack of RCT evidence comparing corticosteroids and colchicine, establishing the effectiveness, safety and cost-effectiveness of corticosteroids compared with colchicine in those who cannot have NSAIDs will inform treatment decisions in those people in whom this evidence is most needed.

This study was designed in response to a NIHR HTA commissioned call to fund a RCT comparing either a NSAID or oral corticosteroids with colchicine in people having a gout flare who have relative contraindications to commonly used treatments. We proposed a trial comparing oral corticosteroids and colchicine in people having a gout flare who have relative contraindications to NSAIDs (including people with CKD). The literature reviews for the 2020 American College of Rheumatology (ACR) and 2022 National Institute for Health and Care Excellence (NICE) gout guidelines identified no direct randomised comparisons of corticosteroids and colchicine for flares,[8,22] and in the ACR guideline network meta-analysis, indirect estimates of their relative effectiveness were imprecise (standardised mean difference 0.27 (95% confidence interval -0.31, 0.86); low certainty of evidence).[23] The ongoing non-inferiority COPAGO trial is comparing the effectiveness of oral prednisolone and colchicine for gout flares in a population that is not restricted to those with contraindications to NSAIDs [24].

The OCCUR (**O**ral **C**orticosteroids and **C**olchicine for the treatment of go**U**t fla**R**es) trial will compare the clinical and cost-effectiveness of oral prednisolone and colchicine for gout flares in people who should not

receive NSAIDs, the clinical population for whom this question is most relevant since NSAIDs are the most commonly used treatment for gout flares [15] but contraindications to NSAIDs are common in people with gout.[3,16]

2 RESEARCH QUESTION

What is the clinical and cost-effectiveness of oral prednisolone versus colchicine in people currently experiencing a gout flare who have relative contraindications to NSAIDs?

3 OBJECTIVES

3.1 Primary objective

To compare the effectiveness of oral prednisolone and colchicine at reducing pain in people with a gout flare and relative contraindications to NSAIDs.

3.1.1 Secondary objectives

1 To compare the effect of oral prednisolone and colchicine on self-reported:

- change in pain intensity from baseline
- joint swelling
- joint tenderness
- treatment side-effects
- treatment adherence
- treatment satisfaction
- physical function
- quality of life
- global assessment of treatment response
- flare relapse/recurrence (defined as recurrence after 48 hours without a flare)
- sleep
- use of walking aids
- analgesic use
- healthcare utilisation
- work/education absence

2 To compare the cost-effectiveness of oral prednisolone and colchicine.

4 TRIAL DESIGN

A multicentre pragmatic randomised open-label two-arm parallel group superiority trial, with 12-month health economic evaluation and 12-month internal pilot. Our research methods have been designed to, where possible, include strategies such as providing information electronically to reduce carbon emissions

from buildings, consumables and from travel, without adversely impacting on the validity and reliability of the research.

5 TRIAL SETTING

This multicentre trial will be based within the National Health Service (NHS) primary care setting within the United Kingdom (UK). We will recruit from approximately 100 general practices nationally, including populations traditionally underserved in research and broad ethnic diversity by recruiting from inner city, suburban and rural locations.

6 PARTICIPANT ELIGIBILITY CRITERIA

6.1 Inclusion criteria

- Aged ≥18 years.
- Current clinician-diagnosed gout flare.
- Fulfils Gaffo flare criteria, a validated definition of a gout flare requiring three out of four of patient-defined flare (or clinician-defined flare if the patient had not had gout previously):
    - pain score at rest of >3 on a 0–10 numeric rating score (NRS),
    - at least one swollen joint, and at least one warm joint [25]
- Contraindication/caution to NSAIDs. At least one of:
    - age≥65 years [26]
    - known estimated glomerular filtration (eGFR) <60 ml/min/1.73m^2
    - prescribed anticoagulants
    - allergy to aspirin or NSAID
    - physician diagnosed
        - asthma
        - peptic ulcer disease
        - hypertension
        - cardiovascular disease
        - heart failure
        - cerebrovascular disease [16]

6.2 Exclusion criteria

- Known eGFR<15 ml/min/1.73m^2 [27], or undergoing dialysis
- Solid organ transplant recipients
- Poorly controlled diabetes mellitus, defined as glycated haemoglobin (IFCC HbA1c) >64mmol/mol [28]
- Current active infection

- Known blood dyscrasias
- Severe hepatic impairment
- Previous intolerance of or hypersensitivity to prednisolone or colchicine (or excipients)
- Taken prednisolone or colchicine for a gout flare in the previous 72 hours
- Currently prescribed prednisolone for another indication
- Currently prescribed verapamil, diltiazem, macrolides, HIV protease inhibitors, Azole anti-fungals or ciclosporin
- Known galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption
- Pregnancy or Breastfeeding
- Women of childbearing potential unless using effective contraceptive measures. *
- Unable or unwilling to provide informed consent
- Has been randomised in the trial for a previous flare
- Currently taking part in another gout CTIMP

** Contraceptive methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods.*

7 RECRUITMENT

7.1 Participant recruitment

We have a track-record of successfully recruiting people with gout to clinical trials in primary care, evident from our previous successful NIHR-funded multisite primary care-based CONTACT trial of NSAID versus colchicine for gout flares [10] and our current NIHR HTA-funded T2T trial In CONTACT, we recruited 399 people having a gout flare over 24 months from 100 general practices, with 87% retention at 1 and 4 weeks. In view of current NHS pressures on primary care, we have modified the CONTACT recruitment protocol to streamline the entry of potential participants into the OCCUR trial, reduce the burden on practices, and ensure compatibility with remote consultation methods, which remain widely used post-COVID-19 pandemic. It seems likely that people known to have gout and having a recurrent flare, who made up 78% of CONTACT trial participants [10], may be more likely to be offered a remote consultation for a gout flare in usual practice.

Deprivation and ethnicity are known to have differential impacts on gout and, therefore, related conditions such as chronic kidney disease are likely to be more prevalent in our target population. [29-33] Our trial recruitment processes have, therefore, been informed by completion of the INCLUDE Framework. We will encourage participation of those in hard-to-reach groups and traditionally under-served by research. For example, we will recruit via the Deep End Research Alliance (DERA) Sheffield Research Delivery network (9 practices in Sheffield's most marginalised communities, 68,000 population), which has strong links to ethnic minority and underserved communities across South Yorkshire and Humber, including members from South Asian, Black African and Caribbean Communities, and engages community research link workers to ensure culturally appropriate research and research team diversity.[34].

General practices will be identified with support from the Regional Research Delivery Networks (RRDNs) in each of the areas.

We will supplement the Participant information sheet with a short animation which summarises the information to reach those with varying health literacy levels, this will be hosted on the trial website and the link will be provided in the initial invitation. Participants will have the option to complete electronic or paper questionnaires to avoid digital exclusion. Patient-facing materials will also be translated into other languages, as required.

7.2 Trial Training Participating site staff will receive specific training to administer trial procedures. This training will cover trial specific processes and relevant aspects of GCP, including informed consent and data management. To maintain a pragmatic approach and to accommodate the preferences of individual practices, the primary care healthcare professional may be a GP or another suitably qualified healthcare professional of the practice team who typically manages patients with gout. The eligibility assessment will be signed off by a medically qualified doctor and the prescription issued by a healthcare professional that is authorised to do so. We will collaborate closely with each participating site to identify and train all relevant staff deemed appropriate for this role.

All trained participating site staff will be documented on the delegation log and formally authorised to carry out the specified trial activities.

Keele CTU staff working on the trial will receive specific training on the trial protocol, relevant aspects of GCP and data management. Keele CTU staff taking part in the informed consent process will have received specific informed consent training and will be authorised in the trial delegation log and permitted to take informed consent.

The training will be supplemented by trial specific working instructions providing clear guidance for completing trial paperwork. Case Report Forms to capture data will be regularly monitored against the protocol. Individual feedback will be given to participating sites if required. Refresher training will also be offered where needed.

7.3 Participant identification and screening

7.3.1 METHOD 1

General practices that have agreed to take part will run a trial-designed clinical system search to identify people aged 18 years and over who have had a SNOMED CT code for gout in the preceding two years and who are potentially eligible for the trial. The search will automatically exclude anyone who has an active SNOMED CT code indicating dissent from receiving research invitations. The general practice will then contact potentially eligible participants via SMS text message (using the GP practice 'usual' text service) and/or postal invitation. A SMS will contain a secure web link, which once clicked, will take the potential participant to a landing page where the invitation to participate will be available with links to an online Participant Information Sheet (PIS) a short animation and an online reply form.

Postal invitations will include an invitation letter, PIS, a reply form for return by post to Keele CTU (with a pre-paid return envelope) and access to online participation. Potentially eligible participants need to complete and submit/return the reply form to express their interest in taking part or not and to provide their consent to be contacted by Keele CTU.

Potentially eligible participants that receive an invitation via SMS but who are unable or unwilling to complete this online will be able to opt for postal completion by contacting Keele CTU.

Participating sites will either upload pseudonymised data to REDCap or send a pseudonymised file, via secure transfer, to Keele CTU for upload upon sending invites. These files are to include the NHS ODS Organisational Code, invite date and method of invitation for each person sent an invitation to take part in

the trial, plus NHS number, age, and sex. When reply forms are received into the CTU (online or paper) the information will be matched to the corresponding NHS number from the import to ensure that the correct person is taking part in the trial and allows reminders to be sent from the sites to the correct people. NHS numbers of individuals that do not respond to the trial invitation will be securely deleted.

This invitation will be sent at approximately three-monthly intervals during the recruitment period to inform any new potentially eligible participants and to remind anyone that has not responded that the trial is taking place. This invitation will exclude those who have already consented to participate or have returned a reply form to indicate their opt-out. A list of NHS numbers of those that have responded or opted out will be provided to the participating site via secure access/ file transfer so that they can be excluded from any reminder mailings.

If the potential participant has agreed to further contact but has not provided a contact telephone number or other necessary information for them to proceed, a missing information letter will be sent by postal mailing, stating that if they are interested in participating to either contact Keele CTU or return their details on the form in the prepaid envelope provided.

Potentially eligible participants who return a reply form and have given their consent to be contacted will be contacted by trained and authorised CTU staff to discuss their participation and to be given the opportunity to ask questions. If contact is unsuccessful, then they will be advised to contact Keele CTU if they are still interested in participating. If they are interested and willing to participate, they will then be asked to provide their consent in writing either electronically or by returning a paper consent form in the post to Keele CTU.

Where confirmation of consent in writing has not been received within 7 days from the initial consent discussion, contact will be made to remind them to return it. If after a further 5 calls or if 7 days have lapsed from the reminder, the patient has still not returned their written consent, a written reminder will be sent either electronically or by paper. Following the reminder, if written consent has still not been obtained the patient will not receive any further contact.

Consented participants will be sent information on how to contact Keele CTU if they suspect that they are experiencing a gout flare during the 24-month recruitment period. Those that have opted for paper completion will also be sent a 7-day diary but advised not to start to complete this until they have contacted the CTU at the time of a gout flare.

Reminders will be sent 3-monthly along with a gout flare wallet card to remind participants to contact Keele CTU when they suspect they are experiencing a gout flare. These reminders will stop once a participant is randomised, if they opt out of receiving them or if they are found to be subsequently ineligible. The participating site will be asked to inform Keele CTU of any deaths or departures of consented participants.

On the first day of their gout flare, potential participants will be able to contact Keele CTU, continued consent will be discussed and verbally confirmed, and baseline data collection will be obtained electronically or verbally over the telephone. Keele CTU will then notify the participant's general practice to ask them to arrange a trial appointment with the participant, on the same day. If a same day appointment is not possible, an appointment will be made as soon as possible, and it is at the participant's discretion whether they want to continue in the trial or return to usual care. If they do not participate during this flare, then they are able to recontact Keele CTU should they experience another gout flare during the recruitment period.

At the appointment a trained clinical member of staff from the general practice will confirm the participant's identity. Eligibility will be assessed and confirmed by a medically qualified doctor. The trained clinician will then proceed to randomisation and prescription. If the potential participant is deemed to be ineligible at the appointment, the GP practice will continue with usual care and the patient will not continue with trial participation, this will be recorded on CTU Clinical Data Management System (REDCap).

7.3.2 METHOD 2

People experiencing a gout flare who were not identified in the search and who have not received the trial invitation in advance or consented to participate previously, will be invited to participate when they consult a participating general practice for a gout flare. In those general practices where it is feasible, an electronic on-screen “pop-up” reminder will be installed in the electronic patient record system which will remind the general practice clinicians about the trial and eligibility criteria when a gout clinical code is entered. Eligible potential participants will be provided with the Participant Information Sheet when they consult and given time to consider the information prior to agreeing to take part. The general practice clinician will subsequently obtain informed consent to participate and arrange for the baseline questionnaire to be completed either on paper or electronically. Eligibility will be assessed and confirmed by a medically qualified doctor. The trained clinician will then proceed to randomisation and prescription. If the potential participant is deemed to be ineligible at the appointment, the GP practice will continue with usual care and the patient will not continue with trial participation.

Posters may also be displayed in participating practices, to prompt patients to mention the trial during their consultation if they are interested in participating.

For both recruitment methods, the GP of each trial participant will be sent a notification to confirm that their patient is taking part in the trial.

7.4 Recruitment in Primary care

For recruitment method 1, we will work closely with practice staff including administration staff to ensure that patients contacting Keele CTU are offered a same day appointment, where possible. The site training will emphasise this and participating sites will be made aware of this when they sign up to be involved in the trial.

For recruitment method 2, patients will consult at their GP practice in the usual way according to normal NHS clinical attendance procedures. The clinical consultation will take place according to usual practice. In those practices in which it is feasible, an electronic on-screen “pop-up” reminder will be installed on the electronic patient record system which will remind GPs about the study and eligibility criteria when a gout SNOMED CT code is entered. Patients who fulfil trial eligibility criteria will be asked if they wish to be considered for trial participation. Patients who do not wish to take part will receive normal clinical care according to usual practice.

7.5 Informed consent

Due to the pragmatic nature of the trial and to reduce burden on the general practice, we have taken a layered approach to providing trial information to potential participants. For recruitment method 1, potential participants will have two opportunities to discuss their participation with an authorised and trained member of the research team

1. Potential participants who are invited to take part will be sent the PIS for consideration in their own time. A trained and authorised member of the research team will contact potential participants who have returned a reply form to discuss each consent item. Informed consent will then be obtained in writing on paper or electronically and will be countersigned by the research team member.
2. Prior to randomisation at the participating site, a trained and authorised member at the general practice will also discuss and confirm the participant’s consent and capacity to participate.

For recruitment method 2, potentially eligible participants will be provided with the PIS when they consult and will be given time to consider the information prior to agreeing to take part. A trained and authorised member of the general practice will then obtain informed consent to participate, which will be documented electronically or on paper prior to randomisation. Patients will have the opportunity to ask questions about trial involvement.

The rights of a patient refusing participation without giving reasons will be respected. Participants are free to withdraw at any time from the trial without giving reasons and without prejudicing any further treatment. For those that withdraw, we will utilise all data collected up to the point of withdrawal (unless they specify that they do not wish for this to occur) and continue to collect data from their General Practice records for safety reporting purposes. Any intention to utilise such data will be outlined in the consent literature and Participant Information Sheet.

Signed consent forms will be kept by Keele CTU and a copy held by the participating site. A copy will also be sent to the participant electronically/via post, or a copy will be given to them at their appointment for those that attend face to face via method 2. For method 2, the practice will be asked to send a copy to Keele CTU and the original will be kept in the investigator site file.

7.5.1 Loss of capacity following informed consent

Where valid informed consent is obtained from the participant and the participant subsequently becomes unable to provide ongoing informed consent by virtue of physical or mental capacity, 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 analysis and fulfil regulatory requirements for Pharmacovigilance purposes.

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

7.5.2 Consent responsibilities

The Principal Investigator (PI) at each general practice retains overall responsibility for the conduct of research at their site, this includes confirming informed consent from participants at their site.

7.6 Baseline data

Participants will be asked to self-complete a baseline questionnaire either electronically, via paper or over the telephone with an authorised member of the research team. Baseline assessment will include all core domains (pain, joint swelling, joint tenderness, patient global assessment, and physical function) for acute gout (gout flare) trials specified by the Outcome Measures in Rheumatology (OMERACT) group.[39] Baseline data will also be collected on analgesic, allopurinol and febuxostat use, sleep, quality of life, previous gout flares, age at gout diagnosis and affected joints.

7.7 Randomisation

Prior to randomisation, the following must be completed:

- Eligibility assessment
- Informed consent
- Baseline questionnaire

Randomisation will be undertaken by authorised personnel (PI or a delegated person) via the CTU Clinical Data Management System (REDCap). This is a secure web-based data collection system that uses a randomisation module; the randomisation sequence will be computer-generated. The following information will be required for randomisation:

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

Stratification factors: geographical region, first gout flare(Y/N), CKD

7.8.1 Method of implementing the randomisation/allocation sequence

Participants will be randomised individually in a 1:1 ratio (stratified by geographical region, first gout flare, CKD) to oral prednisolone or colchicine. The interventions will then be administered as described below by the general practice clinician, including a routine NHS prescription for oral prednisolone or colchicine.

7.8.2 Back up randomisation procedure

If, during office hours, the general practice is unable to access the Clinical Data Management System to perform randomisation, the site will be instructed to call Keele CTU and an authorised member of the CTU will access the randomisation tool to perform randomisation and inform the participating site of allocation. If this occurs outside of office hours, the practice will continue with usual care for the patient, and they will not be included in the trial.

Confirmation of the participants' randomisation allocation will also be sent electronically to the participating site.

7.9 Blinding

In this open label trial, participants and treating clinicians will not be blind to treatment allocation. The Participant Information Sheet and staff training will emphasise equipoise to minimise expectation bias in patient-reported outcomes. The lead trial statistician will remain blind to treatment allocation until all data collection and the main intention-to-treat analyses of clinical effectiveness at 4 weeks have been completed. To ensure they remain blind to treatment allocation, there will be an unblinded trial statistician who will be allocated role permissions within the Clinical Data Management Systems. The blinded statistician will not be permitted to access data which would result in unblinding.

8 TRIAL TREATMENTS

8.1 Name and description of investigational medicinal product(s)

8.1.1 Prednisolone

We have chosen prednisolone as the oral corticosteroid as (i) in our anecdotal experience from primary and secondary care, it is the most commonly used oral corticosteroid to treat gout flares, (ii) it is very commonly used in primary care to treat acute exacerbations of other inflammatory conditions such as chronic obstructive pulmonary disease (COPD) and asthma, (iii) there are published RCTs supporting its effectiveness for gout flares [11-14], (iv) it is recommended to treat gout flares in international gout

management guidelines [35] and (v) GPs are used to prescribing this drug and are aware of the risks/benefits. In four RCTs demonstrating similar effectiveness of oral prednisolone to an NSAID in people with gout flares, two trials used 30mg daily for five days [12,13] and two 35mg daily (one for five days, one for four days) [11,14] Adverse event rates were low in all studies and none were serious. Our PPIE group had no preference for either dose. We have opted for the lower 30mg dose to minimise possible side-effects and since this is a typical dose used in primary care to treat other inflammatory conditions such as COPD/asthma/ exacerbations.

Composition: Supplied as Prednisolone 5mg tablets

Supplier details: this is an off-the-shelf product and has a marketing authorisation in the UK. Although prednisolone does not have a specific marketing authorisation for gout flares, it is widely used in clinical practice to treat a wide range of inflammatory conditions including rheumatic disorders and gout and is recommended to treat gout flares in the British Society for Rheumatology (BSR), European Alliance of Associations for Rheumatology (EULAR) and NICE gout management guidelines [7,22,35]. Please refer to the trial's supplied summary of product characteristics (SPC).

Route of administration: Tablet – oral use

Dose: 30mg (Six 5mg tablets) taken once daily for five days.

PLEASE NOTE: Co-prescription of a proton-pump inhibitor will be at the clinician's discretion.

8.1.2 Colchicine

This medicinal product will be used as recommended in the British National Formulary (BNF) and BSR gout guideline and similar to the dose used in our CONTACT trial. [7,10,36]

Composition: Supplied as Colchicine 0.5mg 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's supplied SPC.

Route of administration: Tablet – oral use

Dose: 0.5mg three times daily for four days (twice daily if aged ≥70 years or known GFR 15-29), consistent with the dose range 0.5mg two to four times daily (maximum total 6mg per course). This dose differs from that stipulated in the trial's SPC but corresponds to the recommended dose in both the BNF and BSR gout management guideline [7,25] and is widely used in primary care.

PLEASE NOTE: Participants prescribed a statin will be advised to omit the statin for the duration of colchicine treatment, as per usual clinical practice. Statins are a relative contraindication to prescribing colchicine but when statins are stopped for a short period of a few days, we consider this will not impact significantly on long-term cardiovascular risk status and is in line with what we previously did with the CONTACT trial [10]

8.2 Drug storage, labelling and supply

All medicines management will be controlled within the NHS. Participants will be issued with a prescription from a General Practice clinician for either of the trial drugs for them to collect from a community pharmacy (as per usual 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 usual care.

8.3 Treatment delivery

Participants will be randomised during their consultation to receive either a five-day course of oral prednisolone 30mg once daily (six 5mg tablets once daily) or a four-day course of Colchicine 0.5mg three times daily (twice daily if aged ≥70 years or known GFR 15-29), as per BNF guidance. The General Practice will issue a prescription to the participant for the trial drug that they have been randomised to receive. The participant will collect this from their preferred pharmacy (as per usual care). Participants will be provided with an expense claim form 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 general practice clinician will be blind to treatment allocation. This approach is in line with the Consort statement extension relating specifically to pragmatic trials [37] and will maximise the applicability of the trial results to usual clinical care by replicating as closely as possible the delivery of these interventions in normal practice. One potential source of bias in the trial may relate to General Practitioner and patient prior beliefs about the two medications. In order to address this, we will provide trial specific training for participating general practices, and participants in both arms will be given a drug-specific information sheet, which will also contain general advice about non-pharmacological treatment (rest, application of topical ice to the affected joint). Existing urate-lowering therapy such as allopurinol or febuxostat will be continued in both groups, as will all other usual care. Additional treatment is permitted, as per usual care.

8.4 Cross over between trial arms

Participants cannot be crossed-over from one arm of the trial to the other during their participation in the trial. At the end of their 4-week participation, they will return to usual care and cannot be randomised again for another flare. If the intervention needs to be discontinued, participants will remain in the trial according to the principle of intention-to-treat unless the participant wishes to withdraw.

8.5 Known drug reactions and interaction with other therapies

Co-prescription of a proton-pump inhibitor for participants randomised to prednisolone will be at the clinician's discretion.

Colchicine interacts with a number of medications. As described above (Section 6), because of interactions with verapamil and diltiazem, people taking these medications will not be eligible to participate in the trial. Participants prescribed a statin who are randomised to colchicine will be advised to omit the statin for the duration of colchicine treatment, as per usual clinical practice and as advised in our CONTACT trial [10], which we consider will not impact significantly on long-term cardiovascular risk status.

8.6 Concomitant medication

Existing urate-lowering therapy such as allopurinol or febuxostat will be continued in both groups, as will all other usual care.

8.7 Assessment and management of risk

It is considered that there are minimal risks to patients associated with their participation in this study as both medicines are to be applied in accordance with usual well established clinical care and recommendations in NICE and BSR gout management guidelines [7,22] and are commercially available for use during gout flares.

Prednisolone and colchicine have well-understood safety, and the occurrence of severe side-effects is uncommon, therefore the incidence of SAEs is expected to be low in this patient population.

A full trial-specific risk assessment has been conducted in accordance with Keele University HSCR QMS. The trial risk assessment will be reviewed regularly by the CI to ensure the document is still current and the implementation of mitigations have been conducted as necessary. This trial has been assessed and meets the definition of a Type A trial, (no higher than the risk of standard medical care) following CTIMP classification by the CI and completion of the trial specific risk assessment.

9 TRIAL DATA COLLECTION

9.1 Outcome assessments

Data will be collected at baseline, prior to randomisation, twice daily during days 1-7, and at weeks 2, 3 and 4 (see table 1 for timepoints for each outcome).

Outcomes will be collected electronically or via paper diary (during days 1-7), as per participant preference. Those expressing preference for paper data collection will be sent a paper diary, along with a pre-paid envelope, following completion of informed consent. If they have misplaced the diary, participants will have the opportunity to obtain another if their appointment is face-to-face at the general practice or they can contact Keele CTU for a replacement.

Participants preferring to complete an electronic diary will receive a twice daily SMS/email containing a URL link to enable secure data collection during days one to seven.

All participants will be sent a postcard (via post or electronically) during week 1 to optimise completion. If diary data has notbeen received by approximately day 8 , participants will be contacted by telephone by a member of the trial team (who is blind to treatment allocation) as a courtesy call and(to attempt to capture key outcome data (worst pain intensity, patient global assessment of treatment response, and treatment side-effects).

Brief questionnaires will also be sent at weeks 2 and 3 to capture key outcome data.

Participants preferring to complete online data collection will then be sent a 4 week follow up questionnaire electronically. Non-responders to the questionnaire will be sent a reminder after 1 week. Those who do not respond to this reminder will be sent a further reminder 2 weeks after the initial questionnaire was sent.

Participants preferring to complete postal data collection will then be sent a 4 week follow up questionnaire in the post. Non-responders to the questionnaire will be sent a reminder after 2 weeks. Those who do not respond will be sent a repeat questionnaire 4 weeks after the initial mailing.

This follow-up procedure has been used successfully in our previous trials at Keele CTU [10,38,39].

Those who do not respond to the second reminder (postal or electronic) regarding the 4-week questionnaire will be telephoned by a member of the trial team, to attempt to capture the key outcome data. However, if after 5 phone call attempts or if a further 2 weeks have lapsed, then a paper 4 week follow up short questionnaire will be sent to the participant to try to capture key outcome data. Non-responders to the 4-week follow-up short questionnaire will not be contacted again regarding follow-up data collection.

Owing to differences in speed of delivery, the time between postal reminders is purposely longer than those that receive electronic reminders. Participants who choose online data collection will complete their diary and questionnaires electronically. These will be recorded in the CTU Clinical Data Management System (REDCap). Appropriate field validation will be added to ensure expected data is provided. Participants who prefer paper-based data collection will be asked to return their completed diary and questionnaires to Keele CTU using a pre-paid envelope. Upon receipt, the documents will be reviewed by CTU trial staff before

being entered into the REDCap system. Data will be reviewed by Keele CTU staff in line with the Trial specific monitoring plan.

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

9.1.1 Primary outcome

The primary outcome will be change in pain intensity from baseline over days 1-7, agreed with the PPIE group. Participants will rate worst pain intensity experienced in the last 12 hours (0-10 NRS).

9.1.2 Secondary outcomes

Secondary outcomes will be:

- pain intensity (worst pain intensity experienced in the last 12 hours (0-10 NRS))
- swelling and tenderness
- treatment side-effects
- adherence and treatment satisfaction
- physical function (Health Assessment Questionnaire-Disability Index [40])
- quality of life (EQ-5D-5-L [41])
- participant global assessment of treatment response
- flare relapse/recurrence
- sleep
- use of walking aids
- use of analgesics
- health care utilisation
- work/education absence

Outcomes include all core domains (pain, joint swelling, joint tenderness, patient global assessment, and activity limitation) for acute gout (gout flare) trials specified by the Outcome Measures in Rheumatology (OMERACT) group.[42]

Table 1: Data collection and timepoints

Measure	Description	Prior to start of recruitment	Baseline	General Practice consultation	Day 1 – 6	Day 7	Week 2	Week 3	Week 4	Minimum data
Participant identification	GP system search and report / pop up	✓		✓						
Informed consent confirmed	Performed at participating site			✓						
Eligibility assessment	Performed at participating site			✓						
Comorbidities	Performed at participating site			✓						
Web-based randomisation	Performed at participating site			✓						
Pain	Self-reported worst gout pain intensity experienced in the last 12 hours (0-10 NRS)		✓		✓	✓	✓	✓	✓	✓
First gout flare	Self-report Yes/No		✓							
Age at gout diagnosis	Self-report		✓							
Affected joints	Self-report body manikin		✓							
Joint tenderness	Self-report Likert scale		✓		✓	✓	✓	✓	✓	

Measure	Description	Prior to start of recruitment	Baseline	General Practice consultation	Day 1 – 6	Day 7	Week 2	Week 3	Week 4	Minimum data
Joint swelling	Self-report Likert scale		✓		✓	✓	✓	✓	✓	
Allopurinol and Febuxostat use	Self-report Yes/No		✓							
Analgesic use	Self-report from a list		✓		✓	✓	✓	✓	✓	
Sleep	Self-report		✓		✓	✓			✓	
Physical function/activity limitation	Self-report Health Assessment Questionnaire-Disability Index (-DI)		✓			✓			✓	
Use of walking aids	Self-report HAQ-DI		✓			✓			✓	
Quality of life	Self-report EQ-5D 5-L		✓			✓			✓	
Side-effects	Self -report from a list				✓	✓	✓	✓	✓	✓
Time elapsed between symptom onset and starting trial medication	Self-report from a list				✓					
Treatment adherence	Self-report from a list				✓	✓	✓	✓	✓	
Treatment satisfaction	Self-report 5-point scale from ‘very satisfied to ‘not at all satisfied’					✓			✓	

Measure	Description	Prior to start of recruitment	Baseline	General Practice consultation	Day 1 – 6	Day 7	Week 2	Week 3	Week 4	Minimum data
Participant global assessment of response to treatment	Self-report 6-point scale from ‘completely better now’ to ‘much worse now’					✓			✓	✓
Healthcare utilisation	Self-report								✓	
Work/education absence	Self-report								✓	
Gout flare relapse/recurrence	Self-report								✓	
Medical record review	Performed at participating site								✓	

9.2 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 treating clinician or the participant 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 (electronically or postally). If a participant discontinues from the trial intervention for any reason, an opt-out CRF (Case Report Form) to indicate early cessation of trial treatment must be completed within 7 days of the site research team becoming aware of this.

Participants will be free to opt-out/withdraw from the research at any time without giving reasons and without affecting their care. If the participant is willing to give a reason, then this reason will be recorded.

Participants may also be withdrawn at the discretion of the local Principal Investigator, if it is considered to be in their best interests. The participants will be made aware that withdrawal will not affect their future care.

The PI should make every effort to ensure that the specific wishes of the participant who wishes to withdraw consent for further involvement in the trial are defined and documented using the Opt-Out/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 participants 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.

9.3 End of trial

The end of the trial is defined as the date on which all data collection (as defined within the protocol) is complete. The CI will notify the REC and MHRA of the end of the trial within 90 days of trial completion, or 15 days if the study is terminated prematurely. The Chief Investigator (or their delegate) will inform participants in the event of the premature study closure and ensure that the appropriate follow-up is arranged for all participants involved. The end of study notification will be reported to the Sponsor, REC and MHRA. A Final Summary Report of the study will be provided to the REC and MHRA within 1 year of the end of the research.

Please refer to Section 18 for details of the trial archiving requirements.

10 INTERNAL PILOT STUDY

We will undertake a 12-month internal pilot to test participant screening, invitation, recruitment and follow-up. Recruitment will continue during this time.

10.1 Objectives

- to check the numbers of participants recruited overall by month 12 and per month.
- to determine the percentage of overall pain score responses completed during days 1-7.

10.2 Methods

The internal pilot will last for 12 months, commencing from the start of recruitment. Data collection methods will be identical to the main trial as described above.

10.3 Outcomes

- numbers of participants with a gout flare recruited overall by month 12 and per month
- percentage of overall pain score responses completed during days 1-7.

10.4 Sample size

Sixty-six participants are required to estimate the crude overall pain score response rate over 1-7 days follow-up with at least 95% confidence (lower limit 1-sided alpha 0.05) with a 2-3% margin of error, assuming a crude overall response rate of about 80%.

10.5 Progression criteria

A success criteria traffic-light system relating to the internal pilot trial objectives will be used to inform whether to stop, proceed to the main trial, or proceed but with protocol amendment(s) (see table 2).

Table 2. Progression criteria for the internal pilot

Progression criteria	Do not proceed to main trial	Proceed to main trial with protocol amendment(s)	Proceed to main trial
Overall recruitment by month 12	n<66 (<50%)	n=66-131 (50-99%)	n≥132 (100%)
Number recruited per month[a]	n<6	n=6-11	n≥12
Percentage of overall pain score responses completed during days 1-7	<50%[b]	51-79%[b]	>80%[bc]

[a] in months 4-12 of internal pilot to allow for phased in recruitment over months 1-4

[b] percentage completed of overall pain score responses sent by 12 months

[c] 80% is the response required by the main sample size calculation (denominator number is 1848, i.e. 132 internal pilot participants invited to complete 14 pain score assessments each)

11 PHARMACOVIGILANCE

11.1 General definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant.

	The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions. It is important to note that this is entirely separate to the known side effects listed in the SPC. It is specifically a temporal relationship between taking the drug, the half-life, and the time of the event or any valid alternative etiology that would explain the event.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" 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 were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the reference safety information: • in the case of a product with a marketing authorisation, this could be in the summary of product characteristics (SPC) for that product, so long as it is being used within its licence. If it is being used off label an assessment of the SPCs suitability will need to be undertaken. • in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event,

which may be of relatively minor medical significance. “Seriousness” is the regulatory definition supplied above.

11.2 Recording and reporting of AEs and ARs

AEs and ARs will be recorded for all participants from the commencement of trial intervention up until completion of the 4-week questionnaire. Information about AEs and ARs volunteered by the participant will be collected and recorded in the 7-day diary and in week 2, 3 and 4 follow-up questionnaires. AEs and ARs will also be collected via GP report, participant self-report and during review of participant’s medical records once recruitment and follow-up are complete.

Those occurring over the 4-week follow-up period will be processed, reviewed and reported in accordance with the Medicines for Human Use (Clinical Trials) Regulations and Keele University HSCR SOP for Pharmacovigilance. Both drugs are known to have early side-effects, but it appears unlikely that short courses of either drug would result in side-effects starting after cessation of treatment.

11.3 Recording and reporting of SAEs and SARs and SUSARs

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. Therefore, it is not expected that there will be high numbers of SAEs and SARs in this trial.

SAEs/SARs occurring during the 4-week follow-up period will be identified by participant and clinician report and by a medical record review of the participant’s general practice record after week 4. Those occurring over the 4-week follow-up period will be processed, reviewed and reported in accordance with the Medicines for Human Use (Clinical Trials) Regulations and Keele’s SOP for Pharmacovigilance.

In the first instance, all events must be reviewed and classed by the CI (or Keele delegate) or the local PI (or another medically qualified member of the clinical team approved by the local PI). All suspected SAEs, SARs and SUSARs occurring from the point when participants are randomised in the trial must be notified to Keele CTU within 24 hours of the participating site becoming aware of the event. Staff at the participating site will then access and complete the appropriate Case Report Form (CRF) which must be completed within 24 hours. Any follow-up information should be added to the CRF as it becomes available. Events will be followed up until the event has been resolved or a final outcome has been reached. Only one event will be reported on each CRF (details of multiple symptoms should be listed if they relate to the same event). Any change of condition or other follow-up information should be sent to Keele CTU and escalated to the Sponsor as soon as it is available or at least within 1 working day of the information becoming available.

- For each suspected SAE, SAR or SUSAR 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 and delegated medical doctor. If an authorised medical doctor is unavailable, initial reports without causality assessment should be submitted to Keele CTU within 1 working day but must be followed up with assessment by an authorised medical doctor as soon as possible thereafter.*

11.3.1 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 a gout flare 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.

11.3.2 Pregnancies

If a participant 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 recording, monitoring and follow up to outcome. If a participant becomes pregnant or it becomes known that they were pregnant during trial participation, Keele CTU must be informed within 7 days of the participating site being made aware.

Information relating to participants who become pregnant during trial participation will be collected by the local PI (or delegate) subject to the participant's consent and will be followed up until delivery. Any outcome that could be considered to be a SAE must be reported to Keele CTU.

11.3.3 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 relatedness to IMP. If related to IMP, the protocol and trial approved Reference Safety Information (the SPC) for either Colchicine or Prednisolone (whichever treatment the participant has been allocated) will be used to determine whether an SAR is expected (see Table 2 and 3).

11.3.4 Expected SARs

When determining whether an SAR is expected or not, trial approved Reference Safety Information (the SPC) for either Colchicine or Prednisolone (whichever treatment the participant has been allocated) will be used (see Table 2 and 3). Expected SARs within this trial will not be considered as SUSARs unless the severity or outcome of the event is considered to be unexpected.

Table 2: Expected SARs for Prednisolone in the OCCUR Trial

The reference safety information for Prednisolone will be section 4.8 of the Summary of Product Characteristics, which lists the medical events that define which reactions are expected.

Table 3: Expected SARs for Colchicine in the OCCUR Trial

The reference safety information for Colchicine will be section 4.8 of the Summary of Product Characteristics, which lists the medical events that define which reactions are expected.

11.3.5 SUSARs

All SAEs assigned by the CI or local PI (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 1 working day 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.

11.4 Monitoring of adverse and serious adverse events

Adverse events (AEs) will be monitored via a number of methods:

- self-reported treatment side-effects will be collected from days 1-7 in the diary and at weeks 2, 3 and 4 in follow-up questionnaires. These AEs will be recorded on REDCap
- Participating sites will be required to report all SAEs to Keele CTU within 24 hours of the research staff at the participating site becoming aware of them
- AEs will also be collected via GP report and participant self-report and during review of participant's medical records once recruitment and follow-up are complete.

11.5 Deaths

All deaths occurring up to 4 weeks after randomisation must be notified to Keele CTU within 24 hours of the participating site becoming aware of the event. Each site will be asked to complete the appropriate CRF. Deaths occurring after 4 weeks post-randomisation will not be collected unless related to trial treatment.

11.6 Overdose

All medicines management is controlled within the NHS. As such, any overdose will be managed as per usual care. If overdose is associated with a SAE this will be reported in line with section 11.3.

11.7 Reporting urgent safety measures

If any urgent safety measures are taken the CI, CTU or sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, given written notice to the REC/MHRA of the measures taken and the circumstances giving rise to those measures.

12 PHARMACOVIGILANCE RESPONSIBILITIES

12.1 Local Principal Investigator (GP practice – participating site)

1. Using medical judgement in assigning seriousness, causality and whether the event/reaction was anticipated using the Reference Safety Information approved for the trial.
2. Ensuring that all SAEs are recorded and reported to Keele CTU within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs are chased with Keele CTU if a record of receipt is not received within 2 working days of initial reporting.
3. Ensuring that AEs and ARs are recorded and reported to the sponsor in line with the requirements of the protocol.

12.2 Chief Investigator (or nominated medically qualified individual in CI's absence)

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement in assigning the SAEs seriousness, causality and whether the event was anticipated (in line with the Reference Safety Information) where it has not been possible to obtain local medical assessment.
3. Immediate review of all SUSARs.
4. Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.
5. Assigning Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all SAEs and SARs.
6. Preparing the clinical sections and final sign off the Development Safety Update Report (DSUR).

12.3 Keele CTU

1. Expedited reporting of SUSARs to the MHRA, main REC, DMC and Sponsor within required timelines.
2. Preparing Development Safety Update reports in collaboration with appropriate members of the Trial Management Group 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.

12.4 Sponsor (delegated to CI / CTU)

1. Central data collection and verification of AEs, ARs, SAEs, SARs and SUSARs according to the trial protocol onto a database.
2. Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.
3. Reporting safety information to the independent oversight committees identified for the trial (Data Monitoring Committee (DMC) and / or Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.
4. Expedited reporting of SUSARs to the Competent Authority (MHRA in UK) and REC within required timelines.
5. Notifying Investigators of SUSARs that occur within the trial.
6. Checking for (annually) and notifying PIs of updates to the Reference Safety Information for the trial.
7. Preparing standard tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the MHRA and REC.

12.5 Trial Management Group (TMG)

The TMG, comprising the CI, Keele CTU team, other key internal members of staff and external collaborators involved in the trial have responsibility for the ongoing management of pharmacovigilance in the trial.

12.6 Trial Steering Committee (TSC)

1. The TSC provides overall supervision of the trial in accordance with the Trial Terms of Reference for the TSC.
2. The TSC monitors trial progress and conduct and advise on scientific credibility. The TSC will consider and act, as appropriate, upon the recommendations of the Data Monitoring Committee (DMC) and ultimately carries the responsibility for deciding whether the trial needs to be stopped on grounds of safety or efficacy.

12.7 Data Monitoring Committee (DMC)

1. In accordance with the Trial Terms of Reference for the DMC, periodically reviewing 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.

13 STATISTICS AND DATA ANALYSIS

13.1 Sample size calculation and planned recruitment rate

140 participants per arm are needed to detect a 1-point minimum clinically important between-group difference in overall change in pain from baseline over days 1-7 (90% power; two-tailed significance 5%; follow-up change score SD 3.3; drop-out 20%; 14 repeated follow-up measures in days 1-7; intra-correlation 0.7; baseline-outcome correlation 0.5).[10,43] Unpublished data from the CONTACT trial indicates that the MCID for change in pain is between 1 and 2 points (for which we have taken the lower, more conservative value, which aligns to a 'moderate' standardized effect size of 0.3).

In CONTACT, the crude recruitment rate was 399 over 23 months from 100 GP practices (approximately 0.2 per practice per month (0.2ppm)). The percentage of patients who had any side-effects from use of naproxen in the first week of treatment was 60%. The prevalence of gout has been estimated as 2.5% (incidence as 1.8 per 1000 person-years) in the general UK population [1]. Thus, in a typical UK GP practice size of 10,000 patients (GPonline, 2024) we can expect to have around 200 patients with gout over about 1-2 years. In CONTACT approximately 1-in-10 patients who were mailed an invitation questionnaire were eligible and consented to take part in the study. Although our proposed recruitment methods in this study will expect to identify and increase the mailing pool of potentially eligible patients for the study by comparison to CONTACT, by contrast the additional inclusion criteria of contraindication to NSAIDs will reduce the number (since the study relates to a minority subpopulation of gout patients with contraindication to NSAIDs). We may expect around 1-in-4 gout patients to have potential contraindication to use of naproxen. Thus, we may anticipate around 1-in-40 gout patients will fulfil strict eligibility and give consent to study. We can therefore expect to recruit 5 patients per practice (5ppp) and around 3ppp taking into account staggered recruitment over two years providing the sample size for the study.

13.2 Statistical/Data analysis plan [DAP]

A detailed statistical analysis plan will be agreed with the TSC and DMC. It will be kept as a separate document to this protocol and represents the *a priori* analysis plan. Methods and analysis reporting will follow the statistical guidance provided in the SPIRIT (for protocol) and CONSORT (for trial evaluation) statements. It will be written using standard operating procedures for Keele CTU and an approved version will be signed off by the TSC and DMC. Consequently, only a brief outline of the analysis plan is below.

13.3 Primary outcome analysis

Summary measures to be reported: a descriptive summary of baseline and follow-up data will be presented split by treatment group. Numerical variables will be summarised using mean (standard deviation (SD)), or median (interquartile range (IQR)) if the data are skewed. Summary data will be included for pain change across all follow-up timepoints (including split for day / night) as well as the primary endpoint of average pain change over 1-7 days. We will summarise categorical data using frequency counts and percentages split by treatment group and showing numerator and denominator counts for variables. A CONSORT-style flowchart of target population, recruitment and participant flow through the trial will be presented and reasons for ineligibility, non-participation and withdrawal provided. Follow-up pain NRS trajectories will be presented graphically to show the comparative summary data between treatment arms.

Data on side-effects will be summarised using counts/incidence split by treatment group. The DMC will receive these adverse event data and protocol violations and withdrawals disaggregated by trial arm, prepared by an unblinded trial statistician.

Method of analysis: the main between-group analysis will be by intention-to-treat (ITT) analysing all available data by the treatment arm to which participants are allocated. The primary analysis will estimate the between-group mean difference in change in pain from baseline over days 1-7 by linear mixed model adjusting for age, sex, baseline pain score, geographical region, first gout flare, CKD and including participant identifier as a random factor. Similar ITT mixed model analysis with appropriate link function (for linear or generalised linear mixed model) will be performed to estimate between-group differences for secondary outcomes adjusted for the same baseline covariates plus corresponding baseline score (as appropriate) with participant ID random factor. This is a longitudinal individual patient-level analysis with clustering of follow-up patient data being accounted for in the analysis through inclusion of the random factor for patient ID. For the primary outcome measure, in addition to the primary endpoint of pain change on average over 1-7 days, between-group estimates of pain change at all individual timepoints will be provided through including an interaction term for treatment group x time. Sensitivity analyses will be carried out on the primary outcome measure to check the robustness of the estimates provided by the main analysis. Statistical testing will be carried out on follow-up data only; there will be no formal statistical testing of baseline characteristics by treatment group. For primary and all secondary between-group comparisons of follow up outcome measures, we will provide 95% two-sided confidence intervals with p-values (with between-group differences being presented as mean differences for numerical outcome measures and odds ratios for categorical outcome measures). Final analysis of the primary pain outcome will be carried out independently by two statisticians (including a blinded statistician) following the outlined methodology in the final signed-off DAP document to verify the data estimates and to support scientific integrity.

Plans for handling multiple comparisons, missing data, non-compliers, spurious data and withdrawals in analysis: the primary analysis will estimate the between-group mean difference in change in pain from baseline over days 1-7 by linear mixed model, which models for missingness under a ‘missing at random’ assumption. There is one single pre-defined primary endpoint (pain change on average over 1-7 days follow up) and no interim analysis; hence there will be no multiple comparisons adjustment. In this context, interpretation of the test results of the secondary analyses are to be viewed with this in mind (to provide signals and add to the strength of evidence provided by the main result rather than providing evidence for those measures per se). For the main ITT analysis missing data (including where withdrawn) is handled through the mixed model and available data for non-compliers and protocol violations are used in the analysis. Sensitivity analysis will address intercurrent events including protocol deviations such as non-compliers.

Plans for predefined subgroup analyses: subgroup analysis will be undertaken (for the primary 1-7 days pain change measure) with the decision on most relevant subgroup factors (e.g. with/without diabetes; with/without CKD) to be decided in discussion with the TSC).

Statement regarding use of ITT analysis: As detailed above, the main between-group analysis will be by ITT analysing all available data by the treatment arm to which participants are allocated (analysed as randomised). For any outcome, participants will be included in an analysis if baseline and at least one follow-up measurement is available for that outcome.

13.4 Secondary outcome analysis

Analysis of secondary outcome measures will follow similarly to the analysis of the primary outcome measure (pain change) using ITT mixed model analysis and with appropriate link function for linear or generalised linear mixed models (depending on the data type: numerical or categorical). Adjustment for the same baseline covariates will be undertaken with the addition of the corresponding baseline value if applicable (and including participant ID random factor). Subgroup and sensitivity analyses will not be carried out for the secondary outcome measures (these will be undertaken solely for the primary outcome measure). Summary results will be provided through 95% confidence intervals and p-values will be included (with emphasis on the interpretation of these results being aligned to hypothesis generating rather than providing firm conclusions (by contrast to the main outcome measure).

13.5 Subgroup analyses

Subgroup analyses will explore whether treatment group effect for pain change could potentially be different by pre-specified subgroup factors (e.g. with/without diabetes; with/without CKD; choice of subgroups will be decided in discussion with the TSC). All subgroup variables will be in dichotomised form (any numerical subgroup variables will be dichotomised by a pre-assigned cut-off decided by the TSC). The subgroup analysis will be undertaken through statistical modelling the interaction between treatment group and the subgroup factor (rather than separate statistical models per subgroup category). The subgroup analysis will be undertaken for the primary pain change measure (focused on overall 1-7 days pain change) and will be modelled via the addition of the interaction treatment group x subgroup variable (alongside the corresponding main effect terms) within the statistical model. The model will include the same baseline covariates adjustment as detailed for the primary analysis. A hypothesised direction of effect for these subgroup analyses will be discussed with the TSC and stated in the Statistical Analysis Plan.

13.6 Adjusted analysis

The primary analysis (linear mixed model of pain change) will be carried out adjusting for age, sex, baseline pain score, geographical region, first gout flare, CKD (fixed effect covariates) and including participant identifier as a random factor. Similarly, for secondary outcome measures, the same baseline adjustment variables will be used along with the corresponding baseline value of the secondary measure (if available). Numeric covariates will be included on the numerical scale (age, baseline pain score, corresponding baseline numerical score); categorical covariates will be included in the form of dummy factors. The statistical adjustment for baseline covariates will help improve statistical balance between treatment arms and enhance statistical power of the statistical models.

13.7 Interim analysis and criteria for the premature termination of the trial

There is no planned formal interim analysis. Unblinded data on the primary outcome measure will be shared with the DMC. There are no up-front rules on stopping the trial for futility or superiority. The expectation is that statistical modelling and testing will be carried out at the end of final participant follow up. Upon reviewing the unblinded data, the DMC will have authority to make judgement and suggestion on stopping the trial early on safety concerns or on logistical grounds e.g. very sub-standard recruitment (but there will be no formal interim between-group comparisons). A 12-month internal pilot review of the recruitment and follow-up data will assess at an earlier stage the performance against pre-specified progression criteria for those feasibility measures.

13.8 Procedure(s) to account for missing or spurious data

The linear and generalised mixed models specified above analyse all available data and assume that missingness is 'missing at random' (MAR) rather than 'missing completely at random' (MCAR). A sensitivity analysis will also be conducted using a multiple imputation (MI) approach where missing data due to an intercurrent event will be differently imputed than missing data due to other reasons. The details of the sensitivity analysis will be included in the DAP.

13.9 Health economics analysis

The health economic evaluation will assess the cost-effectiveness of oral prednisolone compared with colchicine over a 4-week period and will be conducted from an NHS and personal social services perspective, following an agreed Health Economics Analysis plan, and adhering to the recommendations of the NICE Reference Case [44].

Resource use information will consider healthcare contacts and medication (including co-prescription of a proton pump inhibitor in the prednisolone arm) and this will be obtained mainly from patient-completed questionnaires. To value resource use data, unit costs from standard sources such as the BNF, Personal Social Services Research Unit (PSSRU) publication on costs and NHS reference costs will be obtained (BNF, 2022) [45]. Total healthcare costs will be calculated by multiplying the resource items by the respective unit cost and summing over all resource use items.

The 5-level version of the EuroQoL-5D (EQ-5D-5L) questionnaire will be used to obtain health-related quality of life data from patients and quality-adjusted life-years (QALYs) estimated for each trial participant,[41] using the area under the curve method. Imbalances in baseline utility (EQ-5D-5L) scores between the two trial arms will be controlled for by using a regression approach. Following best practice, missingness mechanisms in cost and outcomes will be explored, and multiple imputation methods will be used where appropriate.

A within-trial analysis will be conducted following best practices. Initially, a cost-consequences analysis will be conducted to describe important costs and outcomes. Subsequently, a cost-utility analysis with the QALY as the primary outcome will be conducted. Differences in mean costs and QALYs between oral prednisolone and colchicine will be estimated and incremental cost-effectiveness ratios (ICERs) estimated by dividing the difference in mean cost between the trial arms by the difference in mean QALYs.

Non-parametric bootstrapping will be used to illustrate and quantify uncertainty. This will be achieved through a Monte Carlo method involving the simulation of 1000 replications of the ICERs from a joint distribution of incremental costs and incremental QALY. To determine the probability of each intervention being cost-effective, cost-effectiveness acceptability curves will be constructed to show the probability that the interventions are cost-effective, across a range of values that represent a decision makers' willingness-to-pay for an additional QALY.

The base-case analysis will be from an NHS perspective with a sensitivity analysis considering wider societal costs. Although not anticipated to be necessary, more extensive economic modelling using decision analytic methods may be considered in order to extend the time horizon and decision context if costs and QALY profiles are non-convergent. Such modelling will draw upon the best available information from the literature and stakeholder consultations to supplement the trial data.

14 DATA MANAGEMENT

Data management will be carried out in accordance with Keele University HSCR QMS and Keele CTU SOPs. A trial specific data management plan will be developed and maintained by Keele CTU which will outline all the details and information about the processes that will be involved in managing the trial data from beginning to end.

In accordance with Keele CTU SOPs data information flows will be developed to inform data management processes.

Any data breaches will be reported to Keele University's Data Protection Officer (DPO) who will onward report to the relevant authority according to the appropriate timelines if required. If these data breaches also meet the definition of a protocol non-compliance or a potential serious breach, they will also be reported as such.

Any requests for the final trial data set will be managed in accordance with HSCR and Keele CTU SOPs.

14.1 Source Data

Source data should be accurate, legible, contemporaneous, original, attributable, complete, consistent and available when needed. Each data element should only have one original source. For this trial, the (e)CRF's, participant self-completed data and the participants medical record (where this is the first record relating to eligibility or Pharmacovigilance) will be the source data. Further details are outlined within the Data Monitoring Plan (DMP).

15. MONITORING, AUDIT AND INSPECTION

Data will be monitored for quality and completeness by Keele CTU. A Monitoring plan will be developed and agreed by the Trial Management Group. This will be informed by a Trial Risk Assessment which will consider the safety or physical or mental integrity of the trial participants and the scientific value of the research. This monitoring plan will detail the timing and content of reports to monitor trial conduct, implementation, Source Data Verification (SDV) and adherence with the Consolidated standards of Reporting Trials (CONSORT).

Investigators and participating sites involved in this research project will permit related monitoring and audits on behalf of the Sponsor, REC, and regulatory inspection(s). In the event of audit or monitoring, the Investigator agrees to allow the representatives of the Sponsor direct access to all trial records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all trial records and source documentation.

The trial will be managed in accordance with Keele University HSCR and CTU SOPs. The Chief Investigator is responsible for the conduct of the trial and will convene a Trial Management Group. Regular meetings of the TMG will take place throughout the trial. It will oversee the protocol completion, obtaining regulatory approval, site set-up and development of Clinical Data Management Systems. The group will monitor recruitment procedures, review against timelines and complete regulatory reporting requirements. In addition, they will also oversee the analyses and the interpretation of the results. The group will also ensure there is sufficient staffing support available for the trial.

An independent DMC will review the safety of the trial. Detailed blinded reports will be prepared by Keele CTU for the DMC at least annually, as required by the funder, and at the discretion of the TSC/DMC.

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

- rates of occurrences of SAEs, SARs and SUSARs
- rates of AEs deaths.

16 ETHICAL AND REGULATORY CONSIDERATIONS

16.1 Management of protocol non-compliance

The research will be conducted in compliance with this protocol and GCP principles. Deviations from trial protocols and GCP occur commonly in health and social care research. The majority of these instances are technical non-compliances that do not result in harm to the participants and do not compromise data integrity or significantly affect the scientific value of the reported results of the research.

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the Sponsor and therefore will not be implemented, except where necessary to eliminate an immediate hazard to a participant or participants as an Urgent Safety Measure (USM).

Protocol non-compliance (deviations, violations) must be reported to Keele CTU who will report to the Chief Investigator. They will be recorded and monitored by the research team and escalated to the Sponsor in accordance with HSCR and CTU SOPs.

Deviations and violations are non-compliance events discovered after the event has occurred.

16.2 Serious breaches of the protocol and GCP

A serious breach is a breach which is likely to affect 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.

If a potential serious breach is identified by the Chief investigator, a Principal Investigator or a member of the research team or participating site, Keele CTU must be notified immediately and escalate to the Sponsor within a timeframe to allow compliance with regulatory requirement to report serious breaches within 7 calendar days.

In collaboration with the CI and CTU, the Sponsor will assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to research ethics committee and MHRA as necessary**.**

15.3 Ethical considerations

The trial will be performed in accordance with the GCP principles as detailed in the UK Medicines for Human Use (Clinical Trials) Regulations 2004 and any subsequent amendments.

Informed electronic/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 will 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 not commence until a Clinical Trial Authorisation (CTA) from the MHRA, favourable REC opinion and HRA approval is obtained.

Before any site can enrol patients into the trial, Keele CTU will ensure that appropriate approvals from participating organisations are in place.

15.4 Amendments

For any substantial amendment to the trial, the Chief Investigator and Keele CTU in agreement with the Sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator and Keele CTU will work with sites so they can put the necessary arrangements in place to implement the amendment to confirm their support for the trial as amended.

15.5 Confidentiality

All information collected during the course of the trial will be kept strictly confidential. Information will be held securely on paper and/or managed electronically by Keele University through Keele CTU. Keele CTU will comply with all aspects of the Data Protection Act 2018 and the UK General Data Protection regulation. Operationally this will include:

- appropriate storage, restricted access and disposal and anonymisation arrangements for participant personal and health-related details
- personal data can only be linked to research data by individuals with appropriate permissions
- 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 research participation
- consent from participants for the anonymous data collected for the research to be used to evaluate safety and develop new research.
- where anonymisation of documentation is required, participating sites are responsible for ensuring only the instructed identifiers are present before sending to Keele CTU.

The trial data will be held on Keele University securely managed servers. Provision of appropriate client server links/permissions will be given to authorised members of the trial team at Keele CTU, the participating sites and Keele University Information and Digital Services' (IDS) infrastructure team. In accordance with HSCR and Keele CTU SOPs, the data will go through a series of data cleaning stages, prior to the final dataset being locked down for analysis and 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 trial analysis, unless they explicitly withdraw from any further use of their data.

Published results will not contain any personal data and be of a form where individuals are not identified, and re-identification is not likely to take place.

17 PEER REVIEW

This trial has been subject to internal peer review, and independent external peer review by the funding body (NIHR HTA programme).

18 ARCHIVING

After the end of the trial, data will be securely archived in line with the Sponsor's procedures in accordance with applicable UK Clinical Trials Regulations, HSCR and Keele CTU SOPs. Archived data will be held at the designated, regulatory compliant archive facility and the investigator site file will be archived at the

participating sites. Following the archive period and authorisation from the Sponsor, arrangements for confidential destruction will then be made.

19 STATEMENT OF INDEMNITY

The Sponsor is responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator, research staff, TSC and DMC members working on behalf of the trial.

The following arrangements are in place to fulfil the Sponsor's responsibilities:

- sites participating in the trial will be liable for clinical negligence and other negligent harm to individuals taking part in the trial and covered by the duty of care owed to them by the sites concerned. The Sponsor requires individual sites participating in the trial to arrange for their own insurance or indemnity in respect of these liabilities
- sites which are part of the United Kingdom's National Health Service will have the benefit of NHS Indemnity. Agreements between the Sponsor and participating NHS organisations detailing trial conduct and the responsibilities to be honoured by each party will be fully executed before the trial can start at any participating site.

20 PUBLIC AND PATIENT INVOLVEMENT AND ENGAGEMENT (PPIE)

PPIE has been included in all stages of developing this protocol. Our lay co-applicants feel the trial is important and have helped to design the trial. We held three PPIE meetings with nine people with lived experience of gout flares from the West Midlands, East Midlands and the North-West of England. They helped us to decide the outcomes, when the outcomes should be collected, how long follow-up should be and reviewed our participant facing documents. Our PPIE lead will support all PPIE activities throughout the trial. During the trial, our TMG meetings and external advisory group meetings will include public contributors.

We have formed a PPIE Advisory Group for this trial who will be involved at all stages of the research, including assisting with our ethics application, helping us to understand the results, writing easily understandable messages to explain its findings, and advising us how to publicise the findings widely.

Our patient advisory group will be recruited through multiple targeted strategies. Firstly, we will be supported by Keele's PPIE group and Keele's Impact Accelerator Unit (IAU) to recruit members to our PPIE Advisory Group. Keele's PPIE group has considerable experience of involving the public in research and uses the NIHR INVOLVE Values and Principles Framework and UK Standards for Public Involvement.[33] Keele's IAU was a pilot site for the NIHR Framework for Public Involvement in Research and we will work closely with their Race Equality Ambassador for Involvement in Research.

We will also invite members of the DERA (Deep End Research Alliance) PPI group to join the trial's PPIE Advisory Group. We will publicise the trial via the NIHR RDN Ethnic Minority Inclusion Group in Yorkshire and Humber. We will co-produce videos (e.g. YouTube), and translations of materials into common languages in recruitment areas to explain all aspects of the trial and facilitate participation of people with lower levels of health and English language literacy. Participants will have the option of completing electronic or paper questionnaires to avoid digital exclusion. Consent processes and participant-facing material will be co-designed with our PPIE group. Recruitment across all sites will be monitored for recruitment by postcode deprivation indices, ethnicity, age and sex. We will also work with Keele's IAU and DERA-Sheffield to optimise dissemination our findings to underserved communities.

21 DISSEMINATION AND IMPLEMENTATION POLICY

We are committed to the translation of our results in ways that positively affect primary care and patient outcomes. Our main findings on the clinical and cost-effectiveness of the interventions will have important implications for patients, healthcare professionals and the NHS. To ensure that our outputs influence clinical practice, the following dissemination strategy has been developed based on NIHR 'Push the Pace' guidance [46] and the NIHR Dissemination Guidance Principles,[47] draws on our extensive existing communication channels and networks and will be supported by Keele's IAU.

The five key audiences for this research dissemination and implementation include: i) people with gout and the wider public; ii) healthcare professionals; iii) integrated care boards/commissioning organisations; iv) external bodies, patient groups and charities; and v) academia. To maximise its effectiveness, our dissemination strategies will be coordinated in time and use multiple channels to reach multiple audiences.

Our dissemination and implementation strategies will include:

- publishing the findings on a website accessible to participants and participating General Practices [i, ii]
- collaborative dissemination events in the West Midlands, East Midlands, South Yorkshire and Wessex regions of England on the primary care management of people with gout [i, ii, iii]
- linking with key local, national and international organisations including local Integrated care systems, the Academic Health Science Network, NIHR Applied Research Collaboration West Midlands, the Royal College of General Practitioners, Versus Arthritis, European Alliance of Associations for Rheumatology (EULAR), and the National Institute for Health and Care Excellence (NICE) [all]
- use of electronic media including a trial website and social media (e.g., blogs, Twitter) [all]
- publications including HTA monograph, open-access journals, and local NHS and research newsletters [all]
- high-profile national and international conferences e.g., Society for Academic Primary Care, Royal College of General Practitioners, British Society for Rheumatology, and EULAR [ii, iii, iv, v]
- registering the trial on the Academic Health Science Network's national Innovation Pipeline Portfolio Management System [all]

22 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 TSC.

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 trial 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.

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1. APPENDICIES

1.1 AMENDMENT HISTORY

Amendment number	Protocol version	Protocol version date	Brief details of changes
N/A	1.1	4th July 2025	Updates in response to REC request for further information.
	2.0	2nd December 2025	