What is the clinical and cost effectiveness of using a goal-directed allopurinol-based treat-to-target protocol in people with recurrent gout flares? Protocol for a randomized controlled trial and internal pilot study

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TRIAL PERSONNEL AND CONTACT DETAILS

Sponsor:
Contact name

University of Nottingham
Ms Angela Shone
Research and Innovation
University of Nottingham
East Atrium
Jubilee Conference Centre
Triumph Road
Nottingham
NG8 1DH
Email: sponsor@nottingham.ac.uk

Chief investigator:

Professor A Abhishek
Professor of Rheumatology
Honorary Consultant Rheumatologist
Academic Rheumatology
University of Nottingham
Nottingham NG5 1PB
Phone: 01158 23193
Email: Abhishek.abhishek@nottingham.ac.uk

Co-investigators:

Professor Edward Roddy
Professor of Rheumatology
Honorary Consultant Rheumatologist
School of Medicine
Keele University
Staffordshire, ST5 5BG
Phone: 01782 734715
Email: e.roddy@keele.ac.uk

Dr Miriam Santer
Associate Professor in Primary Care Research
Primary Care & Population Sciences
University of Southampton
Aldermoor Health Centre
Southampton SO16 5ST
Phone: 02380 591789
Email: m.santer@soton.ac.uk

Professor Sue Jowett
Professor of Health Economics
Health Economics Unit
Institute of Applied Health Research
University of Birmingham

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Phone: 0121 414 7898
Email: s.jowett@bham.ac.uk

Professor Christian Mallen
Executive Dean, Faculty of Medicine and Health Sciences
Director, NIHR School of Primary Care Research
NIHR Research Professor in General Practice
Associate Director, Research and Innovation, Midlands Partnership University Foundation NHS Trust
Keele University
Staffordshire, ST5 5BG
Phone: 01782 734879
Email: c.d.mallen@keele.ac.uk

Professor Paul Little
Professor of Primary Care Research
University of Southampton
Phone: 02380241062
Email: p.little@soton.ac.uk

Professor Weiya Zhang
Professor of Epidemiology
Academic Rheumatology
University of Nottingham
Nottingham NG5 1PB
Phone: 0115 823 1750
Email: weiya.zhang@nottingham.ac.uk

Professor Maarten Taal
Professor of Medicine
Academic Unit for Translational Medical Sciences
University of Nottingham
Derby DE22 3NE
Phone: 01332 724842
Email: m.taal@nottingham.ac.uk

Professor Michael Doherty
Professor of Rheumatology (Emeritus)
Academic Rheumatology
University of Nottingham
Nottingham NG5 1PB
Phone: 0115 8231755
Email: michael.doherty1@nottingham.ac.uk

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Trial Statisticians:

Professor Julius Sim
Professor of Health Care Research
School of Medicine

Keele University
Staffordshire, ST5 5BG
Phone: 01782 734253
Email: j.sim@keele.ac.uk

Dr Ivonne Solis-Trapala
Reader in Biostatistics
Director, Keele Clinical Trials Unit
School of Medicine
Keele University
Staffordshire, ST5 5BG
Phone: 01782 734711
Email: i.solis-trapala@keele.ac.uk

Dr Royes Joseph
Lecturer in Biostatistics
School of Medicine
Keele University
Staffordshire, ST5 5GB
Email: r.joseph1@keele.ac.uk

Trial Coordinating Centre:

Keele Clinical Trials Unit (CTU),
David Weatherall Building,
Keele University,
Staffordshire, ST5 5BG
Tel: 01782 732950

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1. SYNOPSIS

Title	What is the clinical and cost effectiveness of using a goal-directed allopurinol-based treat-to-target protocol in people with recurrent gout flares? Protocol for a randomized controlled trial and internal pilot study
Acronym	T2T
Short title	Treat-to-target in gout
Chief Investigator	Professor A Abhishek
Objectives	*Internal pilot:* To assess consent rate, randomization rate, attrition, quality of outcome data, delivery of treat-to-target urate-lowering treatment (ULT) and preliminary estimate of the effect of the intervention. *Full trial:* *Primary objective:* To evaluate the effectiveness of allopurinol-based treat-to-target ULT versus usual general practitioner (GP) care on number of gout flares over two years. *Secondary objectives:* To evaluate the effects of allopurinol-based treat-to-target ULT versus usual GP care on • gout flare severity, • serum urate level, • tophus count, • size of largest tophus, • quality of life, • treatment satisfaction, • drug adherence, • renal function, • adverse events, and • cost-effectiveness *Long-term extension:* To evaluate the effects of allopurinol-based treat-to-target ULT versus usual GP care on • number of gout flares, • healthcare utilization due to gout, • comorbidities, and • death.
Trial Configuration	Parallel group
Setting	Primary care
Sample size calculation	Using 90% power and 5% two-tailed significance, and assuming a dispersion parameter of 1.50 to account for variability between participants (estimated from our recent trial, and inflated by 25%), in order to detect a rate ratio of 0.650 (based on mean numbers of flares over 24 months of 3.54 and 2.30 in standard and active arms respectively), 190 participants per group are required for this trial. Using 10,000 simulations conducted in R assuming a negative binomial model, assuming a correlation between baseline and follow-up counts of flares of 0.33, an adjusted sample size for the inclusion of baseline

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	flares as a covariate is 186 per group. Allowing for up to 20% loss to follow-up based on our experience of conducting a two-year Nottingham gout treatment trial, target recruitment is therefore 233 per group, 466 in total.
Number of participants	466
Eligibility criteria	*Inclusion criteria:* • age ≥18 years. • ability to give informed consent • meets the clinical American College of Rheumatology/European League Against Rheumatism classification criteria for gout • ≥1 flare of gout in the previous 12 months (assessed at screening questionnaire stage) • serum urate ≥360 µmol/l regardless of current ULT *Exclusion criteria:* • dementia, severe psychological disturbance i.e. mental health illness that makes receiving the study information and initial screening questionnaire from GP a stressful experience, • unable to comply with study procedures (including patients unable or not willing to have allopurinol and febuxostat due to side-effects or personal preference.) • life expectancy less than 12 months, • cancer treatment i.e. surgery, radiotherapy, or chemotherapy in the previous 12 months, • solid organ transplant, • cirrhosis of liver, • autoimmune rheumatic disease, •Inflammatory bowel disease, • current long-term daily prednisolone defined as continuous use for ≥ 30 days or current other immunosuppressive treatments, • stage 4/5 chronic kidney disease (CKD), • pregnant, breast feeding or planning to become pregnant. • Current participation in another trial that may influence the outcome of this study (e.g. another gout study or a dietary and lifestyle intervention study).
Description of interventions	*Intervention*: Allopurinol-based treat-to-target ULT. *Control:* Usual GP care of gout, including ULT.
Duration of study	80 months Each participant in the study for at least four years

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Randomization and blinding	Randomization in a 1:1 ratio, stratified by region, prior intolerance to colchicine, using randomly permuted blocks of varying sizes from 2 to 6. The clinical members of the trial management group and the trial steering committee will be blind to group allocation. Study participants will not be blinded. The statistician will not be blind to group allocation, owing to differences in serum urate that will be apparent. Unblinded data will be made available to the data monitoring committee where appropriate. In such an event, the statistician will prepare the relevant data summaries and the identity of the treatment groups. Unblinding to the study team will only occur once the main trial analyses have been completed. Randomization will occur online via a web-based system based in Keele Clinical Trials Unit (CTU).
Outcome measures	*Internal pilot:* *Primary outcome:* consent rate *Secondary outcomes:* drop-out rate, quality of outcome data, serum urate level as a continuous variable at 1 year, and proportion achieving the target serum urate level (<360 µmol/L) at 1 year, gout flare counts in months 7-12. *Full trial:* *Primary outcome:* Gout flare counts over 2 years. *Secondary outcomes:* • Gout flare counts in months 1-12 • Gout flare counts in months 13-24 • tophus count, • size of largest tophus, • pain due to gout flare, EQ-5D-5L during gout flares, and gout impact scale (GIS) after flare resolution, • serum urate level: proportion achieving the target serum urate level (<360µmol/L) at year 1 and 2 • serum urate level: proportion achieving <300µmol/L at year 1 and 2 • serum urate level as continuous variable at year 1 and 2, • EQ-5D-5L between gout flares, • treatment satisfaction, • Morisky medication adherence scale (MMAS)-8 scale, • serum creatinine and estimated glomerular filtration rate (GFR), • urine albumin creatinine ratio, • primary-care consultations for gout, • hospitalizations due to gout, • ULT prescriptions, • prescriptions for treating flares of gout, • investigations for gout, • incident cardiovascular diseases, hypertension, diabetes, • incidence or progression of CKD, • death, • adverse events and • cost-effectiveness. Safety Outcomes • new intervention-related AEs reported during the study,

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	• discontinuation due to intervention-related AEs. *Long-term extension:* • number of gout flares in years 3-4, • primary-care consultations for gout, • hospitalizations due to gout, • ULT prescriptions, • prescriptions for treating flares of gout, • investigations for gout, • incident cardiovascular diseases, hypertension, diabetes, • serum urate, creatinine and estimated GFR, • urine albumin creatinine ratio, • incidence or progression of CKD, and • death.
Statistical methods	Analysis will be on an intention-to-treat (ITT) basis, according to a pre-specified SAP. The primary outcome, number of gout flares over 24 months post-randomization, will be analysed between groups through negative binomial regression, adjusting for number of flares in the year prior to trial entry and including the stratification factors in the model. The fit of a negative binomial model to the data will be assessed through plots of residuals, and if poor, an alternative model (e.g. zero-inflated negative binomial or Poisson) will be used. As a secondary analysis on the primary outcome, flares occurring during months 1–12 and between months 13–24 will be analysed between groups. Generalized mixed-effects models will be fitted for other continuous or binary outcomes, at both 1- and 2-year follow-up. Assumptions of all analyses will be checked and significance will be set at $p \leq .05$, with 95% CIs calculated for between-group estimates. Appropriate sensitivity analyses will be performed, as specified in the SAP.

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2. ABBREVIATIONS

AE Adverse Event

BNF British National Formulary

CI Chief Investigator overall

CRF Case Report Form

CKD Chronic Kidney Disease

CTU Clinical Trials Unit

DMC Data Monitoring Committee

GP General Practitioner

GIS Gout Impact Scale

GCP Good Clinical Practice

GFR Glomerular Filtration Rate

HRA Health Research Authority

ICF Informed Consent Form

ITT Intention to Treat

MPR Medication Possession Ratio

MMAS Morisky Medication Adherence Scale

NHS National Health Service

NRS Numeric Rating Scale

PI Principal Investigator at a local centre

PIS Participant Information Sheet

QALY Quality adjusted life year

REC Research Ethics Committee

R&D Research and Development department

SmPC Summary of product characteristics

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SAE Serious Adverse Event

SAP Statistical Analysis Plan

SMS Short Message Service

TMG Trial Management Group

TSC Trial Steering Committee

ULT Urate Lowering Treatment

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3. TRIAL BACKGROUND INFORMATION AND RATIONALE

Gout affects 2.5% adults in the UK, with higher prevalence reported in other countries, and poses a substantial healthcare burden [1–6]. It results from sustained hyperuricemia, which causes intra- and peri-articular monosodium urate crystal deposition. When these crystals are released, they induce intense inflammation, which manifests as a flare of gout [7]. Acute gout is one of the most painful conditions known, and resulted in 110,000 GP consultations and 7,916 hospital admissions, including 3,496 emergency admissions, in England alone in the year 2008–2009 [3, 4, 8]. Apart from this, 252,525 individuals consulted their GP about gout at least once in the year 2007 in England and Wales [3]. The healthcare burden of gout is likely to have increased in the last decade as the prevalence of gout has increased steadily by 4.2% per year in the UK [2]. Gout is now the most common cause of hospitalization for rheumatic diseases, having overtaken rheumatoid arthritis, with incremental direct costs between US$3,165–5,515 per year, increasing to US$10,222–21,467 per year when there are frequent flares and tophi [5, 6].

Gout is a direct consequence of hyperuricemia, and there is sufficient evidence that high serum urate is associated with gout, and with frequent gout flares [9–10]. It is also logical that lowering serum urate should provide freedom from future gout flares. Gout presents with self-limiting flares in its early stages, and there was an absence of high-quality RCT data on whether treat-to-target ULT prevents gout flares in a cost-effective manner compared to treating only when symptoms worsen.

A recent randomized controlled trial (RCT) from Nottingham (n=517) with community-based recruitment and intervention delivery compared Academic centre-based research nurse-led of care to usual (GP-led) care of people with gout over a two-year period (11). The nurses were trained about gout and delivered a package of care reflecting recommended best practice (12,13), specifically: individualized holistic assessment with enquiry and discussion of illness perceptions; full information on the nature, causes, possible consequences and treatment options for gout (appendix 3); a treat-to-target ULT strategy; and full patient engagement in management decisions. Compared to usual care, nurse-led care resulted in very high ULT uptake (96% v 56% at year 2); achievement of target serum urate <360µmol/L in more patients (95% v 30% at year 2); lower flare frequency during year 2 (mean 1.5 v 2.4); reduced presence of tophi (3% v 11% at year 2); and improved quality of life (SF-36 physical component) at year 2. The intervention was cost-effective in improving patient-centred outcomes and modelled to be cost-saving at year 5. Flare frequency during year 1 was comparable in both arms (mean 3.6 vs. 3.5) possibly because only 3 participants in the nurse-led arm elected to have flare prophylaxis, even though this option was considered and discussed. Whether such care is generalizable and could be equally well delivered by non-research practice-based nurses, or other healthcare professionals, is unknown. On *post hoc* analysis, the number of flares over the total two-year treatment period were not statistically different between the two arms (MD unpublished data). Thus, it remains unknown if an allopurinol-based treat-to-target ULT regime that included flare prophylaxis, reduces the number of gout flares from treatment initiation.

This lack of clarity has resulted in sub-optimal gout management and culminated in discordant recommendations from primary care and rheumatology gout treatment guidelines, exemplified by the recent American College of Physicians' recommendation to treat gout patients to avoid symptoms rather than treat to a target serum urate level, due to lack of high-quality RCT evidence [12–16]. Previous research has demonstrated that gout

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management in the UK is sub-optimal, with only 30–40% of eligible patients receiving ULT, mostly at a fixed low-dose, e.g. 300 mg allopurinol/day [2], which usually does not lower the serum urate sufficiently to eliminate the monosodium urate crystals in the majority of gout cases [17]. Thus, a study that demonstrates the effectiveness of treat-to-target ULT in gout will provide the much-needed evidence to improve the management of gout in the UK and worldwide. The NIHR-HTA board have issued a call for research studies to answer this important question, and, after competitive bidding and peer review, this grant has been awarded to the research team.

Evidence explaining why this research is needed now: Most published RCTs of ULT in gout with the exception of one study [11], are one year or shorter in duration [18]. Most are industry-funded and compare allopurinol (300 mg/day) to new xanthine oxidase inhibitors or a combination of fixed dose allopurinol with new uricosuric drugs [18–22]. Moreover, the goal of managing gout (i.e. treat-to-target serum urate vs. treat-to-avoid-symptoms) differ between American College of Physicians and rheumatology guidelines due to absence of high-quality evidence [12–16, 18, 23]. Thus, a study comparing treat-to-target serum urate vs. treat-to-symptom is urgently needed.

Uricosuric drugs are effective in lowering serum urate, but, are either not available globally (e.g. Lesinurad, Sulfinpyrazone (as of 2021)), or not licenced for the treatment of gout in the UK e.g. Probenecid and Benzbromarone, and are therefore unsuitable for use in primary-care treat-to-target gout studies.

We have recently completed a single-centre RCT comparing a research nurse-led package of care for gout that involved both pharmacological and non-pharmacological interventions against usual GP care [11]. The experience of conducting this study provides us with a unique understanding of the obstacles to recruitment, reasons for non-participation, reasons for adhering to ULT [24], and other trial processes that places us ideally to deliver this commissioned multi-centre treat-to-target trial in primary care. The proposed study builds on our experience of delivering a nurse-led package of care for gout that included treat-to-target ULT in a single centre trial, to a multicentre primary care-based study, with inclusion of flare prophylaxis, and flares in the first two years treated as primary outcome measure in the proposed study.

4. TRIAL OBJECTIVES AND PURPOSE

4.1 Purpose

The overall purpose of this study is to determine the clinical and cost-effectiveness of treat-to-target ULT in people with recurrent gout flares compared to usual GP care.

4.2 Primary Objective

To evaluate the effect of allopurinol-based treat-to-target ULT versus usual GP care on number of gout flares in the first two years of treat-to-target ULT.

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4.3 Secondary Objectives

To evaluate the effects of allopurinol-based treat-to-target ULT versus usual GP care on:

- Gout flare count in months 1-12
- Gout flare count in months 13-24
- Tophus count,
- Size of largest tophus,
- Gout flare severity,
- Serum urate level,
- Quality of life,
- Treatment satisfaction (assessed using treatment satisfaction questionnaire version 2 [25]),
- Drug adherence,
- Renal function,
- Adverse events, and
- Cost-effectiveness.

Internal pilot:

We will assess consent rate, randomization rate, attrition, quality of outcome data, delivery of treat-to-target ULT and preliminary estimate of the effect size of the intervention in a 1-year internal pilot.

4.4 Long-Term Extension

Primary objectives:

To evaluate the long-term effect of continued allopurinol-based treat-to-target ULT versus usual GP care on number of gout flares in years 3-4.

Secondary objectives

To evaluate the long-term effect of continued allopurinol-based treat-to-target ULT versus usual GP care on healthcare utilization for gout in years 3-4, incidence of comorbidities, and mortality.

5. DETAILS OF PRODUCT(S)

5.1 Description

The study will involve the use of licenced urate lowering drugs, and medicines that are recommended to be used for gout flare prophylaxis. The description of each of the individual medicine is outlined below:

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Table 1 Drug names and appearance

Drug	Appearance
Allopurinol	circular, biconvex, white, uncoated
Febuxostat	oblong, biconvex, yellow, film-coated
Naproxen	yellow, capsule-shaped, biconvex uncoated tablets
Omeprazole	hard gelatin capsules of size 2, opaque yellow cap and body, containing white to off-white spherical pellets.
Colchicine	disc, white or yellow, uncoated or coated

5.2 Manufacture

The names of manufacturer(s) and marketing authorization numbers are available from the summary of product characteristics of each of these medicines.

5.3 Packaging and Labelling

Each product will be packaged and labelled as per the marketing authorization and usual National Health Service (NHS) community pharmacy policies. Drug manufacturers and community pharmacies respectively will perform these activities.

5.4 Storage, Dispensing and Return

The medicines will be stored in community pharmacies and dispensed on receiving a GP or a prescribing nurse practitioner prescription. Participants will be requested to return any unused medicines at the one- and two-year research assessment visits.

5.5 Treatment in the Control Arm

This trial does not involve the use of placebos. However, participants in the control arm will receive gout treatment from their GPs, or hospital rheumatologists, and can be prescribed any of the ULT, colchicine, naproxen or other non-steroidal anti-inflammatory drug (NSAID), corticosteroids and proton pump inhibitors outlined earlier, depending on their clinical need. However, they will not receive a structured nurse-led treat-to-target ULT protocol.

5.6 Known Side Effects

The known side effects of each product are outlined below. They are classified as:

- Very common (≥1/10 (≥10%)),
- Common (≥1/100 and <1/10 (≥1% and <10%)),
- Uncommon (≥1/1000 and <1/100 (≥0.1% and <1%)),
- Rare (≥1/10,000 and <1/1000 (≥0.01% and <0.1%)),
- Very rare (<1/10,000 (<0.01%))

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Table 2 Side effects to Allopurinol

Infections and infestations

Very rare: furunculosis,

Blood and lymphatic system disorders

Very rare: thrombocytopenia, aplastic anaemia, agranulocytosis

Frequency not known: leucopenia, eosinophilia, haemolytic anaemia

Very rare reports have been received of thrombocytopenia, agranulocytosis and aplastic anaemia, particularly in individuals with impaired renal and/or hepatic function, reinforcing the need for particular care in this group of patients.

Reports of transient reduction in the number of circulating formed elements of the blood are usually in association with a renal and/or hepatic disorder, reinforcing the need for particular care in this group of patients.

Immune system disorders

A delayed multi-organ hypersensitivity disorder (known as hypersensitivity syndrome or DRESS) with fever, rashes, vasculitis, lymphadenopathy, pseudo lymphoma, arthralgia, leucopenia, eosinophilia, hepato-splenomegaly, abnormal liver function tests and vanishing bile duct syndrome (destruction and disappearance of the intrahepatic bile ducts), occurring in various combinations. Other organs may also be affected (e.g. liver, lungs, kidneys, pancreas, myocardium, and colon). If such reactions do occur, it may be at any time during treatment, Allopurinol tablets should be withdrawn immediately and permanently.

When generalized hypersensitivity reactions have occurred, renal and/or hepatic disorder has usually been present particularly when the outcome has been fatal.

Uncommon: hypersensitivity reactions

Very rare: angioimmunoblastic lymphadenopathy, anaphylaxis

Frequency not known: arthralgia

Associated vasculitis and tissue response may be manifested in various ways including hepatitis, interstitial nephritis and, very rarely, epilepsy. Corticosteroids may be beneficial in overcoming them. When generalized hypersensitivity reactions have occurred, a renal and/or hepatic disorder has usually been present, particularly when the outcome has been fatal.

Metabolism and nutrition disorders

Very rare: diabetes mellitus, hyperlipidaemia

Frequency not known: exacerbation of gout flares

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Psychiatric disorders

Very rare: depression,

Nervous system disorders

Very rare: ataxia, coma, headache, neuropathy, paraesthesia, paralysis, somnolence, taste perversion, dysgeusia

Frequency not known: dizziness

Eye disorders

Very rare: cataract, macular changes, visual disorders

Ear and labyrinth disorders

Very rare: vertigo

Cardiac disorders

Very rare: angina, bradycardia

Vascular disorders

Very rare: hypertension

Frequency not known: vasculitis

Gastrointestinal disorders

Uncommon: nausea, vomiting

Very rare: changed bowel habit, stomatitis, steatorrhoea, haematemesis

Frequency not known: diarrhoea, abdominal pain,

Hepatobiliary disorders

Uncommon: asymptomatic increases in liver function tests

Rare: Hepatitis (including hepatic necrosis and granulomatous hepatitis)

Skin and subcutaneous tissue disorders

Common: rash

Rare: Severe cutaneous adverse reactions (SCARs): Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported (see section 4.4). The highest risk for

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SJS and TEN, or other serious hypersensitivity reactions, is within the first weeks of treatment.

Very Rare: alopecia, angioedema, discoloured hair, fixed drug eruptions.

Frequency not known: skin reaction associated with eosinophilia, urticaria.

Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) has been reported. Some cases have had a fatal outcome.

Skin reactions are the most common reactions and may occur at any time during treatment. They may be pruritic, maculopapular, sometimes scaly or purpuric, associated with exfoliation, fever, lymphadenopathy, arthralgia and/or eosinophilia resembling Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and/or Lyell's. Allopurinol should be withdrawn immediately should such reactions occur.

If desired, after recovery from mild reactions, allopurinol may be reintroduced at a low dose (e.g. 50mg/day), which may be gradually increased. If the rash recurs, allopurinol should be permanently withdrawn.

The HLA-B*5801 allele has been identified as a genetic risk factor for allopurinol associated SJS/TEN in retrospective, case-control, pharmacogenetic studies in patients of Han Chinese, Japanese and European descent. Up to 20–30% of some Han Chinese, African and Indian populations carry the HLA-B*5801 allele whereas only 1–2% of Northern European, US European and Japanese patients are estimated to be HLA-B*5801 carriers. However, the use of genotyping as a screening tool to make decisions about treatment with allopurinol has not been established.
The clinical diagnosis of SJS/TEN remains the basis for decision making. If such reactions occur at any time during treatment, allopurinol should be withdrawn immediately and permanently.

Renal and urinary disorders

Very rare: haematuria, uraemia, azotaemia

Frequency not known: nephrolithiasis

Reproductive system and breast disorders

Very rare: gynaecomastia, impotence, infertility, erectile dysfunction

Frequency not known: nocturnal emissions

General disorders and administration site conditions

Very rare: asthenia, general malaise, oedema, pyrexia*

Investigations

Common: blood thyroid stimulating hormone increased**

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* Fever has been reported to occur with and without signs and symptoms of a more generalized allopurinol hypersensitivity reaction.
** The occurrence of increased thyroid stimulating hormone (TSH) in the relevant studies was not reported as having any impact on free T4 levels or as having TSH levels indicative of subclinical hypothyroidism.

Table 3 Side effects to Febuxostat

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Blood and lymphatic system disorders

Rare: pancytopenia, thrombocytopenia, agranulocytosis

Immune system disorders

Rare: anaphylactic reaction, drug hypersensitivity

Endocrine disorders

Uncommon: blood thyroid stimulating hormone increased

Eye disorders

Rare: blurred vision

Metabolism and nutrition disorders

Common: gout flares

Uncommon: diabetes mellitus, hyperlipidemia, decrease appetite, weight increase

Rare: weight decrease, increase appetite, anorexia

Psychiatric disorders

Uncommon: libido decreased, insomnia

Rare: nervousness

Nervous system disorders

Common: headache

Uncommon: dizziness, paraesthesia, hemiparesis, somnolence, altered taste, hypoaesthesia, hyposmia

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Ear and labyrinth disorders

Rare: tinnitus

Cardiac disorders

Uncommon: atrial fibrillation, palpitations, ECG abnormal

Vascular disorders

Uncommon: hypertension, flushing, hot flush

Respiratory system disorders

Uncommon: dyspnoea, bronchitis, upper respiratory tract infection, cough

Gastrointestinal disorders

Common: diarrhoea, nausea

Uncommon: abdominal pain, abdominal distension, gastro-oesophageal reflux disease, vomiting, dry mouth, dyspepsia, constipation, frequent stools, flatulence, gastrointestinal discomfort

Rare: pancreatitis, mouth ulceration

Hepato-biliary disorders

Common: liver function abnormalities

Uncommon: cholelithiasis

Rare: hepatitis, jaundice, liver injury

Skin and subcutaneous tissue disorders

Common: rash (including various types of rash reported with lower frequencies, see below)

Uncommon: dermatitis, urticaria, pruritus, skin discolouration, skin lesion, petechiae, rash macular, rash maculopapular, rash papular

Rare: toxic epidermal necrolysis, Stevens-Johnson syndrome, angioedema, drug reaction with eosinophilia and systemic symptoms, generalized rash (serious), erythema, exfoliative rash, rash follicular, rash vesicular, rash pustular, rash pruritic, rash erythematous, rash morbilliform, alopecia, hyperhidrosis

Musculoskeletal and connective tissue disorders

Uncommon: arthralgia, arthritis, myalgia, musculoskeletal pain, muscle weakness, muscle spasm, muscle tightness, bursitis

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Rare: rhabdomyolysis, joint stiffness, musculoskeletal stiffness

Renal and urinary disorders

Uncommon: renal failure, nephrolithiasis, haematuria, pollakiuria, proteinuria

Rare: tubulointerstitial nephritis, micturition urgency
Reproductive system and breast disorder

Uncommon: erectile dysfunction

General disorders and administration site conditions

Common: oedema

Uncommon: fatigue, chest pain, chest discomfort

Rare: thirst

Investigations

Uncommon: blood amylase increase, platelet count decrease, WBC decrease, lymphocyte count decrease, blood creatine increase, blood creatinine increase, haemoglobin decrease, blood urea increase, blood triglycerides increase, blood cholesterol increase, haematocritic decrease, blood lactate dehydrogenase increased, blood potassium increase

Rare: blood glucose increase, activated partial thromboplastin time prolonged, red blood cell count decrease, blood alkaline phosphatase increase, blood creatine phosphokinase increase

Table 4 Side effects to Colchicine

Blood and lymphatic system disorders

Not known: bone marrow depression with agranulocytosis, aplastic anaemia and thrombocytopenia.

Nervous system disorders

Not known: peripheral neuritis, neuropathy.

Gastrointestinal system disorders

Common: abdominal pain, nausea, vomiting and diarrhoea.

Not known: gastrointestinal haemorrhage.

Hepatobiliary disorders

Not known: hepatic damage.

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Skin and subcutaneous tissue disorders

Not known: alopecia, rash.

Musculoskeletal and connective tissue disorders

Not known: myopathy and rhabdomyolysis.

Renal and urinary disorders

Not known: renal damage.

Reproductive system and breast disorders

Not known: amenorrhoea, dysmenorrhoea, oligospermia, azoospermia.

Table 5 Side effects to Naproxen

Blood and lymphatic system disorders:

Rare: haemolytic anaemia

Very rare: granulocyctopenia, thrombocytopenia, agranulocytosis

Frequency not known: aplastic anaemia, neutropenia

Immune system disorders:

Rare: allergic and hypersensitivity reactions, anaphylaxis

Metabolism and nutrition disorders:

Rare: hyperkalaemia

Psychiatric disorders:

Uncommon: depression, cognitive dysfunction, insomnia, loss of concentration, abnormal dreams
Frequency not known: hallucinations

Nervous system disorders

Common: confusion, dizziness, drowsiness, headache
Very rare: convulsions, aseptic meningitis
Frequency not known: vertigo, paraesthesia, malaise, exacerbation of Parkinson's disease

Eye disorders

Common: visual disturbances
Frequency not known: optic neuritis, papilloedema

Ear and labyrinth disorders

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Common: tinnitus

Frequency not known: hearing impairment

Cardiac disorders

Uncommon: palpitations

Frequency not known: cardiac failure

Vascular disorders

Rare: vasculitis

Very Rare: arterial thrombotic events e.g. myocardial infarction or stroke

Frequency not known: hypertension

Respiratory, thoracic and mediastinal disorders

Rare: aggravated asthma, eosinophilic pneumonitis

Frequency not known: bronchospasm, dyspnoea, rhinitis, pulmonary oedema

Gastro-intestinal disorders

Very Rare: pancreatitis

Frequency not known: thirst, peptic ulcers, perforation or GI bleeding, nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease, gastritis

Hepatobiliary

Rare: hepatitis (sometimes fatal), jaundice

Frequency not known: abnormal liver function,

Skin and subcutaneous tissue disorders

Common: rash, pruritis, purpura

Uncommon: urticaria, photosensitivity

Rare: alopecia, pseudo-porphyria
Very rare: erythema multiforme, Stevens Johnsons syndrome, toxic epidermal necrosis, epidermolysis bullosa

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Frequency not known: angio-oedema, epidermal necrosis, exfoliative and bullous dermatoses, lichen planus

Musculoskeletal and connective tissue disorders

Rare: myalgia, muscle weakness

Renal and urinary disorders

Very rare: glomerular nephritis, haematuria, interstitial nephritis, nephritic syndrome, renal papillary necrosis
Frequency not known: renal failure, nephropathy, increase in serum creatinine

Reproductive system and breast disorders

Frequency not known: impaired female fertility

General disorders and administration site complications

Common: fatigue

Frequency not known: mild peripheral oedema, pyrexia

Table 6 Side effects to Omeprazole

Blood and lymphatic system disorders

Rare: leukopenia, thrombocytopenia

Very rare: agranulocytosis, pancytopenia

Immune system disorders

Rare: hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock

Metabolism and nutrition disorders

Rare: hyponatraemia

Not known: hypomagnesaemia

Psychiatric disorders

Uncommon: insomnia

Rare: agitation, confusion, depression

Very rare: aggression, hallucinations

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Nervous system disorders

Common: headache

Uncommon: dizziness, paraesthesia, somnolence

Rare: Taste disturbance

Eye disorders

Rare: blurred vision

Ear and labyrinth disorders

Uncommon: vertigo

Respiratory, thoracic and mediastinal disorders

Rare: bronchospasm

Gastrointestinal disorders

Common: abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting, fundic gland polyps (benign)

Rare: dry mouth, stomatitis, gastrointestinal candidiasis

Not known: microscopic colitis

Hepatobiliary disorders

Uncommon: increased liver enzymes

Rare: hepatitis with or without jaundice

Very rare: hepatic failure, encephalopathy in patients with pre-existing liver disease, skin and subcutaneous tissue disorders

Uncommon: dermatitis, pruritus, rash, urticaria

Rare: alopecia, photosensitivity

Very rare: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

Not known: subacute cutaneous lupus erythematosus

Musculoskeletal and connective tissue disorders

Uncommon: fracture of the hip, wrist or spine

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Rare: arthralgia, myalgia

Very rare: muscular weakness

Renal and urinary disorders

Rare: interstitial nephritis
Reproductive system and breast disorders

Very rare: gynaecomastia

General disorders and administration site conditions

Uncommon: malaise, peripheral oedema

Rare: increased sweating

Reference source for tables 2-7: Summary of product characteristics (SmPC) Tables 2-3, 5-6, and British National Formulary (BNF) for Table 4.

6. TRIAL DESIGN

6.1 Trial Configuration: Full RCT

Study design: Parallel-arm multicentre RCT with one-year internal pilot and two-year long-term extension phase.

Setting: primary care.

Main trial:

6.1.1 Primary outcome measure

- Gout flare count in the first 2 years

6.1.2 Secondary outcome measures

- Gout flare count in months 1-12
- Gout flare count in months 13-24
- Tophus count,
- Size of largest tophus,
- Daily pain score during gout flare,
- EQ-5D-5L during gout flares,
- GIS measured after flare resolution,
- Serum urate level: proportion achieving the target serum urate level (<360 µmol/L) at year 1 and 2,
- Serum urate level: proportion achieving <300µmol/L at year 1 and 2

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- Serum urate level as a continuous variable at year 1 and 2,
- EQ-5D-5L between gout flares,
- ULT (name and dose),
- Treatment satisfaction,
- MMAS-8 scale,
- Serum creatinine and estimated GFR,
- Urine albumin creatinine ratio,
- Primary-care consultations for gout,
- Hospitalizations due to gout,
- Prescriptions for treating flares of gout,
- Investigations for gout,
- Incident cardiovascular diseases (defined as ischaemic heart disease, myocardial infarction, stroke and/or transient ischaemic attack), hypertension, diabetes,
- Incidence or progression of CKD,
- Death,
- Adverse events (AE), and
- Cost-effectiveness.

6.1.3 Safety outcomes

- New intervention-related AEs reported during the study,
- Discontinuation due to intervention-related AEs.

6.2 Internal Pilot

6.2.1 Outcomes

- Consent rate,
- Randomization rate,
- Drop-out rate,
- Missingness of outcome data,
- Serum urate level: proportion achieving target and serum urate level (<360µmol/L) at year 1,
- Serum urate level as a continuous variable at year 1, and
- Number of gout flares in month 7-12.

6.3 Long-Term Extension

6.3.1 Primary outcome measure

- Number of gout flares in years 3-4

6.3.2 Secondary outcome measures

- Primary-care consultations for gout,
- Hospitalizations due to gout,
- Urate lowering treatment prescriptions,
- Prescriptions for treating flares of gout,
- Investigations for gout,

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- Incident cardiovascular diseases (defined as ischaemic heart disease, myocardial infarction, stroke and/or transient ischaemic attack), hypertension, diabetes,
- Serum urate, creatinine and estimated GFR,
- Urine albumin creatinine ratio,
- Incidence or progression of CKD, and
- Death.

6.4 Randomization and Blinding

6.4.1 Randomization and blinding

Randomization will be in a 1:1 ratio, stratified by region, contraindication to or intolerance of colchicine, using random permuted blocks of varying sizes from 2 to 6. Ten randomization lists will be prepared by the study statistician and stored on a Keele University managed storage service, to which no members of the trial team will have access. One of these lists will be randomly selected by the database manager for use in the trial.

The clinical members of the trial management group and the TSC will be blind to group allocation; none of these individuals will have contact with study participants. The statistician will not be blind to group allocation, owing to differences in serum urate that will be apparent. Unblinded data will be made available to the DMC where appropriate. In such an event, the statistician will prepare the relevant data summaries and the identity of the treatment groups. Unblinding to the study team will only occur once the main trial analyses have been completed.

Randomization will be during office hours using a secure centralized web-based, automated computer-generated randomization system provided by the Keele University Clinical Trials Unit (CTU). Authorized personnel at the trial site will be allocated personalized log-in details by Keele CTU, in order to access the randomization system. Alternatively, the research nurse can call Keele CTU and the CTU will perform the randomization on the site's behalf. Authorized staff at the CTU will access the randomization tool to perform randomization and inform the nurse of the allocation. The participants' GP and usual care team will be informed of the participants' allocation verbally and in writing within two working days.

6.4.2. Maintenance of randomization codes and procedures for breaking code

Patients' GP and usual care team will be aware of their group allocation and treatments, and any medical emergency can be managed without the need to break any code. The investigators will be informed of the suspected unexpected serious adverse events (SAEs) related to the study intervention. In this instance, the patient's GP or trained healthcare professional will inform the CI or a member of the study team. The CI will inform the Sponsor within 7 days of becoming aware of this. Even if the trial treatments are discontinued, the study participants will be requested to attend for continued follow-up and assessment.

Unblinding will not be part of managing an SAE as participants in both arms can be commenced on ULT and flare prophylaxis. If accidental unblinding occurs as part of managing an SAE, it will be reported to the Sponsor with the SAE, however, in cases where accidental un-blinding was not associated with an SAE, such actions will also be reported to the Sponsor immediately as practicable by phone or fax, followed by a written narrative of the event within 48 hours.

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Planned interim analysis will occur at the end of the internal pilot. The results of the interim analysis at this time-point will be available to the trial management group (TMG), TSC, and DMC. For monitoring purposes, the TMG and TSC will monitor patterns of SAEs across the blinded treatment groups. The DMC will review unblinded safety data and will report their assessment of whether there are any safety concerns to the TSC chair.

6.5 Trial Management

The study will be managed by the chief investigator, in collaboration with the co-investigators and the Keele CTU. An independent DMC and a TSC will be constituted. The DMC and TSC will have a named chair, and members with statistical, clinical trial, clinical rheumatology and primary-care expertise.

TRIAL STEERING COMMITTEE

The role of the TSC will be to provide overall supervision for the project on behalf of the Sponsor and Funder and to ensure that the project is conducted to the rigorous standards set out in the Department of Health's Research Governance Framework for Health and Social Care and the Guidelines for Good Clinical Practice.

The main responsibilities of the TSC will be as follows:

- To provide advice, through its Chair, to the Funder, the Sponsor, the Chief Investigator, the Host Institution and the Contractor on all appropriate aspects of the trial.
- To monitor progress of the trial, adherence to the protocol, patient safety (where appropriate) and the consideration of new information of relevance to the research question.
- Safeguard the rights, safety and well-being of the participants.
- To ensure appropriate ethical and other approvals are obtained in line with the project plan.
- To agree proposals for substantial protocol amendments and provide advice to the Sponsor and Funder regarding approvals of such amendments.
- To provide advice to the investigators on all aspects of the trial.

The TSC members will be contracted by the Sponsor using the Sponsor's standard TSC contract and charter which will detail the constitution and composition of the TSC.

The responsibility for calling and organizing TSC meetings lies with the Chief Investigator, in association with the Chair. There may be occasions when the Sponsor or the Funder will wish to organize and administer these meetings. This is unlikely, but the NIHR reserves the right to attend any meeting, and should therefore be included in relevant invitations, and also reserves the right to convene a meeting of the TSC/SSC in exceptional circumstances.

The Role of the Chair of the TSC:

The Chair of the TSC is directly answerable to the relevant NIHR programme, as funder. The Chair's responsibilities are also detailed in the Sponsor's TSC contract and charter.

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DATA MONITORING COMMITTEE

The role of the DMC is as follows:

- To monitor trial data and make recommendations to the TSC on whether there are any ethical or safety reasons why the trial should not continue
- The safety, rights and well-being of the trial participants are paramount
- The DMC considers the need for any interim analysis advising the TSC regarding the release of data and/or information
- The DMC may be asked by the TSC, Sponsor or Funder to consider data emerging from other related studies
- There are also rare occasions when the DMC chair might be asked by the Funder to provide a confidential interim or futility analysis if serious concerns are raised about the viability of the study or if the research team are requesting significant extensions.

The standard Sponsor DMC contract and Charter will be prepared containing details of membership, terms and conditions and full details of stopping guidelines. The DMC will report their assessment to the independent chair of the TSC.

The Chief Investigator has overall responsibility for the study and shall oversee all study management.

The data custodian will be the Chief Investigator. The Chief Investigator will delegate the data custodianship to the CTU Lead Statistician for the period of the trial, defined as the period up until the publication of the main trial results The CTU shall collect, hold and analyse the Data during the course of the Project in accordance with the Protocol.

Following the publication of the main results of the RCT, the Data shall be transferred to Nottingham in encrypted format, along with any information needed to de-encrypt the data, for final archiving.

6.5.1 Trial Data Sharing

During the trial any data access requests will be agreed with the Chief Investigator. No work based on the data shared under a data access request should be submitted for publication or included in presentations until the outcome of the main trial has been published in accordance with the terms of the funder and the collaboration agreement.

After the trial data transfer to the University of Nottingham, any future internal or external data requests will be handled by the University of Nottingham, who will keep the CTU informed about the number and outcomes of such requests. The Chief Investigator may be supported in handling these requests by the CTU Lead Statistician for the duration of their involvement with the trial.

6.6 Duration of the Trial and Participant Involvement

Study Duration: 80 months.
Enrolment begins: month 4

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Last visit of last participant in trial: month 56
End of study: month 80

Participant Duration: 2 years, with further 2 years' follow up after the last study visit.

End of the Trial

The end of the trial will be the point at which all long-term follow-up data has been received and cleaned for analysis.

6.7 Selection and Withdrawal of Participants

6.7.1 Recruitment

Trial setting: Primary care.

Recruitment: Primary care and community-based recruitment.

A. GP surgery lists

- Practice staff will search the GP records electronically to identify people with gout based on either any previous diagnosis, previous colchicine prescription, or current or previous ULT prescription.
- The GP (or nominated clinical deputy e.g. practice nurse) will review the patient list to exclude potentially unsuitable participants. e.g. those with dementia, terminal cancer, and severe enduring mental illness.
- Potential study participants will be posted a covering letter, a brief participant information sheet (PIS) containing a QR code to access the full participant information leaflet (a telephone number will be provided to request a paper copy for patients unable to access the QR code) and a brief questionnaire by the GP surgery staff to (a) assess eligibility, (b) enquire about willingness to participate in the study and for further contact by the research team to assess preliminary eligibility and arrange for a screening research visit, and (c) enquire about contact details. The pack will include a freepost envelope addressed to Keele CTU.
- In case of non-response after 4 weeks, the GP surgery will send a reminder letter to the participant.

B. Local community advertising:
In order to recruit participants who may not have consulted their local GP about gout, we will:

- Put up study posters in participating GP surgeries, GP surgery websites, or local pharmacies to inform people with gout who may not have been identified in GP electronic medical record search,
- Put up study posters in up to ten local community centers in each region, and
- Advertise the study in local newspapers.

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- Advertise the study on social media through Keele CTU.

We may utilize the following methods to recruit participants if required:

- Advertise and screen for the study using GP check in screens
- SMS invites sent by GP practices to all those patients registered with permission to be contacted by SMS and coded as having a diagnosis of Gout.

The posters and advertisements will signpost people interested in participating in the study to contact Keele CTU. Keele CTU will then contact them as described above.

Initial screening for eligibility:

- Keele CTU will assess eligibility based on questionnaire responses.
- Details of potentially eligible participants will be passed to the regional trial staff in the Clinical Research Network areas associated with their practices, using nhs.net email with participant consent and the appropriate data transfer agreements.
- It will be explained to the study participants that their identifiable details will be passed by the Keele CTU to trial staff in these areas.
- Trial staff will contact the patient by telephone to assess preliminary eligibility based upon the trial inclusion/exclusion criteria. During this call trial staff will confirm the patient has read the full version of the patient information leaflet. Those that do not meet the inclusion criteria will be thanked for their time and interest. Those that do meet the inclusion criteria will be invited to attend a screening visit.
- Staff in the Keele CTU and regional trial staff will arrange for the potential participants to be invited for a screening visit at their GP surgery. Screening visits can also be arranged at the participants' own homes if they are unable to attend the GP surgery due to other commitments, e.g. due to work.

Screening visit: The screening visit will be conducted by the regional trial staff. This may be conducted at the GP surgery, participants' homes or where the former are unavailable at a local NHS hospital, At the screening visit written informed consent will be obtained, participants' eligibility for participation in the trial will be assessed further (see section below), and for those potentially eligible based on verbal enquiry, blood will be collected for measuring serum urate, urea and creatinine. Participants will be asked about the presence of subcutaneous tophi using verbal description and examination of target sites (ears, elbow-tips, finger-pads, backs of hands, front of knees, Achilles tendon and dorsal aspect of feet). For those with a gouty tophus, a tophus count will be undertaken and maximum tophus size will be measured.
If the participant or the site or both prefer the baseline visit to be done remotely blood-pressure will be measured at the screening visit.

As serum urate can reduce during a gout flare, care will be taken to schedule screening visits at least 2 weeks after self-reported resolution of the gout flare.

Participants who do not meet the eligibility criteria at the screening visit will be informed and the reason(s) for this will be explained. Similarly, participants who give blood for serum urate and creatinine measurement, and have a serum urate level < 360 µmol/L, or eGFR < 30 ml/min will be explained that they do not meet the eligibility criteria for participating in this study. They will be thanked for their time and contribution and advised to consult their GP for gout flares

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as usual. It will be explained to them that their data collected so far will be used anonymously in the analysis. Screen failures will be replaced with other participants willing to take part in the study.

It will be explained to potential participants that entry into the trial is entirely voluntary and that their treatment and care will not be affected by their decision. It will also be explained that they can withdraw at any time without having to provide a reason. In the event of their withdrawal, it will be explained that their data collected so far cannot be erased and we will seek consent to use the data in the final analyses where appropriate.

Participants who have completed the trial will be sent a letter approximately four years after their randomisation date to thank them for their time taking part.

6.7.2 Eligibility criteria

6.7.3. Inclusion criteria

- Age ≥18 years,
- Ability to give informed consent,
- Meets the clinical American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for gout [26],

Table 7 ACR/EULAR classification criteria for gout

ACR/EULAR classification criteria for gout: A score of 8 or more is sufficient to classify the participant as having gout	
History of at least one episode of swelling, pain, or tenderness in a peripheral joint/bursa should be present before the classification criteria are applied	
Clinical classification criteria	
Pattern of joint/bursa involvement during episodes	
Joint/bursa other than ankle, midfoot or 1st MTPJ (or involvement in a polyarthritis)	0
Ankle OR midfoot (as part of monoarticular/oligoarticular episode without 1st MTPJ)	1
1st MTPJ (as part of monoarticular or oligoarticular episode)	2
How many characteristics during episode(s)? Erythema overlying joint (reported or observed); can't bear touch or pressure to joint; great difficulty with walking or inability to use joint.	
No characteristics	0
One characteristics	1
Two characteristics	2
Three characteristics	3
How many episodes with the following time-course? ≥2 time course symptoms, regardless of anti-inflammatory use: (1) Time to maximal pain < 24 hours; (2) Resolution of symptoms in ≤14 days; (3) Complete resolution (to baseline level) between symptomatic episodes.	
No typical episodes	0

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One typical episode	1
Recurrent typical episodes	2
Evidence of tophus. Draining or chalk-like subcutaneous nodule, located in typical locations: joints, ears, olecranon bursae, finger pads, tendons (e.g., Achilles).	
Absent	0
Present	4
Serum urate	
< 240 µmol/L	–4
≥ 240 or < 360 µmol/L	0
≥ 360 or < 480 µmol/L	2
≥ 480 or < 600 µmol/L	3
≥ 600	4

- ≥1 flare of gout in the previous 12 months (assessed at screening questionnaire stage), and
- Serum urate ≥360 µmol/L regardless of current ULT

6.7.4. Exclusion criteria

- Dementia, severe enduring mental illness i.e. mental health illness that makes receiving the study information and initial screening questionnaire from GP a stressful experience,
- Unable to comply with study procedures (including patients unable or not willing to have allopurinol and febuxostat due to side-effects or personal preference).
- Life expectancy less than 12 months,
- Cancer treatment, i.e. surgery, radiotherapy, or chemotherapy in the previous 12 months,
- Solid organ transplant,
- Cirrhosis,
- Autoimmune rheumatic disease i.e. rheumatoid arthritis, psoriatic arthritis, systemic lupus erythematosus, connective tissue diseases, vasculitis, giant cell arteritis, polymyalgia rheumatica, inflammatory arthritis associated with inflammatory bowel disease, reactive arthritis, ankylosing spondylitis,
- Inflammatory bowel disease
- Current long-term daily oral corticosteroid treatment defined as continuous use for ≥30 days or current immunosuppressive treatments,
- Stage 4/5 CKD i.e. eGFR < 30 ml/min/1.73m^2,
- Pregnant, breast feeding or planning to become pregnant in the next 4 years. Current participation in another trial that may influence the outcome of this study (e.g. another gout study or a dietary and lifestyle intervention study).

Patients who consent to contact and return the screening survey but are ineligible because they have not experienced a gout flare in the previous 12 months, will be sent a letter to ask them to contact Keele CTU if they experience a flare and are still interested in participating in the study, a reminder letter will also be sent at-least 6 months later and at-least 3 months before close of recruitment to those who have not re-contacted. Patients who contact Keele CTU that have experienced a gout flare will be screened as per the process above.

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6.7.5. Removal of participants from therapy or assessments/participant withdrawal

Study participants will be allowed to discontinue treat-to-target ULT if they:

[1] experience side-effects from the treat-to-target ULT protocol and are unwilling to continue on it,

[2] develop a temporary or permanent contra-indication to ULT, such as pregnancy, terminal illness, or

[3] wish to discontinue treat-to-target ULT without specifying a reason.

However, every attempt will be made to keep them in the study. If they agree to continue in the study, they will be invited to attend research assessment visits and provide outcome data.

Intent to withdraw from the study:

If a participant indicates a wish to withdraw, the participant will be requested to at least permit primary outcome data to be collected (ideally at the end of the participant's follow-up period), ensuring that enough data are recorded to support the planned analysis. Phone-calls, and letters to the participant will be used for re-contacting and reminding non-responders and non-attendees.

Study participants will be withdrawn from the study:

[1] if consent is withdrawn,

[2] at the participants' own discretion, or

[3] at the discretion of the Chief Investigator.

- The participants will be made aware that withdrawing from the study will not affect their future care, and that abrupt termination of study treatment does not affect their safety.

- Participants who withdraw from the study will have data on the date of withdrawal and reason of withdrawal collected where possible.

- Participants will be made aware (via the PIS and consent form) that should they withdraw, the data collected to date cannot be erased or destroyed and will still be used in the final analysis.

Enrolled participants who are not yet randomized can be replaced (though keeping their trial ID), but participants who withdraw after randomization will not be replaced.

6.7.6. Informed consent

All participants will provide written informed consent at the screening visit. The Informed Consent Form will be signed and dated by the participant before he or she enters the trial. The

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nurse or researcher will explain the details of the trial and provide a further copy of the PIS, ensuring that the participant has had sufficient time to consider participating or not. The nurse/researcher will answer any questions that the participant has concerning study participation.
Due to Covid-19 restrictions, if the site wishes to reduce the length of the face to face screening visit, the informed consent process may be started verbally during the telephone screening visit. During this phone call the nurse or researcher will be able to provide details about the trial, answer any questions the participant has concerning study participation and assert whether the participant would like to proceed with a face to face screening visit for the trial. This consent to proceed does not replace the written consent process and all participants will be provided with the opportunity to ask any further questions before being asked to provide written consent during their face to face screening visit. A further copy of the participant information sheet will be provided at this visit if required.

Informed consent will be collected from each participant before he or she undergoes any interventions (including physical examination and history taking) related to the study. One copy of this will be kept by the participant and one will be kept by the Investigator at site. In addition, a copy of the signed consent form will be sent securely to Keele Clinical Trials Unit (CTU), separately to any study data or case report forms. The consent forms will be stored in a secure location at Keele CTU in a different location to study data.

Should there be any subsequent amendment to the final protocol that might affect a participant's participation in the trial, continuing consent will be obtained using an amended consent form, which will be signed by the participant.

7. TRIAL STUDY TREATMENT AND REGIMEN

7.1 Treatment in intervention arm

Allopurinol-based treat-to-target ULT is the healthcare technology being assessed. It will be delivered by allied healthcare professionals or GPs trained in delivering and managing a protocol driven allopurinol-based treat-to-target regimen either face to face or remotely, for example by a phone call or a video-call as is being used at the site for consultations. The study-trained healthcare professionals can be practice nurses, clinical research network nurses, physician associates, GPs, or GP based paramedics. If a practice uses pharmacist to deliver pharmacological treatment for common conditions to their patients, they can also be trained in delivering the T2T intervention.

The steps of the treat-to-target ULT protocol are consistent with national and international recommendations and recent studies [12–14, 34–35]. These are:

- Allopurinol commenced at a dose of 100 mg/day at the initial intervention visit in the experimental arm. Participants already on sub-therapeutic dose of allopurinol will have its dose increased by 100 mg/day. Individualized education about gout and principles of management including treat-to-target-ULT discussed. Lifestyle risk-factors of gout discussed. Advice for improving them provided as adjuncts to treat-to-target-ULT. Arthritis Research UK (recently renamed Versus Arthritis) leaflet on gout provided.
- Participants of Han Chinese, Thai or Korean ethnicities will be commenced on

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Febuxostat 80 mg/day as first line ULT, as they are at a high risk of developing DRESS syndrome from Allopurinol treatment.

- A booklet containing study contact details, and a table for recording current ULT dose, serum urate level, date of next serum urate blood test, and date of next repeat ULT or flare prophylaxis prescription will be provided to participants in the intervention arm.
- Serum urate measured after approximately 4 weeks, as serum urate is a negative acute phase reactant [13] and the urate level commonly reduces during a flare. If a participant is experiencing gout flare at this time, the visit will be postponed till 2 weeks after the flare has resolved completely. This is a treatment visit and will be conducted by general practice nurses, phlebotomists or other suitably trained staff.
- Allopurinol dose increased by 100mg/day if the serum urate is ≥360 µmol/L at week 4.
- Process repeated approximately 4-weekly until serum urate is <360 µmol/L, or maximum licensed or tolerated dose of allopurinol reached.
- Due to the COVID pandemic, if a participant is unwilling to attend for regular frequent blood-tests or if a site is restricting the number of blood-tests performed/arranged by it, the T2T-ULT protocol allows for the dose of allopurinol to be increased in 100 mg/day increments at 4-weekly intervals till a maximum daily allopurinol dose of 300 mg/day is reached. This is because >96% participants require at-least 300 mg Allopurinol per day and the serum urate measurements are not a safety blood test. The decision to use this option rests with the GP and the participant depending on local conditions and participant and/or GP preference.
- If a participants' Allopurinol dose is increased to up to 300 mg/day without checking serum urate at each dose increment during COVID pandemic and, if the serum urate is <180 µmol/L when measured, the dose of Allopurinol will be reduced by 100 mg/day and the serum urate measured again four weeks later. This is consistent with the recommendation in the 2016 EULAR gout treatment guidelines that the serum urate levels are not maintained to a level less than 180 µmol/L in the long term that is, for several years [13]. In our clinical and research experience it is extremely rare to achieve a serum urate <180 µmol/L with allopurinol 300 mg/day. Prior to any change of dose participants will be contacted by telephone by the practice nurse (or other HCP leading the intervention arm) to confirm the participant is not experiencing any side effects and are happy to have their dose altered accordingly.
- Allopurinol discontinued if unable to achieve serum urate <360 µmol/L due to side effects or intolerance of high doses, or failure to do so despite maximum licensed dose, and febuxostat 80 mg/day started as per the NICE Technology Appraisal 164.
- The dose of febuxostat increased 4 weeks later to 120 mg/day if the serum urate ≥360 µmol/L.
- If serum urate is ≥360 µmol/L despite maximum licensed dose of allopurinol or febuxostat, participants can remain in the trial to provide outcome data.
- Once the treatment target is reached (i.e. serum urate < 360 µmol/L), the practice-staff will confirm with the participant that this was at least two weeks clear of the previous gout flare. For participants experiencing a gout flare in this period, the serum urate will be measured at least 2 weeks from the date of self-reported resolution of the gout flare. If the serum urate is ≥360 µmol/L at this point, the dose of ULT will be increased as outlined above.

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- Once serum urate is <360µmol/L, ULT prescription will occur 2-monthly without any face-to-face visits. Four-weekly serum urate measurements will stop once the serum urate level is <360µmol/L.
- The dose of ULT ought to be reduced in people with CKD 4 or higher. As they are excluded from the trial, all study participants will be given the same ULT dose increase regardless of their renal function.
- Participants will have serum urate measured at year 1 and year 2 research assessment visits (see later page 42). The practice-staff of participants randomized to the intervention arm will be made aware of the results of these tests. They will inform the study participants, and those no longer achieving treatment target will be reviewed to discuss adherence with ULT. Participants adherent to ULT will have the dose of ULT increased where possible using treat to target strategy outlined above. Participants in the intervention arm with a serum urate lower than 180µmol/L at the two-year follow up point will be highlighted to the practice staff to consider reducing the ULT dose.
- Participants can request further clinical visits, or telephone advice from their study-trained healthcare professional or GP, for their gout, as needed.
- The lead applicant, and two of the clinical co-investigators (ER, MS with CDM and PL deputizing in case of leave) will advise the study-trained healthcare professional or GP and the GP signing the prescription if required.
- Each participating GP surgery will have a nominated GP for signing the ULT prescription, and the research trained healthcare professionals will not treat control arm gout patients for the study duration. The study-trained healthcare professionals will be required to not disseminate their experience with ULT to other staff members during the study.

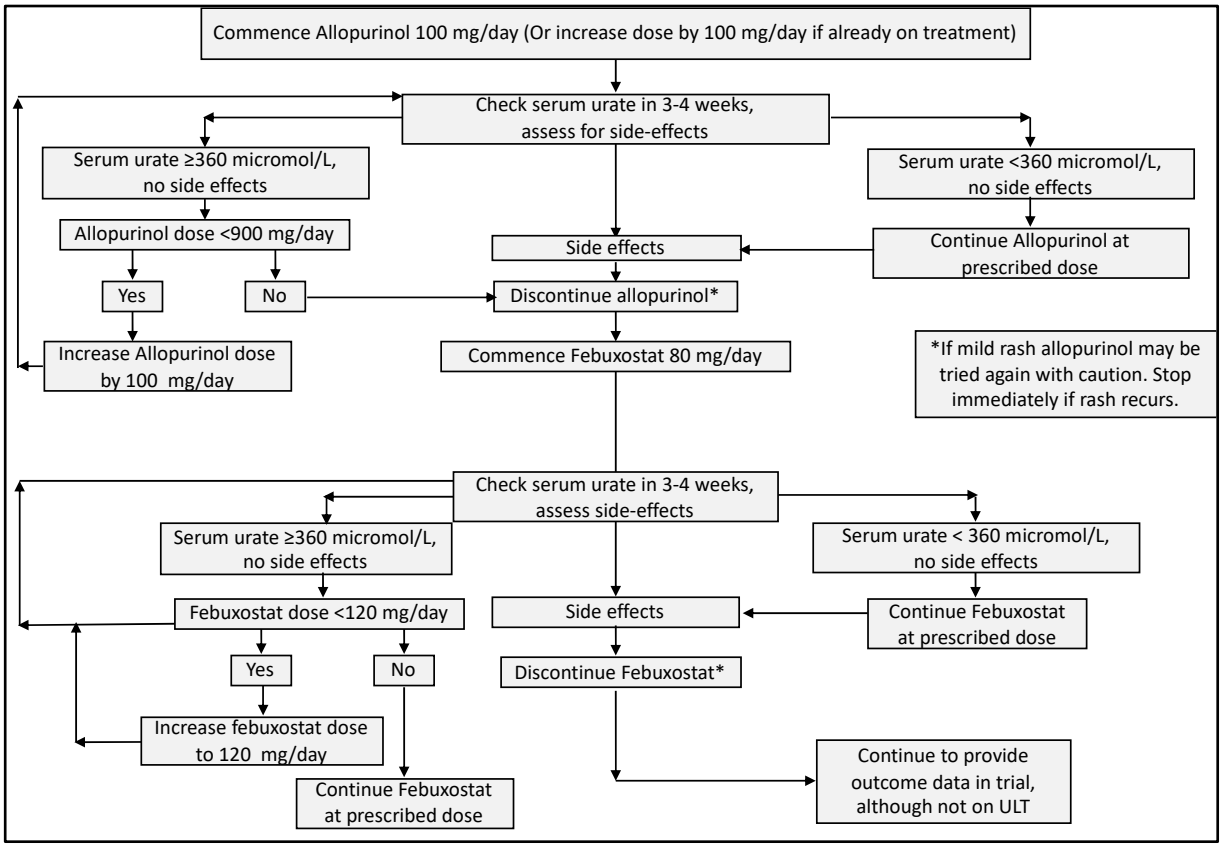
Participants unable to initiate allopurinol due to prior side-effects to the medicine will be offered Febuxostat first line instead of allopurinol. This is consistent with routine clinical practice and NICE technology appraisal.

Prophylaxis: As the initiation of ULT can increase the risk of gout flare occurrence, prophylaxis to prevent gout flares will be prescribed for six months as part of the treat-to-target ULT regimen, as recommended in national and international gout treatment guidelines [12–14].

- Colchicine (0.5 mg twice a day) will be used first line for this purpose. The dose of colchicine will be halved if the study participant is on any medication for which this is recommended by the British National Formulary (See Appendix 1), or is aged over 70 years, or has renal impairment. Additionally, if colchicine is not tolerated due to side effects such as diarrhoea, its dose will be halved. If half-dose colchicine is not tolerated, it will be discontinued. Colchicine will not be prescribed if there are contraindications to its use as per the BNF (See Appendix 2).
- Naproxen (250 mg twice a day) along with a generic proton pump inhibitor (e.g. omeprazole 20 mg/day if not already prescribed) will be used second-line if there are contraindications to colchicine prescription or it is not tolerated. Low-dose NSAIDs will not be prescribed in the presence of contra-indications specified in the BNF and NICE clinical knowledge summary for NSAIDs (See Appendix 2).
- Participants unable to tolerate either of the two prophylactic medicines will continue on ULT without prophylaxis, but will be provided with rescue packs of oral prednisolone (30 mg/day for 1 week) to treat gout flares should they occur.

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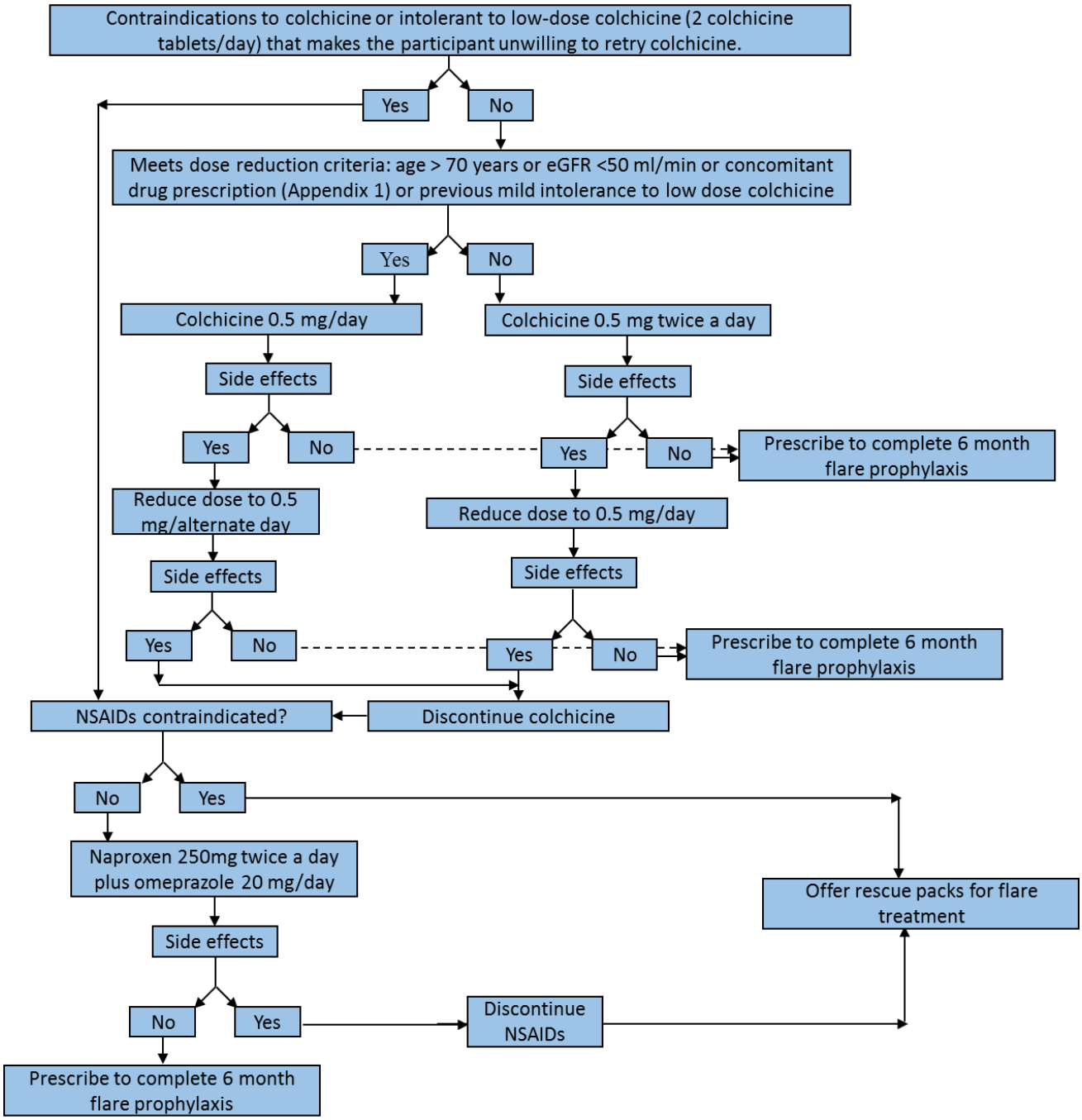
Figure 1 Treat to target urate lowering treatment protocol*



Due to the COVID pandemic, if a participant is unwilling to attend for regular frequent blood-tests or if a site is restricting the number of blood-tests performed by it, the T2T-ULT protocol allows for the dose of allopurinol to be increased in 100 mg/day increments at 4-weekly intervals till a maximum daily allopurinol dose of 300 mg/day is reached.

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Figure 2 Flare prophylaxis



[1]Contraindications to colchicine as per BNF. [2]Colchicine dose reduction criteria: either of interacting medicines (See appendix 1), or age > 70 years, or eGFR 30-50 ml/min.

Treatment of flares of gout: Participants in both arms of the study will be able to get treatment for flares of gout from their GP as before they entered the study.

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7.2 Treatment in control arm

Study participants will be able to consult their GP as usual and receive treatment for flares of gout and ULT according to the GP's usual practice and their symptoms. Participants in both arms will attend at the screening, baseline, year 1 and year 2 research assessment visits.

7.3 Concomitant treatments

All concomitant treatments will be allowed in the control arm. Participants in the intervention arm will be commenced on treat-to-target urate lowering treatment, and flare prophylaxis. They will also be allowed to continue on, or, commence any other concomitant treatment as necessary. They will not have access to a structured allopurinol-based study-trained healthcare professional led treat-to-target ULT. Our own clinical experience and published research suggests that such treat-to-target-ULT is very uncommonly prescribed by GPs in the UK, with the vast majority of gout patients not being prescribed any ULT, or being prescribed sub-therapeutic fixed doses of ULT e.g. allopurinol 300 mg/day [2].

7.4 Internal pilot

The first ninety participants randomized will be recruited into the internal pilot, randomized to active or control arm, receive study interventions to be used in the randomized controlled trial as detailed above, and be followed up until year 1 research assessment. Participants in the internal pilot will continue on ULT while progression to the main trial is confirmed as there will be no halt in recruitment between the pilot and main trial phases. Any participants over and above the first 90 participants will continue on ULT while the progression criteria are assessed and progression to the main trial is confirmed. The criteria for progression to the main trial are described in the statistics section. Data from baseline to year 1 research assessment will be used to assess feasibility outcomes, and gain a preliminary estimate of treatment efficacy.

7.5 Study visits

Research assessment visits at baseline, year 1 and year 2 will occur at the GP surgery, local NHS hospitals, or at the participants' own homes if they are unable to attend the GP surgery during opening hours. The research visit date will be calculated using the date of randomization with a one-month window either side. If a participant moves to a GP practice during the trial (post randomization) which is not taking part, the participant can remain in the trial and provide primary outcome data, and those secondary outcome measures feasible for telephone/postal collection will be collected by the outcome assessor. Where feasible with the new GP blood and urine samples will be collected from patients at the year one and year two follow up visits.

Treatment visits will occur at the GP surgery or delivered by primary-care staff over the telephone, with the blood for measuring serum urate being collected at the GP surgery, or in local hospitals depending on local arrangements. Once the serum urate level is available, the dose of ULT may be increased at a face-to-face visit or over the phone, during a consultation with the practice staff.

During the COVID-19 pandemic baseline research assessment may be performed remotely.

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For this, the participant will be sent a baseline CRF to complete at home and post to the Keele CTU using a self-addressed envelope. Participants willing to complete the research assessment questionnaire online will be given the option to do so. The Keele CTU will randomize participants on confirmation that the baseline questionnaire is completed and at-least packed in the envelope (or check online data entry completed) to allow data collection at the baseline visit to occur with the participant blinded to the group allocation. The decision whether the baseline visit is remote or face-to-face will depend on the Site and participant preference.

For participants who would prefer to complete the research visit questionnaire online for their 1 and/or 2 year follow up, Keele CTU will send a weblink to the participant via email. For participants who are unable to complete the research questionnaire at their 1 and/or 2 year follow up appointment, Keele CTU will be able to arrange for a paper copy of the questionnaire to be sent via post or an online version of the questionnaire sent via email for the participant to complete and return.

If a site withdraws from taking part in the research, participants will be given the opportunity to continue in the study. For participants who are still to attend their 1 and/or 2 year follow up appointment, these appointments will be conducted via telephone by a member of the study team at Keele CTU. The relevant data as per Table 8 will be collected where possible, where it is not feasible for samples to be taken this data will not be collected. A research visit questionnaire can be sent to the participant as described above.

Table 8: Study visits

	Screening	Baseline	Treatment	Treatment	Treatment	Treatment	Treatment	Treatment	Treatment	Res. Yr. 1	Res. Yr. 2	Final visit
Week	**0**	**1**	**5**	**9**	**13**	**17**	**21**	**25**	**29**	**52**	**104**	**208**
Informed Consent	X											
Inclusion / Exclusion	X											
Research questionnaires[1]		X								X	X	
Tophus count/size	X									X	X	
Body Mass Index		X*								X	X	
Blood Pressure		X**								X	X	
Blood collection	X[2,3]		X[2]	X[2,4]	X[2,4]	X[2,4]	X[2,4]	X[2,4]	X[2,4]	X[2,3]	X[2,3]	

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Urine collection		X[5]								X[5]	X[5]	
Randomize		X										
Gout flare and healthcare utilization diary[6] given[7]		X										
Start T2T-ULT/dose change		X	X	X	X	X	X	X	X	X		
Gout flare SMS data collection												
Unused medication return										X	X	X
Flare & healthcare use diary collect			X	X	X	X	X	X	X	X	X	
Data collection from GP records										X	X	X

[1]current ULT, co-morbidities, GIS 2.0, EQ-5D-5L, and at year 1 and year 2 research assessment treatment satisfaction questionnaire, MMAS-8 for people prescribed ULT. [2]Serum urate, [3]Serum creatinine, [4]Serum urate measured if prior serum urate ≥360µmol/L, [5]Urine albumin-creatinine ratio, [6]To capture data on GP, hospital, A&E, or out-of-hours GP surgery attendance for gout, drugs taken to treat gout flares, Gout Impact Scale after each gout flare, [7]Replaced as needed. ongoing data collection, intervention arm *calculated using height and weight measurements at baseline visit or using self-report height and weight. ** may be collected at the time of screening visit if the baseline visit will not be face to face

7.6 Data Collected at Research Assessments

The research nurse/researcher in each region will collect data from study participants at the baseline, year 1 and year 2 research assessment visits.

Table 9: Research assessments

		Research assessment		
	Screening	Baseline	Year 1	Year 2
Sex	X			
Date of birth	X			
Ethnicity		X	X(***)	X(***)
Serum urate	X		X	X
Serum creatinine	X		X	X
Inclusion criteria	X			

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Exclusion criteria	X	X		
Prescription drugs		X	X	X
Comorbidities		X	X	X
Body mass index		X*	X	X
Blood Pressure	X**	X**	X	X
Tophus count	X			X
Tophus size	X			X
Urine collection		X	X	X
Side-effects to ULT			X	X
GIS [1]		X	X	X
EQ-5D-5L		X	X	X
TSQ[2]			X	X
MMAS-8[3]			X	X
Gout flare and Healthcare use diary		Given	Collected	Collected

[1]Gout impact scale, [2]Treatment satisfaction questionnaire, [3]Morisky Medication Adherence Scale-8.* can be calculated from self-reported height and weight if baseline research assessment is not face-to-face. ** may be collected at the time of screening visit if the baseline visit will not be face to face. *** May be collected at research visit if not collected at baseline visit.

During the COVID-19 pandemic and when its consequences are affecting NHS services, every effort will be taken to minimize face-to-face patient contact and, all of the baseline assessments, and the self-reported components of the year 1 and year 2 research assessment may be undertaken via post or email depending on the current situation in the site (GP surgery) and participant preference. Participants willing to complete the research assessment questionnaire online will be given the option to do so.

7.7 Data Collected from GP Surgery

Data about serum urate, current ULT and flare prophylaxis treatment (name and dose), any temporary treatment discontinuations and reasons, side-effects, and recommended treatment if applicable (name and dose) will be collected by general practice staff at each dose increase visit in the intervention arm as part of usual medical care.

Data about the following variables will be collected from GP surgery records at year 1 and year 2 research assessment visits, along with their dates. This will be collected by GP surgery staff or the local research staff depending on local preference at the GP surgery.

Ethnicity
Serum urate (results, dates)
ULT prescriptions (name, daily dose, duration, dates of prescription)
Flare prophylaxis prescriptions (name, daily dose, duration, dates of prescription)

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GP surgery consultations for flares (dates)
GP telephone consultations for flares (number, dates)
Out-of-hours emergency GP surgery attendance for flares (dates)
Flare treatments (name, daily dose, total quantity, dates of prescription)
Referral to hospital outpatient clinic for gout (dates of referral)
Hospitalization for gout flare (number, admission and discharge dates)
A&E attendance for gout flare (number, admission and discharge dates)
Side-effects to ULT (specify event, dates)
Side-effects to flare prophylaxis (specify events, dates)
Side-effects to flare treatment (specify events, dates)
Covid-19 vaccinations (brand, administration dates)
Influenza vaccinations (brand, administration dates)

Data about the following variables will be collected at year 4 from GP surgery records:

- Ethnicity
- Number of Primary-care consultations for gout in previous 24 months,
- Hospitalizations due to gout in previous 24 months,
- Latest urate lowering treatment (drug name, dose, prescription), and number of prescriptions in previous 24 months
- Prescriptions of NSAIDs, colchicine or corticosteroids that are used for treating flares of gout in previous 24 months (drug name, dose, duration),
- Investigations for gout ((Serum urate, CRP, ESR), and number of referrals for radiographs of hands, foot, knee and ankle),,
- Incident cardiovascular diseases, hypertension, diabetes and diagnosis date,
- Serum creatinine and estimated GFR (latest result if done due to clinical reasons and date),
- Urine albumin creatinine ratio (latest result if done due to clinical reasons and date),
- Death: Reason and death date.

7.8 Data Collected by Study Participants

Ethnicity data will be collected from randomized participants at their baseline visit. For those participants randomized to the trial prior to the protocol amendment ethnicity data will be collected at the next research visit or GP record review.

Patients' postcodes will be provided by those consenting to further contact during the initial screening questionnaire stage, individual postcode data will be used to measure deprivation score. Where postcode data is not available postcodes will be measured by GP practice postcode.

Electronic acute gout flare diary: A mobile phone text-messaging system will be used to collect data on occurrence and severity of gout flares.

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Text message system:

- Participants will receive a welcome text message at the baseline visit after randomization to confirm their telephone number, welcome them to the study and advise them that they will receive SMS messages going forward.
- Study participants will initiate the text-messaging service by texting the word “gout ” when they experience a flare. If they forget to text on the first day, they can still text “gout” at a later date.
- The messaging system will send short text messages enquiring about pain severity (0–10 numerical rating scale), presence of warm joint, and swollen joint [47]. This will be used to classify self-reported gout flares as meeting the criteria for a flare of gout [47]. For a flare to be present, the episode should meet the flare definition criteria, i.e. at least 3 of the following four: pain severity >3/10, presence of warm joint, swollen joint, and self-reported flare [47]. A single reminder will be sent for non-response.
- On day 1 of self-reported gout flare the messaging system will ask participants how long they have had the flare for, and send a message asking participants to complete EQ-5D-5L in a brief paper diary within next 48 hours.
- The messaging system will then send daily text messages enquiring about pain severity on a 0–10 numerical rating scale (NRS) each morning for up to 7 days, with a reminder to answer the question if needed. This suite of messages will be discontinued if the participants responds with a score of 0 or 1 on 2 consecutive days. The pain numerical rating scale is endorsed by Outcome Measures in Rheumatology Clinical Trials for measuring the severity of flares of gout [48].
- After 7 days, or if there are two days with NRS 0 or 1, the participant will receive a thank-you text, and, a reminder to complete the questions regarding wellbeing during gout flare and gout concern during flare domains of GIS, healthcare utilization during gout flare and date the gout flare resolved in a brief paper diary.
- To mitigate the risk of a single flare being counted as multiple flares, a flare will be defined as an incident flare if there is at least a 48-hour time period between the end of the previous flare reporting period and the start of next flare. If the interval between is smaller than 48 hours, they will be regarded as a single episode.
- Participants who indicate that they have experienced a gout flare and have agreed to send data by SMS **but do not initiate the suite of SMS by texting gout, yet return the brief paper diary,** will be contacted by telephone by a member of the study team. The study team member will elicit information about pain severity (0–10 NRS), presence of warm joint, swollen joint, to classify self-reported gout flares as meeting the criteria for gout flare [47].
- Similarly, participants who inform that they have experienced a gout flare and have agreed to send data by SMS and initiate the suite of SMS by texting gout, but **do not return the brief paper diary,** will be sent a minimal data collection SMS diaryin the post and asked to complete and return to Keele CTU. Following this, those who do not return a diary will be contacted by Keele CTU via telephone in an attempt for minimal data to be collected over the telephone.
- Flares with no reported daily pain NRS will be excluded from analysis of secondary outcomes e.g. flare severity and duration.
- If the participant forgets to text when the flare is occurring, he or she will be able to contact the research team by phone during weekday office hours to report the date of onset and end of the most recent gout flare. The researcher will elicit information about pain severity (0–10 NRS), presence of warm joint, swollen joint, to classify

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self-reported gout flares as meeting the criteria for gout flare [47]. Daily pain severity and EQ-5D-5L will not be available for such episodes.

Online data collection during gout flares: Alternatively, a participant may be able to provide data during gout flares via an online web-based platform using a unique log-in token. If they choose to do so, there will be no need to complete a brief paper diary.

Paper diary:

A paper diary will be available for those who do not have a mobile phone or do not wish to use text-messages or an online data collection form. Participants who initially opt for SMS will also be able to switch to a full paper diary if they feel that the SMS response service is not suitable for them.

- If the participant forgets to text or return the diary when the flare is occurring, he or she will be able to contact the research team by phone during weekday office hours to report the date of onset and end of the most recent gout flare. The study team member will elicit information about pain severity (0–10 NRS), presence of warm joint, swollen joint, to classify self-reported gout flares as meeting the criteria for gout flare [47]. Daily pain severity and EQ-5D-5L will not be available for such episodes.
- Flares with no reported daily pain NRS will be excluded from analysis of secondary outcomes, e.g. flare severity and duration.

Reminders: As study participants can forget completing the gout flare diary, they will receive a text or a letter (if they do not have a mobile phone), every 2 months, reminding them to complete the gout flare diary, and, if they had a flare for which they did not complete the flare diary, they will be encouraged to phone dedicated research staff in the research team to provide these data.

Health related QoL during gout flares: To account for QoL during gout flares, the participants will complete the EQ-5D-5L once within the first 48 hours of onset of each gout flare. The collection of EQ-5D-5L also allows us to bring health status during gout flare into overall cost-utility analysis.

The wellbeing during gout flare and gout concern during flare sub-scales of the GI S, which captures disease specific QoL during the most-recent gout flare, will be completed within 2 days of complete resolution of the acute gout flares.

Loss of productivity during gout flares: Information about the number of days on which gainful paid employment was lost during each flare will be recorded in the gout flare diary.

Healthcare utilization for gout during flares: Medicines taken for gout flare, GP visits, A&E visits, out of hours-GP visits, home GP visits, hospitalization, number of days hospitalized.

Patients randomised to the trial will be contacted by letter periodically during the trial to thank them for their continued participation and to provide any study updates.

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7.9 Minimum Data Collection (MDC)

If a participant does not attend a follow up visit, the study team will initiate the Minimum Data Collection (MDC) procedure to ensure that as much data as possible can be collected from both the site and the patient. The study team will regularly monitor follow ups and identify those participants who have not attended an appointment. The study team will confirm with the site that the participant has not attended a follow up visit and then ask them to retrospectively complete the relevant case report forms to capture as much follow up data as possible (as described in section 7.5 Study visits and 7.7 Data Collected from GP Surgery).

The study team will attempt to contact the participant by telephone in the first instance and if successful will explain the reason for the call, to ask if they would be willing to complete the research visit questionnaire. This will be offered to the participant to complete over the telephone with an administrator or alternatively a paper copy of the questionnaire can be sent via post or an online version of the questionnaire sent via email for the participant to complete and return.

If a participant is uncontactable via telephone, they will be sent a paper copy of the questionnaire via post with a cover letter to explain the reason for the contact, if it is not returned then this will be recorded as missing data.

There may be data that may not be available such as from the Physical Examination questions, and the patient may not complete the research visit questionnaire fully or at all, hence the term ‘Minimal Data Collection’ has been used.

7.10 Compliance

Data on total number and dose of ULT prescriptions issued in the preceding 12 months will be collected at each research visit, i.e. at years 1 and 2, and any unused ULT tablets counted. These will be used to calculate the medication possession ratio (MPR). The eight-item MMAS-8 will be completed at year 1 and year 2 research assessment visits.

7.11 Data Collection in Long-Term Extension Phase

Participants will continue to provide data about the occurrence of flares after their two-year research assessment visit for an additional two-year period. This will be in the form of a text message or paper diary depending on participant preference.

The GP surgery staff or delegated Research Delivery Network (RDN) staff will search the participants medical records for GP consultations or hospitalizations due to gout, ULT prescription, other prescriptions for treating flares of gout, investigations, new diagnosis of cardiovascular diseases, hypertension, diabetes, incidence or progression of CKD, or death two years after each participant’s last visit.

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7.12 Criteria for Terminating the Trial

The trial will be stopped if:

[1] on an interim analysis there is overwhelming and undoubtable evidence of efficacy and/or major safety concerns,

[2] relevant new information becomes available, or

[3] there are or issues with trial conduct such as
(a) poor recruitment,
(b) loss of resources.

The trial may be discontinued in one region if there is:

[1] poor recruitment, or

[2] poor adherence to the protocol.

The decision to terminate the trial in a single region or in all regions will be made after review by the TSC/DMC.

If this were to occur, all unused trial supplies, e.g. medicines, will either be returned to the local NHS Pharmacies by the study participants for disposal as per usual NHS practice, or continue to be taken based on the GP's discretion.

7.13 Laboratory Analyses

Routine haematological and biochemical assessments such as full blood count, urea electrolytes and creatinine, liver function tests, and serum urate measurement will be performed in the local NHS hospitals in each region. The clinical pathology laboratories will use standard NHS practices to analyse and dispose of the samples in accordance with the Human Tissue Act, 2004.

7.14 Transport and Storage of the Tissues

Blood and urine samples for NHS pathology analysis will be labelled in accordance with local NHS procedures. Samples will be shipped and stored according to local protocols and no samples will be stored for research purposes following analysis.

8. STATISTICS

8.1 Statistical Analysis Plan

A detailed statistical analysis plan (SAP) will be drafted by the study statistician and approved by the TMG, the TSC and the DMC; it will be finalized before unblinding of the data (any

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subsequent deviations from the SAP will be approved by the TSC and documented in the final report). A summary of the statistical methods to be used is given below. The SAP will be the formal and up-to-date statement of all analyses to be performed on the trial data, and will take precedence over the study protocol in the event of any discrepancy in the analyses described by the two documents.

8.2 Internal Pilot

Analytical plan: Baseline categorical outcomes will be summarized using frequencies and percentages, and continuous outcomes will be summarized using means (standard deviations) and medians (interquartile range). Particular attention will be paid to missing items and patterns of missing data from the electronic capture of gout flare severity and QoL. No formal statistical comparisons between treatment arms will be made, but 95% CIs will be calculated for [1] the between-group difference in the gout flares count, between months 7–12 in the two arms, and [2] the proportion meeting serum urate treatment target, and the between-group difference in these proportions, at month 12. Adherence with ULT will be assessed in the experimental and control arms (for control-arm participants who are on ULT using the MPR, taking the returned pill count into account, with a MPR ≥80% or MMAS-8 >6 defined as being adherent [53]).

Signal of efficacy outcome measure and time-point: It is difficult to determine signal of efficacy from pilot studies. This is especially true for gout, where flares become more frequent in the first few months of initiating ULT, and continue for 6 months to 1 year (or even longer) after starting treatment. This is a direct effect of urate-lowering, which causes crystal dissolution, encouraging shedding of crystals in to the joint space which triggers a flare. In fact, gout treatment guidelines recommend flare prophylaxis (e.g. colchicine) for at least 6 months after starting ULT. In keeping with these, all study participants will be prescribed flare prophylaxis for 6 months in this study. Thus, we cannot use the number of flares in the first 6 months of ULT to gain a preliminary signal of efficacy. We will therefore estimate the number of gout flares in months 7–12 between the two arms. However, this does not form part of the thresholds to progress to the main trial (see below).

Threshold for progressing to the main trial:

The trial will proceed if the randomization rate from the main method of recruitment is ≥10%, ≥85% data points in the flare diaries are completed by the participant, adherence with ULT is ≥80% and attrition <20%, or pending revisions to the protocol if the randomization rate from the main method of recruitment is ≥5%, 70-84% data points in the flare diaries are completed by the participant, adherence with ULT is 60–79%, and attrition is 20–30%. If these thresholds are not met, discussion with the TSC and the HTA will take place to determine if modifications should be made to the procedures in the trial, or the trial should be terminated.

A main trial will be considered feasible if ≥70% participants achieve serum urate target at month 12 in the intervention arm, and following protocol amendments if this proportion is >50%, with other *a priori* feasibility outcomes being met. Serum urate is a surrogate marker of frequent gout flares [9], and a reduction is a preliminary signal of efficacy. Additionally, a substantial reduction in serum urate in the intervention arm provides confidence that the intervention is being delivered as intended. However, we realize that this does not provide a direct measure of the primary outcome.

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We do not propose to include gout flares in months 7–12 as an efficacy threshold of progression to the main trial due to the fact that gout flares may occur at the same rate even 1 year after starting ULT, and it would be erroneous to include it as a feasibility outcome. However, these data will be presented to the HTA Board and the Trial Steering Committee.

Rationale behind threshold for progressing to main trial

[1] A randomization rate of ≥ 10% from the main recruitment method suggests that the recruitment will be completed from up to 50 GP surgeries as planned. If the recruitment rate is between 5% and 10%, we will approach additional GP surgeries via the NIHR Primary Care Clinical Research Networks. Given our experience of recruiting into gout studies from the primary care in the Midlands and Wessex (e.g. CONTACT study, PI Dr Roddy; and Nottingham study, PI Prof Doherty), we are confident of finding >100 willing GP practices for recruitment, and, the planned recruitment can be achieved if the randomization rate from main method of recruitment is as low as 5%. If the randomization rate is <5%, this will be discussed with the TSC and the funder, keeping the Covid-19 pandemic in context, to identify any remediable measures.

[2] If target serum urate is not achieved in <50% participants by year 1, and <60% are adherent to ULT at year 1, it suggests such low concordance with the intervention that a meaningful effect on the rate of flare occurrence is unlikely, and proceeding with this trial would be futile. If there is need for substantial further training or other remedial action to improve the proportion of intervention arm participants achieving treatment target in the internal pilot, we will discuss the implications of this for conduct of the whole trial, its sample size and analysis with the funder and the TSC

[3] The sample size allows for up to 20% loss to follow-up. A high attrition rate of 21–30% in the pilot study likely indicates poor tolerability of the study processes, and we will explore and address the reasons for this. An attrition rate >30% in internal pilot may affect the validity of the findings, making proceeding with the study futile if the high attrition rate is thought to be not remediable by the TSC and the funder.

[4] If information in the electronic flare diary is 70–84% complete on any outcome measure (e.g. pain severity, flare stop date) we will address any problems. If the flare diary is completed in <70% instances for the primary outcome, this will not be a feasible method for collecting outcome data and other methods of collecting flare data, e.g. paper diary or phone calls, will be used.

Choice of method of outcome measure collection based on internal pilot:

If the data quality (missingness) is substantially better in the paper diary, we will abandon the SMS system for collecting primary outcome data. Similarly, we will abandon the SMS for collecting primary outcome data if a substantial number of people phone in during/after their gout flare to provide data on primary outcome, and do not use real-time SMS.

Completeness of the flare diary in internal pilot

Participants can phone the CTU if they forget to send in text messages when they are experiencing a flare (see above). Apart from this, they will be sent text message reminders at 2 monthly intervals and requested to phone and inform the research team if there were any gout flares they did not report at all. This will be used to assess the completeness of the text message system in collecting data on the primary outcome (number of acute gout flares). Where a flare diary is initiated, we will measure the proportion of completed responses for each

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outcome of interest, i.e. erythema, pain severity, swelling and tenderness on day 1, EQ-5D-5L on day 2, daily pain score.

8.3 Full RCT

Analytical plan: Analysis will be on an intention-to-treat (ITT) basis, according to the pre-specified SAP. The primary outcome, gout flare count over 24 month's post-randomization, will be analysed between groups through negative binomial regression, adjusting for flare count in the year prior to trial entry and stratification factor. If appropriate, a conditional, rather than a marginal, negative binomial model will be used to take account of flare count prior to trial entry (truncating these to be non-zero, in accordance with the corresponding inclusion criteria). The fit of a negative binomial model to the data will be assessed, and if poor, an alternative model (e.g. zero-inflated negative binomial or Poisson) will be used. As a secondary analysis on the primary outcome, flares occurring during months 1–12 and between months 13–24 will be analyzed between groups.

Longitudinal analyses based on generalized linear mixed-effects models will be performed for other continuous or binary outcomes, at both 1- and 2-year follow-up: mean pain intensity and mean duration of gout flares; mean serum urate; treatment satisfaction scores; adherence (those taking >80% of the doses or scoring ≥6 on the MMAS-8 will be considered as adherent) These analyses will similarly adjust for baseline values (where appropriate) and the stratification factor.

All analyses will take use all follow-up data where appropriate, using a generalized mixed-effects regression model, with a random intercept to account for the correlation between observations clustered within participants. Maximum likelihood estimation will be used to fit all the models, as this method of estimation yields parameter estimates that are not affected by the exclusion of missing outcome data if a missing-at-random assumption is plausible. Multiple imputation will be used for explanatory variables if missing at random is a plausible assumption.

Assumptions of all analyses will be checked and significance will be set at $p \leq .05$, with 95% CIs calculated for between-group estimates. No adjustment will be made to alpha for multiplicity because the analysis of each outcome is of clinical interest in its own right. The primary analysis will be on the basis of ITT, but appropriate sensitivity analyses will be performed, as specified in the SAP.

Side-effects from intervention will be tabulated and compared between the two groups.

Definition of CKD

Incident CKD will be defined as a new eGFR<60ml/min/1.73m^2 ~~on 2 occasions at least 90 days apart~~. The results of eGFR at baseline, year 1 and year 2 research assessments will form the qualifying results, eGFR will be calculated using CKD-EPI creatinine Equation (2021)[1]

[1] Inker LA, Eneanya ND, Coresh J, et al. New creatinine- and cystatin C–based equations to estimate GFR without Race. *New England Journal of Medicine*. 2021;385(19):1737-1749. doi:10.1056/NEJMoa2102953

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Progression of CKD will be defined as reduction in GFR of at least 25% and progression to next GFR category (KDIGO Definition). The results of serum creatinine, eGFR and urine albumin creatinine ratio at baseline, year 1 and 2 research assessments will be used to define the progression of CKD.

The proportion of people meeting the KDIGO classification of progression of CKD based on their eGFR and urine albumin creatinine ratio will be compared between the two groups at years 1 and 2 [51].

8.4 Health Economic Analysis

Cost-effectiveness (cost per flare avoided) and cost-utility (cost per quality-adjusted life year (QALY) gained) will be determined within the trial using healthcare resource use data (questionnaires and medical records), primary outcome data and EQ-5D-5L. The economic evaluation will assess the cost-effectiveness and cost-utility of treat-to-target with ULT compared with usual GP care in patients with recurrent gout. This will take the form of an incremental cost-utility analysis to estimate cost per QALY and an incremental cost-effectiveness analysis to estimate the cost per gout flare avoided over 24 months follow-up, using patient-level data on costs and outcomes from the trial. The base-case analysis will be from an NHS and Personal Social Services perspective, with an additional analysis from a societal perspective taking into account productivity losses.

Data collection: In order to calculate QALYs, the EQ-5D-5L questionnaire will be administered to patients at baseline, 12 and 24 months. In order to account for quality of life during gout flares, participants will also complete the EQ-5D-5L once during each gout flare. The crosswalk value set will be applied to patient responses to obtain utility scores, in line with current NICE recommendations. The more recent English value set will be used in a sensitivity analysis. Information on gout-related resource use will collected via patient paper diary filled in prospectively over the 24-month study period. The cost of the intervention will be determined within the trial, taking into account training, and costs of delivering the interventions. Unit costs from standard UK sources will be sought for all health care resource use items. Data on broader costs will also be collected, related to time off work to calculate productivity losses. Information on occupation, further details of typical work activities and the nature of their employment (full time or part time) will be requested. The average wage for each respondent will be identified using UK Standard Occupational Classification coding and annual earnings data for each job type.

Analysis: The number of gout flares per patient will be obtained from the trial. QALYs will be calculated using responses to the EQ-5D-5L, using the “area under the curve” approach. For patients with gout flares, this will also include EQ-5D-5L data collected for each flare, taking into account the duration of the flare, so that flare-related disutility is captured. Unit costs will be applied to all health care resource use items, and mean resource use (for each category of health care usage) and mean total costs will be calculated for all trial participants. Analysis of productivity losses will use the human capital approach, and the self-reported days of absence will be multiplied by the respondent-specific wage rate. The human capital approach assumes that the value of lost work is equal to the amount of resources an individual would have been paid to do that work, and values productivity losses as a result of morbidity (or mortality) by measuring time lost from work and multiplying this with the gross wage of the person. As cost data are likely to have a skewed distribution, the nature of the distribution of

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costs will be explored, and if the data are not normally distributed, a non-parametric comparison of means (using bootstrapping) will be undertaken. Multiple imputation will be used to impute all missing values for the EQ-5D-5L and total cost estimates for non-responders. A cost-consequence analysis will initially be reported, describing all the important results relating to costs and consequences (across the full range of clinical outcomes).

Incremental cost effectiveness analysis and cost-utility analysis will then be undertaken to estimate the incremental cost per gout flare avoided and incremental cost per QALY gained respectively. There will be adjustment for baseline covariates, as specified by the main statistical analysis. The robustness of the results will be explored using sensitivity analysis. This will explore uncertainties in the trial-based data, the methods employed to analyse the data, and the generalizability of the results to other settings. Cost-effectiveness acceptability curves will also be produced to reflect the probability that the intervention will be cost effective at different cost per QALY willingness to pay thresholds.

8.5 Long-Term Follow-Up

The data analysis in this phase will be conducted on the same lines as described in the RCT. Death, and incidence or progression of CKD, myocardial infarction, ischaemic heart disease, stroke will be analysed using a time-to-event survival model. ULT prescription will be included as a time-varying covariate in this analysis. A multivariable linear model will be used to compare healthcare utilization between the groups.

Interim analyses will inform efficacy and trial management. These results will be available to the main analysis team, and the outcome of these analyses may affect the conduct of the study. Unless other interim analyses are requested by the DMC, only one interim analysis is planned, at the end of the internal pilot.

8.6 Sample Size and Justification

Main RCT: Taking the number of gout flares to have a negative binomial distribution, we utilized data from the GP care arm of a recently completed nurse-led complex package of care vs. usual-GP care for gout study to calculate (a) expected rate of gout flares in the control arm, (b) expected correlation between number of flares at baseline and during the 2-year study period, and (c) the dispersion parameter [11]. Sample size is based on simulations, using a negative binomial model. The nominal sample size was determined using the formula described by Zhu and Lakkis [45], and implemented in PASS 15 software. Using 90% power and 5% two-tailed significance, and assuming a dispersion parameter of 1.50 (estimated from our recent trial [11] and inflated by 25%), in order to detect a rate ratio of 0.650 (between-group reduction in mean number of flares over 24 months from 3.54 to 2.30), data are required from 190 participants per group. Using 10,000 simulations conducted in R, assuming a correlation between baseline and follow-up rates of flares of 0.33 [11], an adjusted sample size for the inclusion of baseline flares as a covariate is 186 per group. Allowing for up to 20% loss to follow-up based on our experience of conducting a two-year RCT of gout [11], target recruitment is therefore 233 per group, 466 in total. We chose a rate ratio of 0.650 as this implies a mean between-group reduction of approximately 1 flare of gout over the 2-year study period, assuming an estimated approximate mean 3 acute gout flares in this period in the control arm. This threshold was decided based on PPI input from the two PPI co-applicants (AP, AC) that even one gout flare is so painful that it merits preventing it, if possible. Similar opinion was expressed by a panel

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of Arthritis Research UK Pain Centre PPI members, comprising of one person with gout, one person with a family member with gout, and six people with other forms of arthritis (April 2017, Nottingham). Results from the recently completed two-year Nurse led care of gout RCT from Nottingham provides reassurance that there will be more than three gout flares in the control arm in this period [11].

Internal pilot: We will include data from first 90 participants in the internal pilot in order to provide an acceptable level of precision for estimates of proportions in relation to key feasibility outcomes e.g. consent rate, randomization rate, proportion achieving serum urate target, drop-out rate. [46]. For a two-sided 95% confidence level, a proportion could be estimated with a margin of error between approximately ±0.06 and ±0.08 if the proportion ranged between .1 and .2 (or equivalently, .8 and .9), with such a sample size.

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8.7 Assessment of Efficacy

Table 10: Assessment of efficacy

Endpoints	Efficacy parameter	Timing RCT	Timing extension
Primary			
Number of gout flares	Rate ratio	2 year	4 year
Secondary			
Pain severity during flare	Mean difference	2 year	4 year
Duration of flare	Mean difference	2 year	4 year
Generic HR-QoL (EQ-5D-5L) during flare	Mean difference	During flare	NA
Gout specific HR-QoL (GIS) during flare	Mean difference	During flare	
EQ-5D-5L HR-QoL between flares	Mean difference	1, 2 year	NA
Serum urate	Mean difference	2 year	NA
Serum urate level: proportion hitting the target serum urate level (<360 µmol/L)	Odds ratio	1, 2 year	
Serum urate level: proportion hitting serum urate level (<300 µmol/L)	Odds ratio	1, 2 year	
Serum creatinine and estimated GFR	Mean difference	2 year	NA
Urine albumin creatinine ratio	Mean difference	2 year	NA
Medication possession ratio	Mean difference	2 year	
Treatment acceptability questionnaire	Mean difference	2 year	
Healthcare utilization		2 year	4 year
Primary care consultations for gout	Mean difference	2 year	4 year
Hospitalizations due to gout flares	Mean difference	2 year	4 year
Current ULT		2 year	4 year
Number of ULT prescriptions	Mean difference		
No of prescriptions for treating flares	Mean difference	2 year	4 year
Cost-effectiveness		2 year	NA
Comorbidities			
Death	Hazard ratio	2 year	4 year
Chronic kidney disease progression	Hazard ratio	2 year	4 year
Ischaemic heart disease	Hazard ratio	2 year	4 year
Myocardial infarction	Hazard ratio	2 year	4 year
Stroke	Hazard ratio	2 year	4 year

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median difference or rate ratio will replace mean difference, if appropriate

8.8 Assessment of Safety

Given the fact that the drugs and interventions used in this study have been used in routine clinical practice for several decades, safety data will be reviewed by the DMC annually, and summarized over the whole trial period.

Table 11 Assessment of safety

Endpoints	Timing RCT
Adverse events	2 year
Serious adverse events	2 year
ULT discontinuation due to adverse events	2 year

8.9 Procedures for Missing, Unused and Spurious Data

Patterns of missingness will be explored, maximum likelihood estimation based on all the available data is not affected if outcome data are missing at random. Multiple imputation will be used for explanatory variables if missing at random is a plausible assumption.

The following secondary outcomes would be affected if site withdrawals prevent the collection of follow-up data from the practice:

- Serum urate level
- Serum creatinine and estimated GFR at year 1 and 2
- Urine albumin creatinine ratio at year 1 and 2
- Frequency of tophus at year 1 and 2
- Size of largest tophus (length and width) at years 1 and 2
- ULT (name and dose) at years 1 and 2
- Incident cardiovascular diseases, hypertension, diabetes
- Incidence or progression of CKD
- Medical records review data (Primary-care consultations for gout, prescriptions, referrals, A&E, hospitalisation)

A descriptive summary of the available data will be provided and inferential analyses will be limited to the first three outcome variables. The analysis of these secondary outcomes will be conducted using linear or generalized mixed-effects models with an aligned link function appropriate for the distribution of the outcome data being analysed. As mentioned above, maximum likelihood estimation will be used to fit the models, and this yields parameter estimates that are not affected by the exclusion of missing outcome data, assuming the missing-at-random assumption is plausible, which is likely the case for site withdrawals. Site withdrawals are anticipated to occur very rarely. To mitigate any loss of follow-up data, the original sample size was inflated to accommodate a potential 20% loss to follow-up.

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8.10 Definition of Data Analysed

Safety set: All randomized participants who received at least one treatment.
Full analysis set: All randomized participants.
Adherers-only set: All participants who received the treatment to which they were randomized as prescribed in the protocol.
As-treated set: All participants who received at least one treatment.

9. ADVERSE EVENTS

9.1 Definitions

An adverse event is any unfavourable and unintended sign, symptom, syndrome or illness that develops or worsens during the period of observation in the study.

An AE does include:

1. exacerbation of a pre-existing illness.

2. increase in frequency or intensity of a pre-existing episodic event or condition.

3. condition detected or diagnosed after medicinal product administration even though it may have been present prior to the start of the study.

4. continuous persistent disease or symptoms present at baseline that worsen following the start of the study.

Adverse events that are known side-effects of ULT, flare prophylaxis or omeprazole will be classed as adverse events and do not require reporting, unless they meet the criteria of related-unexpected serious adverse event (SAE), see below.

An AE does not include:

1. medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion); but the condition that lead to the procedure is an AE.

2. a pre-existing disease or condition present or detected at the start of the study that did not worsen.

3. situations where an untoward medical occurrence has not occurred (e.g., hospitalizations for elective surgery, social and/or convenience admissions).

4. disease or disorder being studied or sign or symptom associated with the disease or disorder unless more severe than expected for the participant's condition.

5. overdose of concurrent medication without any signs or symptoms.

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An SAE is any adverse event occurring following study mandated procedures, after receipt of the treatment or intervention that results in any of the following outcomes:

1. Death

2. A life-threatening adverse event

3. Inpatient hospitalization or prolongation of existing hospitalization

4. A disability / incapacity

5. A congenital anomaly in the offspring of a participant

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

All adverse events will be assessed for seriousness, expectedness and causality:

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined using the criteria above. Hence, a severe AE need not necessarily be serious.

9.2 Causality

Not related or improbable: a clinical event including laboratory test abnormality with temporal relationship to trial treatment/intervention administration that makes a causal relationship incompatible or for which other treatments, chemicals or disease provide a plausible explanation**.** This will be counted as “unrelated” for notification purposes.

Possible: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment/intervention administration that makes a causal relationship a reasonable possibility, but which could also be explained by other interventions, chemicals or concurrent disease. This will be counted as “related” for notification purposes.

Probable: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment/intervention administration that makes a causal relationship a reasonable possibility, and is unlikely to be due to other interventions, chemicals or concurrent disease. This will be counted as “related” for notification purposes.

Definite: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment/intervention administration that makes a causal relationship a reasonable possibility, and which can definitely not be attributed to other causes. This will be counted as “related” for notification purposes.

With regard to the criteria above, medical and scientific judgment shall be used in deciding whether prompt reporting is appropriate in that situation.

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9.3 Reporting of Adverse Events

Participants will be asked to contact the study site immediately in the event of any SAE. All serious adverse events will be recorded and closely monitored until resolution, stabilization, or until it has been shown that the study treatment is not the cause. The Chief Investigator shall be informed immediately by email and a follow-up phone call of any SAE and shall determine seriousness and causality in conjunction with any treating medical practitioners.

In the event of a pregnancy occurring in a trial participant or the partner of a trial participant, the participant will be advised to consult their GP as per usual care to discontinue treatment at the discretion of the GP. The outcome will be recorded on the participants CRF.
All treatment-related serious adverse events will be recorded and reported to the Research Ethics Committee (REC) as part of the annual reports. Unexpected intervention related SAE will be reported within the timeframes to the REC as stated below. The Chief Investigator shall be responsible for all adverse event reporting. ER, a clinically active co-investigator with interest in gout research and co-CI on the NIHR grant, will deputize for the Chief Investigator when he is away. If both are away then MS and CMD, both academic GPs, will deputize for the Chief Investigator.

9.4 Trial Treatment-/Intervention-Related SAEs

A serious adverse event that is unexpected in its severity and seriousness *and* deemed directly related to or suspected to be related to the trial treatment or intervention shall be reported to the ethics committee that gave a favourable opinion as stated below.
The event shall be reported immediately of knowledge of its occurrence to the Chief Investigator. The site-PI will complete the SAE form including categorisation of the event according to its seriousness, relatedness and expectedness before sending it to the CI via the Keele CTU.

The Chief Investigator will:

- Assess the event for seriousness, expectedness and relatedness to the trial treatment or intervention taking into account information provided by the site-PI.
- Take appropriate medical action, which may include halting the trial, and inform the Sponsor of such action.
- If the event is deemed related to the trial treatment or intervention, inform the REC using the reporting form found on the HRA web page within 7 days of knowledge of the event.
- Within a further eight days send any follow-up information and reports to the REC.
- Make any amendments as required to the study protocol and inform the REC as required

Expected SAEs such as hospitalization due to gout flare, side-effects of ULT or flare prophylaxis e.g. diarrhoea due to colchicine will not be reported to the ethics committee.

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9.5 Participant removal from the study due to adverse events

Any participant who experiences an adverse event may be withdrawn from the study at the discretion of the Investigator.

10. ETHICAL AND REGULATORY ASPECTS

10.1 Ethics Committee and Regulatory Approvals

The trial will not be initiated before the protocol, informed consent forms and participant and GP information sheets have received approval or favourable opinion from the REC, the respective NHS or other healthcare providers Research & Development (R&D) department, and the Health Research Authority (HRA) if required. Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant and GP information sheets (if appropriate) have been reviewed and received approval or favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately, and the REC will be informed.

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, and the UK Department of Health Policy Framework for Health and Social Care, 2017.

10.2 Informed Consent and Participant Information

The process for obtaining participant informed consent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. The investigator or their nominee and the participant shall both sign and date the Informed Consent Form before the person can participate in the study.

The decision regarding participation in the study is entirely voluntary. The investigator or their nominee shall emphasize to potential participants that consent regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled. No trial-specific interventions will be performed before informed consent has been obtained.

The investigator will inform the participant of any relevant information that becomes available during the course of the study, and will discuss with them whether they wish to continue with the study. If applicable they will be asked to sign revised consent forms.

If the Informed Consent Form is amended during the study, the investigator shall follow all applicable regulatory requirements pertaining to its approval by the REC and use of the amended form (including for ongoing participants).

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10.3 Records

10.3.1 Case Report Forms (CRF)

Each person is allocated a unique study number on mailing of the eligibility questionnaire, so that only anonymized data are used for analysis. The unique study numbers will be generated from the study database and provided to each practice for use when mailing. The number will be made up of site ID followed by a sequence of unique numbers. The study number will be for use on CRFs other trial documents and the electronic database. The documents will also use their initials (of first and last names separated by a hyphen) and date of birth (dd/mm/yy).

CRFs will be treated as confidential documents and held securely in accordance with regulations. The investigator at site will make a separate confidential record of the participant's name, date of birth, local hospital number or NHS number, and Participant Trial Number (the Trial screening Log), to permit identification of all participants enrolled in the trial, in accordance with regulatory requirements and for follow-up as required which will be securely stored and remain at the investigator site. CRFs shall be restricted to those personnel approved by the Chief or local Principal Investigator and recorded on the 'Trial Delegation Log.'

All paper forms shall be filled in using black ballpoint pen. Errors shall be lined out, but not obliterated by using correction fluid, and the correction inserted, initialled and dated.

The Chief or local Principal Investigator shall sign a declaration ensuring accuracy of data recorded in the CRF.

Personal data will be available to investigators working in the GP surgeries. A copy of each participant paper CRF will be sent securely to Keele CTU but will not be sent with any patient identifiable information. CRF Electronic data for the study will be stored on Keele University managed storage services, either on premises at Keele University, or in a cloud environment hosted by a cloud service provider held within the UK and protected by industry standard security tools as described in section 10.4 Data Protection. Access to patient identifiable data is highly restricted using pre-defined roles and privileges, and restricted views of the data so that authorized study team members see only the data that is required to carry out their role. Data access is fully auditable within this system.

10.3.2 Sample labelling

Samples for NHS pathology analysis will be labelled in accordance with local NHS procedures.

10.3.3 Source documents

Source documents shall be filed at the investigator's site (GP surgery) and a copy will be held at Keele Clinical Trials Unit up until the point at which documents are transferred to the sponsor for archiving. A CRF may also completely serve as its own source data. Only trial staff as listed on the Delegation Log shall have access to trial documentation other than the regulatory requirements listed below.

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10.3.4 Direct access to source data/documents

The CRF and all source documents, including progress notes and copies of laboratory and medical test results as applicable shall be made available at all times for review by the Chief Investigator, Sponsor's designee and inspection by relevant regulatory authorities (e.g. DH, Human Tissue Authority).

10.4 Data Protection

All trial staff and investigators will endeavour to protect the rights of the trial's participants to privacy and informed consent, and will adhere to the Data Protection Act, 2018. The CRF will only collect the minimum required information for the purposes of the trial. Paper CRFs will be held securely, in a locked room, or locked cupboard or cabinet. Access to the information will be limited to the trial staff and investigators and relevant regulatory authorities (see above). Confidentiality and anonymity will be maintained for all participants. Any identifying information provided (e.g. names and addresses) will be held in the strictest confidence and stored in a confidential, password protected Clinical Data Management System accessible by only those with permission. All data used for analysis will be kept separate from participant personal data. Electronic data for the study will be stored securely within a Microsoft SQL Server database on Keele University managed storage services, either on premises at Keele University, or in a cloud environment hosted by a cloud service provider held within the UK and protected by industry standard security tools. Access to patient identifiable data is highly restricted using pre-defined roles and privileges, and restricted views of the data so that authorized study team members see only the data that is required to carry out their role. Data access is fully auditable within this system.

Information about the trial in the participant's medical records and hospital notes will be treated confidentially in the same way as all other confidential medical information.

11. QUALITY ASSURANCE & AUDIT

11.1 Insurance and Indemnity

Insurance and indemnity for trial participants and trial staff will be provided by professional and practice indemnity insurance held by the GP practices. There are no special compensation arrangements, but trial participants may have recourse through the NHS complaints procedures.

The University of Nottingham as research Sponsor indemnifies its staff, research participants and research protocols with both public liability insurance and clinical trials insurance.

11.2 Trial Conduct

Trial conduct may be subject to systems audit of the Trial Master File for inclusion of essential documents; permissions to conduct the trial; Trial Delegation Log; curriculum vitae of trial staff and training received; local document control procedures; consent procedures and recruitment

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logs; adherence to procedures defined in the protocol (e.g. inclusion/exclusion criteria, correct randomization, timeliness of visits); adverse event recording and reporting; accountability of trial materials and equipment calibration logs.

11.3 Trial Data

Monitoring of trial data shall include confirmation of informed consent; source data verification against the GP record data at year one and two and adverse events; data storage and data transfer procedures; local quality control checks and procedures. The Trial Coordinator – or where required, a nominated designee of the Sponsor – shall carry out monitoring of trial data as an ongoing activity.

Entries on CRFs will be verified by inspection against the source data. A sample of CRFs (10% or as per the study risk assessment) will be checked on a regular basis for verification of all entries made. In addition the subsequent capture of the data on the trial database will be checked. Where corrections are required these will carry a full audit trail and justification.

The standard data protection procedures operating in Keele CTU will be employed to protect confidentiality and anonymity. Only on receipt of the eligibility questionnaire will Keele CTU have access to personal details of participants. Each person is allocated a unique study number, so that only anonymized data are used for analysis.

Keele CTU has robust data security systems and procedures in place, which are regularly reviewed, and which achieve the legal obligations set by the Data Protection Act (2018) and the General Data Protection Regulation (GDPR) and follow GMC Caldicott Guardian and British Computer Society standards and guidelines. Information of Keele University's Privacy notice will be included in the Patient Information Leaflet. All data will be stored on Keele University managed storage services, either on premises at Keele University, or in a cloud environment hosted by a cloud service provider held within the UK and protected by industry standard security tools. and is protected by industry standard security tools.. Roles and permissions are applied to users within the network as well as within an application to restrict what data a user can access and operations they can perform.

All paper copies of information will be stored securely in locked cabinets and all data used for analysis will be kept separate from participant personal data. Only members of the study team will have access to participants' personal data during the study.

SMS text messaging:

Keele CTU has experience of using 2-way SMS text messages to collect outcome data in previous trials. The software development team within the CTU will support this data collection, and will make use of an in-house bespoke database-driven system to manage the sending and receiving of SMS text messages. The participant will respond to the third party SMS provider. The CTU system will poll the third party SMS provider for returned SMS text messages. On processing of returned SMS text messages, the system will import these into the study database and process the response according to the business logic defined in the project. Interception of the original message by a third party would reveal only what the questions were that were being asked, whilst interception of the response would only yield an alphanumeric string. The third party SMS provider do not store any personal data

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on the participant other than the participant's mobile number which is used only to send the SMS text messages.

A number will be provided to enable participants to contact Keele CTU if they have queries relating to the SMS text messaging during office hours.

Trial data and evidence of monitoring and systems audits will be made available for inspection by REC as required.

11.4 Record Retention and Archiving

In compliance with the ICH/GCP guidelines, regulations and in accordance with the University of Nottingham Research Code of Conduct and Research Ethics, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 7 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The Trial Master File and trial documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities at the University of Nottingham. This archive shall include all trial databases and associated meta-data encryption codes. The trial database schema and applications and a copy of the final locked data set for the main trial will also be archived at Keele CTU in line with Sponsor archiving timeline requirements'.

11.5 Discontinuation of the Trial by the Sponsor

The Sponsor reserves the right to discontinue this trial at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice from the TSC and DMC as appropriate in making this decision.

11.6 Statement of Confidentiality

Individual participant medical information obtained as a result of this study are considered confidential and disclosure to third parties is prohibited with the exceptions noted above. Participant confidentiality will be further ensured by utilizing identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

If information is disclosed during the study that could pose a risk of harm to the participant or others, the researcher will discuss this with the CI and where appropriate report accordingly.

Data generated as a result of this trial will be available for inspection on request by the participating physicians, the University of Nottingham representatives, the REC, local R&D Departments and the regulatory authorities.

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12. PUBLICATION AND DISSEMINATION POLICY

The trial will be publicized to research, clinical and patient communities and other stakeholders, such as commissioners and self-help groups. We will publicize through existing networks (email lists, social media and Twitter accounts) to facilitate dissemination of findings and maximize impact. A website hosted by the University of Nottingham will publicize progress, participants' stories and staff blogs to generate interest in the study. Once analyses are complete, but prior to publication, we will discuss results with key stakeholders, to ensure we include their perspectives of results implications. In addition to our final report for the NIHR HTA Programme, we will publish trial results in peer-reviewed journals and present at national and international meetings. We will seek to disseminate findings through publication in other journals, such as Pulse, newsletters to British Society for Rheumatology, British Geriatrics Society, and Royal College of General Practitioners. We will engage with patients; primary care clinicians; rheumatologists; NICE; NHS England; Royal College of General Practitioners; British Society for Rheumatology; medicine management teams/CCGs; and secondary care NHS trusts along with AHSN and CLARHCs. The PPI volunteers will advise on the content of all public facing content for dissemination.

13. USER AND PUBLIC INVOLVEMENT

The study processes have been developed with active PPI involvement. There are two PPI co-investigators in this study, and they have contributed to the PIS. They will participate in the Trial Management Group meetings. The Trial Steering Committee (TSC) also has one PPI volunteer.

14. STUDY FINANCES

14.1 Funding Source

This study is funded by NIHR HTA programme. Grant number 17/82/02.

14.2 Participant Stipends and Payments

Participants will not be paid to participate in the trial. Travel expenses will be offered for any visits in excess of usual care. Prescription charges will be refunded for participants in the active arm at the year 1 and 2 research visits. Participants with pay-as-you-go mobile phones or those with a mobile contract with limited number of texts per month will have the cost of outgoing text messages reimbursed each year.

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15. SIGNATURE PAGES

Signatories to Protocol:

Chief Investigator: (name)_____

Signature:_____

Date: _____

Trial Statistician: (name)_____

Signature:_____

Date: _____

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17. Appendix 1. Drugs that increase the concentration of colchicine

Commonly prescribed
Statins and other lipid lowering medicines Atorvastatin, Fluvastatin, Pravastatin, Simvastatin, Rosuvastatin Bezafibrate, Ciprofibrate, Fenofibrate, Gemfibrozil
Cardiac medicines Verapamil, Diltiazem, Dronedarone
Antibiotics[1] Azithromycin, Clarithromycin, Erythromycin
Anti-fungal treatments[1] Fluconazole, Isavuconazole, Itraconazole, Ketoconazole, Posaconazole, Voriconazole
Certain HIV treatment Darunavir, Ritonavir, Saquinavir, Tipranavir, Fosamprenavir, Velpatasvir, Lopinavir, Atazanavir, Cobicistat
Drugs used in chemotherapy and immune suppressive medicines Ciclosporin, Imatinib, Lapatinib, Crizotinib, Idelalisib, Vemurafenib, Ceritinib, Nilotinib, Aprepitant , Netupitant, Rolapitant
Miscellaneous medicines Eliglustat, Mirabegron

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18. Appendix 2. Contraindications and cautions to flare prophylaxis

Colchicine (per BNF)

Contra-indications: Blood disorders

Cautions: Cardiac disease, elderly, gastro-intestinal disease.

CONTRAINDICATIONS AND CAUTIONS TO NSAIDs as per the BNF and the NICE clinical knowledge summaries

Contra-indications:

- active gastro-intestinal bleeding or ulcer,
- history of gastro-intestinal bleeding or perforation related to previous NSAID therapy,
- history of recurrent gastro-intestinal haemorrhage (two or more distinct episodes) or history of recurrent gastro-intestinal ulceration (two or more distinct episodes),
- history of hypersensitivity/severe allergic reaction to an NSAID (including aspirin) – for example asthma, rhinitis, angioedema or urticaria
- severe heart failure,
- severe renal impairment (eGFR <30 ml/min), and
- severe hepatic impairment.

Cautions:

- elderly,
- heart failure,
- cardiac impairment,
- ischaemic heart disease,
- uncontrolled hypertension,
- risk factors for cardiovascular events,
- impaired renal function,
- cerebrovascular disease,
- peripheral arterial disease
- coagulation defects,
- connective-tissue disorders,
- Crohn's disease, and
- ulcerative colitis.

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19. Appendix 3. Key points to cover during education for gout

The following points published by Doherty *et al.* [11] should be included in the patient education about gout. Information should be individualised to patient needs. This is part of the intervention, and should be implemented at the first treatment visit and reinforced at subsequent visits if needed.

[1] A clear verbal explanation about gout should be provided, and backed up by written information (i.e. the Arthritis Research UK (recently renamed Versus Arthritis) patient information booklet on gout). The explanation should include the following key messages:

- we know its cause - it is due to deposition of urate crystals in and around peripheral joints,
- crystals form when serum urate levels rise above the critical "saturation point" for crystal formation, (≥360)
- in people with persistently raised serum urate, crystals slowly accumulate without causing any symptoms,
- when sufficient crystals have formed in cartilage some occasionally "spill out" into the joint cavity, triggering severe inflammation of the joint lining and presenting as a gout flare,
- over many years gout flares may increase in frequency and spread to involve other joints,
- in addition to gout flares, continuing deposition may eventually result in hard, slowly expanding lumps of crystals ("tophi") that can damage joint cartilage and bone and even appear as palpable lumps under the skin,
- in some people the joint damage (i.e. osteoarthritis) caused by tophi can result in regular daily pain when using the joints,
- also there is increasing concern that persistently high urate levels increase the risk of atherosclerosis, heart disease, chronic kidney disease and dying younger,
- reduction and maintenance of serum urate levels below the saturation point
    - stops production of new crystals, and
    - encourages existing crystals to dissolve – so eventually there are no crystals and therefore no gout.

[2] An individualised explanation of relevant risk factors that elevate urate above the saturation point (insufficient elimination or too much production of urate) including:

- hereditary factors that result in inefficient renal excretion of urate
- a high body mass – most urate in the body is made by the body's cells by breaking down of chemicals called purines and this production increases with overweight and obesity
- a diet containing plenty of foods that are high in purines
- drugs (such as diuretics) that reduce the kidney's ability to excrete urate
- chronic renal impairment from any cause often greatly reduces urate excretion

[4] Individualised advice on management of a gout flare (selecting from ice packs, oral Colchicine, oral NSAID plus PPI, oral corticosteroid)

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[5] Individualised advice on ways to reduce urate levels by lifestyle modification, if this is appropriate (e.g. reducing weight if overweight or obese, reduction in excessive intake of beer or high-purine foods). Explain this is adjunctive to ULT.

[6] Explanation of ULT regimen used in the trial:

- including a slow upward titration regimen when initiating ULT (with approximately one month between each incremental increase in ULT),
- prophylaxis - to reduce risk of provoking flares through crystal shedding, and
- Allopurinol as the first-line drug to consider (Febuxostat also considered, as appropriate).

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20. Appendix 4. Non notifiable COVID-19 amendments

1. **13th March 2020**
   In light of the current health situation in regards to COVID-19, it has become apparent that some GP practices are now only offering telephone appointments where there may be unnecessary contact. In light of this a letter is to be disseminated to GP practices (sites) which provides them the option to complete the initial intervention appointment by telephone. Under the current protocol (page 42) we permit that intervention follow up appointments can take place via phone call except the initial appointment where advice in regard to gout management and treatment is sought.

2. **27th March 2020**
   As some sites are unable to perform blood tests at present due to COVID-19 restrictions we are providing sites with the option to halt the intervention for those participants in the treat to target arm and for them to remain on their current dose of ULT until their dose titration can restart. Participants will be informed by letter of this and reminded to continue reporting gout flares.
   To enhance data collection during this period we will be providing participants with the option to report their gout flares using an online diary. Additionally, any participants unable to use the online diary can have this data collected by telephone.

3. **1st July**
   Participants who report a gout flare via SMS are expected to return a short paper diary to Keele CTU, however due to COVID19 the postal system at Keele remains inaccessible at present we are unable to confirm these diaries as received. We will therefore contact (by telephone) those participants who report a flare via SMS to confirm they have either completed and returned their paper diary or provide them with the link to the online diary if they wish to complete this online.

   Substantial amendment 2 received approval for the following activity:
   1. **A reminder letter to be sent to those who consent to further contact but have not experienced a flare in the previous twelve months asking them to contact Keele CTU if they experience a flare.**
   2. **A letter to be sent to those participants who report a flare by SMS but do not return a paper diary.**
   3. **Bimonthly letter to be sent to participants who have selected a paper diary preference to remind them to report flares.**

   However due to ongoing COVID restrictions and Keele CTU being inaccessible this activity and implementation of the documents approved within substantial amendment 2 is at present on hold.

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