Changes made to original Protocol after trial commencement

18th July 2013	Alternative recruitment strategy through single local advertisement (p.13). This was advised by the funder due to slower than planned recruitment. Approved as substantial amendment.
28 Dec 2014	Recruitment target reduced from 724 to 512 (p.4) and study end extended to 31st December 2016 (p. 4, 19, 20). Again, these changes were made because of slower than planned uptake by general practices and participant recruitment. Approved as minor amendment.
22nd Dec 2014	Additional question (enquiring about development of new medical conditions in last two years) added to 24 month questionnaire, and blood pressure measurement added to final 24 month assessment (p.17). Approved as substantial amendment.
21st May 2015	Addition of sub-study questionnaires concerning (1) perceived triggers to acute gout attacks and (2) joint pain, stiffness and function in regions not affected by acute attacks (p.15). Approved as substantial amendment.
26th Nov 2015	Addition of incentives to attend for 24 month final assessment and completion of questionnaire (£25) and for completion of questionnaire alone (£15). Approved as substantial amendment.

An analysis plan was also made on 17 July 2013. Please see the further details of this plan at the end of this document

Arthritis Research UK Gout Treatment Trial. Phase 2: Two Year Randomised Controlled Trial of a Nurse Led Package of Care

Version 8 – 18 May 2015

Short title: Arthritis Research UK Gout Treatment Trial – Phase 2

Trial Registration: www.clinicaltrials.gov
NCT01477346

NRES reference: 12/EM/0044

Trial Sponsor: University of Nottingham

Sponsor reference: 11115

Funding Source: Arthritis Research UK

TRIAL / STUDY PERSONNEL AND CONTACT DETAILS

Sponsor: University of Nottingham

Contact name Ms Angela Shone
Research Governance Manager
Research Innovation Services
King's Meadow Campus
Lenton Lane
Nottingham NG7 2NR

Chief investigator: Prof Michael Doherty
Professor of Rheumatology
Academic Rheumatology
Clinical Sciences Building
Nottingham City Hospital
Nottingham NG5 1PB
Phone: 0115 8231756
Fax: 0115 8231757
Email: michael.doherty@nottingham.ac.uk

Co-investigators: Professor Paul Dieppe
Peninsula College of Medicine and Dentistry
Institute of Clinical Education
University of Exeter
PMS Building
St Lukes Campus
Heavitree Road
Exeter EX1 2LU
EM: paul.dieppe@pms.ac.uk

Co-investigator/Trial Statistician: Dr Weiya Zhang
Associate Professor and Reader in Musculoskeletal Medicine
Academic Rheumatology
Clinical Sciences Building
Nottingham City Hospital
Nottingham NG5 1PB
Phone: 0115 8231750
Fax: 0115 8231757
Email weiya.zhang@nottingham.ac.uk

Health Economics Advisor & Statistician:	Dr Matthew Stevenson Reader in Health Technology The University of Sheffield Regent Court, 30 Regent Street Sheffield S1 4DA Phone: 0114-2220691 **Tel:** 0114 222 0691 **Fax:** 0114 272 4095 **E-mail:** m.d.stevenson@sheffield.ac.uk
Statistical Advisor:	Prof Min Yang Professor of Medical Statistics Community Health Sciences Queen's Medical Centre Nottingham NG7 2UH Email: ming.yang@nottingham.ac.uk
Study Coordinator:	Helen Richardson Academic Rheumatology Clinical Sciences Building Nottingham City Hospital Nottingham NG5 1PB Phone: 0115 8231756 Email: helen.richardson@nottingham.ac.uk
CTU Director:	Lelia Duley Nottingham Clinical Trials Unit Nottingham Health Science Partners C Floor, South Block Queen's Medical Centre Nottingham NG7 2UH Phone: 0115 8844944 Email: lelia.duley@nottingham.ac.uk

SYNOPSIS

Title	Nottingham Gout Treatment Trial. Phase 2: Two Year Randomised Controlled Trial of a Nurse Led Package of Care
Acronym	None
Short title	Nottingham Gout Treatment Trial – Phase 2
Chief Investigator	Professor Michael Doherty
Objectives	To determine in community-based patients with untreated or under treated gout the effectiveness and cost effectiveness of a nurse-led complex intervention that reflects recommended best practice (including urate lowering therapy (ULT) to reduce serum uric acid (SUA) levels to <360 µmol/l).
Trial Configuration	Randomised, parallel group controlled trial comparing nurse led intervention with "standard" (GP led) care over a 2 year period. . Multicentre study within the East Midlands and South Yorkshire (EMSY) Region.
Setting	Primary Care, EMSY Region
Sample size estimate	**RCT:** The sample size was estimated according to both primary and secondary outcomes. To achieve 90% power at 5% significant level (2-tailed), the sample size needed are: 70 patients for each group for reduction in SUA (primary outcome); 90 patients for each group for reduction in frequency of acute attacks in the final year, and 233 patients for each group for quality of life (QOL). Allowing a 10% drop-out rate over the 2 years, this requires a total of **512 patients** (233 plus 36 dropouts in each arm) to provide adequate power for the primary outcome and for the 2 key secondary outcomes.
Number of participants	Nurse intervention (RCT) – 256 Standard care (RCT) – 256
Eligibility criteria	All – Adults aged 21 and over with GP diagnosis gout, confirmed following telephone interview to ensure that participants fulfil ACR criteria for gout. Nurse intervention and standard care groups (RCT) – at least one acute attack of gout in the last year.
Description of interventions	Nurse intervention arm – package of care based on best practice, including full information concerning nature and prognosis of gout, addressing illness perceptions of gout and possible barriers to care,

	individualised lifestyle modification advice and ULT to reduce SUA to below the saturation point for sodium urate crystal formation (360 µmol/L). Individuals in this group will be followed up regularly according to their clinical need/monitoring requirements. Standard care/control participants will have a single nurse contact at baseline during which they will be provided with the Arthritis Research UK leaflet on gout and be informed on appropriate management of acute attacks. There will be no discussion on other aspects of gout management – if asked about lifestyle and ULT participants will be asked to question their GP about this. This group will be asked to provide a blood sample at 0, 12 and 24 months and also keep a diary of acute attacks over the next 2 years and complete a questionnaire (including QOL assessment) at 12 and 24 months.
Duration of study	Total – 3 years Per participant – 2 years Planned recruitment start date 1 January 2013
Randomisation and blinding	Study participants in the RCT will be aware that they have been randomised to either a nurse-led intervention or to continue standard care/GP-led management. Randomisation will be undertaken by the CTU using a web based, computer generated, stratified (by GP practice) random block system and undertaken by the CTU. Following randomisation participants and nurses will obviously both know which group they are in. Although participants will be aware that the study objective is to compare cost effectiveness of nurse versus doctor led management of gout they will not be informed prior to randomisation concerning the recommended best practice strategies which include ULT and treating to target.
Outcome measures	Primary outcome – SUA of <360 µmol/L at study end Secondary outcomes – reduction in number of self-reported acute attacks in year two; improved QOL scores (SF36, Gout Assessment Questionnaire - GAQ); reduction in tophus size and number; cost effectiveness and cost utility based on health utilisation cost and SF6D (derived from SF36).

Statistical methods	Intention to treat (ITT) analysis will be undertaken to compare treatment effects between groups. Multi-level models will be used to handle any missing outcome measures. Chi-square test will be used for dichotomous or categorical data and ANOVA test will be used for continuous variable. Adjustment will be made for baseline co-variables as appropriate using multiple regression models. Cost per quality adjusted life year (QALY) will be estimated.

ABBREVIATIONS

Add to / amend accordingly

ADR	Adverse Drug Reaction
AE	Adverse Event
BSR	British Society for Rheumatology
CI	Chief Investigator overall
CRF	Case Report Form
DAP	Data Analysis Plan
DMC	Data Monitoring Committee
EMSY	East Midlands and South Yorkshire regions
EOT	End of Trial
EULAR	European League Against Rheumatism
GAQ	Gout Assessment Questionnaire
GCP	Good Clinical Practice
GPRD	General Practice Research Database
ICF	Informed Consent Form
ITT	Intention to Treat analysis
NHS	National Health Service
P/GIS	Parent / Guardian Information Sheet
PI	Principal Investigator at a local centre
PIS	Participant Information Sheet
QALY	Quality Adjusted Life Year
QOF	Quality and Outcomes Framework
QOL	Quality of Life
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
R&D	Research and Development department
SAE	Serious Adverse Event
SPC	Summary of Product Characteristics
SUA	Serum Uric Acid
TMG	Trial Management Group
TSC	Trial Steering Committee
ULT	Urate Lowering Therapy

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TRIAL / STUDY BACKGROUND INFORMATION AND RATIONALE

Gout is a chronic disabling condition caused by urate crystal deposition. It affects 1-2% of UK adults and is the most common inflammatory arthritis in men and the most common inflammatory arthritis in older women (1, 2). The prevalence increases with age to 7% of men aged >65 and to 3% of women aged >85. Unlike other common forms of arthritis we have a good understanding of gout pathogenesis and have effective strategies and treatments to eliminate the causative agent (i.e. urate crystals) and thus "cure" the disease.

Gout is predominantly managed in primary care. However, the treatment of patients with gout is often suboptimal (3-5). Two recent UK studies, one involving the General Practice Research Database (GPRD) and one an epidemiological study in Nottingham (3, 5), suggest that only one third of patients receive urate lowering therapy (ULT) and that this is inevitably allopurinol. Even when ULT is given it is usually prescribed at a single fixed dose (allopurinol 300 mg daily) that is insufficient for many patients, and without any monitoring of renal function or serum uric acid (SUA) to confirm that the therapeutic target of reducing SUA levels to well below the saturation point for crystal formation (360 µmol/l) has been achieved. The dose of 300mg daily is insufficient for many younger patients with normal renal function, but too much for some older people with renal impairment. Furthermore, very few patients receive information on gout or appropriate advice to modify lifestyle to reduce predisposing risk factors. As a consequence of such management only a minority of patients (<25%) become free of gout attacks, the majority continuing to experience acute attacks and being at risk of progression of their disease and developing irreversible secondary joint damage (6).

To improve current practice, the British Society for Rheumatology (BSR) and the European League Against Rheumatism (EULAR) have developed evidence-based recommendations for management of gout (7, 8). Notwithstanding the absence of randomised controlled trial (RCT) evidence that any intervention reduces the incidence of recurrent gout there is strong consensus on the components of management that will reduce the incidence of recurrent gout (9). Specifically, this is combining patient education and lifestyle advice with appropriate use of ULTs to achieve a target SUA level of ≤360 µmol/l. These elements will form the components of a complex intervention (10).

Whilst these elements have not been shown individually to be effective at reducing recurrent gout, there is good reason, based on knowledge of disease pathogenesis and clinical experience, to believe that such a package has the potential to reduce the incidence of recurrent gout, to reduce the size of tophi (hard palpable lumps of urate crystals which build up under the skin) and to improve quality of life (QOL). However, in phase 1 of the Nottingham Gout Clinical trial we have undertaken a "proof of concept" study in which 106 sub-optimally treated, community-derived patients with gout were managed by Professor Doherty (who saw all patients at their first visit) but subsequently predominantly managed by a trained specialist nurse for one year. At the end of the year the therapeutic target was achieved in 92% of patients. We have also undertaken qualitative work to examine illness perceptions and possible barriers to care in patients with gout and these data have informed the development of the nurse led intervention and the training programme that will be required for the nurses that will deliver it. An RCT is now required to determine the effectiveness of implementing such a strategy and to demonstrate improvement in patient-centred outcomes (reduced frequency of attacks, improved QOL, reduction in size and number of tophi, if present) as a consequence of successful gout management

Despite the existence of evidence based guidelines on management and "cure" of gout it is apparent that it is difficult to alter the behaviour of GPs by education alone and that financial

incentives through a QOF (Quality and Outcomes Framework) are the most effective way of improving the standard of care for a specific condition. Gout would seem ideal for a QOF in that there is a simple measure for standard of care (SUA) and practical national and international guidelines concerning management. The one requirement that is missing is data demonstrating improved QOL as a consequence of successful management. Should we be successful, data obtained from this RCT will be used in a submission to the Department of Health to consider making gout a QOF. Should this happen there will be a significant improvement in the standard of care of the millions of gout sufferers who are currently treated sub-optimally. Furthermore, data from our study could be used to support nurses taking the lead in delivery of gout care, following standard protocols, in the community.

TRIAL / STUDY OBJECTIVES AND PURPOSE

PRIMARY OBJECTIVE:

To determine in community-based patients with untreated or under treated gout the effectiveness and cost effectiveness of a nurse-led complex intervention compared to standard GP led care.

TRIAL / STUDY DESIGN

TRIAL / STUDY CONFIGURATION

This will be a conventional, multicentre, randomised parallel group controlled trial in the EMSY Region comparing, over a 2 year period, the outcomes in patients with gout who receive either (1) a nurse-led package of care reflecting current recommendations or (2) continuing GP led standard care (plus an initial single visit with a nurse to receive an information leaflet and discussion focused just on acute attacks).

The overview of the design of the RCT has been developed according to the MRC framework for complex intervention.

Primary endpoint:

Percentage of patients who hit the therapeutic target at end of year 2 (SUA <360 µmol/L)

Secondary endpoints:

Percentage with reduction of frequency of acute attacks in the second year.
Difference in QOL scores for SF36 and GAQ at end of study.

Percentage with reduction in size of the largest index tophus and reduction in number of tophi.

Safety endpoints

Not applicable

Stopping rules and discontinuation

Not applicable:

This is an adaptive complex intervention and management of participants with gout will continue through the 24 month period unless any participant opts to leave the study. Patients who experience adverse events relating to drug therapy for their gout will have the responsible ULT stopped and an alternative ULT considered. Because of its adaptive nature (i.e. not monotherapy) there is no contingency for early withdrawal from the trial in terms of efficacy or futility of a specific individual treatment.

RANDOMIZATION

At the initial visit the nurse will answer any further queries concerning the study and obtain written consent to participate. Random allocation will be undertaken using computer generated random numbers. Immediately following written consent, the nurse will phone into Academic Rheumatology, the administrative team will generate the group allocation via the website. Once allocated the patient will be informed of which group they are in. The study number will be used as the patient ID to de-identify the patient information throughout the study.

Maintenance of randomisation codes and procedures for breaking code:
Not applicable:
The study team will be made aware of whether the individual has been randomised into the nurse Intervention arm or the control arm of the RCT at the outset to enable the appropriate initial consultation and to arrange follow up of those in the nurse-led intervention group.

TRIAL MANAGEMENT

The trial will be coordinated by the research team in Academic Rheumatology, led by Professor Doherty, Chief Investigator. The Project Manager, will manage recruitment and the day to day running of the trial.

There will be a Trial Steering Committee. Membership of the Steering Committee is to be approved by the funders Arthritis Research UK and will include:

- an **independent** Chairperson (not involved directly with the study other than as a member of the Steering Committee)
- two or more other independent expert members (clinical and/or methodological)
- the Chief Investigator
- if possible a lay/consumer representative
- an observer from Arthritis Research UK

The Steering Committee will have an initial meeting to finalise the protocol then will meet again 3 months after the start of the study and then approximately every 6 months. The CI will keep the committee informed of recruitment progress at regular intervals (monthly) throughout the recruitment phase.
The Steering Committee will monitor and supervise the progress of the study and advise on recruitment rate and unforeseen logistical issues to ensure that its objectives are achieved.

DURATION OF THE TRIAL / STUDY AND PARTICIPANT INVOLVEMENT

The total study duration will be 3 years, 8 months recruitment, 2 years participation and 4 months analysis and writing up. Each participant will be in the study for 2 years from the point of entry.

End of the Trial

The study will end following the last visit of the last participant.

SELECTION AND WITHDRAWAL OF PARTICIPANTS

Recruitment

Participants will be recruited from collaborating GP surgeries and via advertisements/promotion in the media (local newspapers, radio and TV and via the internet) and posters placed on noticeboards approved for this purpose in the local community (e.g. community centres and patient waiting areas in NHS facilities).

Recruitment via collaborating GP surgeries

Staff at the GP's surgeries will be asked to identify patients with gout from their lists and send them a questionnaire together with covering letters from their GP practice and the CI. The questionnaire will enquire concerning their gout (including any acute attacks in the previous year), current drug treatments, comorbidities, QOL, and willingness to receive information on an additional study relating to management of gout. The questionnaire should take approximately 30 minutes to complete. Patients will be asked to return their questionnaires to Academic Rheumatology and the relevant data will be extracted to enable them to be identified as suitable for the trial. GP surgeries will be asked to send one reminder if a reply is not received within 3 weeks.

Suitable patients who indicated willingness to be informed of a management trial will be sent a letter and information sheet concerning this. Approximately 10 days after posting the information to the patient, the research team in Academic Rheumatology will telephone them to answer any questions they may have and, if they have decided they wish to participate, confirm their eligibility. If they respond positively a mutually convenient appointment will be arranged, at the patient's GP's surgery. The research nurse will inform the participant or their nominated representative (other individual or other body with appropriate jurisdiction), of all aspects pertaining to participation in the study.

Recruitment via advertising campaign

Gout sufferers who contact the department in response to an advertisement will be asked a few questions to confirm the diagnosis of gout and that they have experienced an attack of gout in the previous 12 months. Patients who are eligible to participate will be sent an information sheet and again, the study team in Academic Rheumatology will contact them approximately 10 days later to ask if they have any further questions and if they wish to participate. If they respond positively a mutually convenient appointment will be organised to see the patient at home. If a patient specifically requests an appointment at an alternative location, attempts will be made to arrange to see the patient at their GP's surgery.

As this study aims to determine, the effectiveness and cost effectiveness of a nurse-led complex intervention in community-based patients with gout, all participants will be seen, by research nurses, at their GP practice or in their own homes (i.e. not in a hospital setting).

If needed, the usual translator services will be available to assist with discussion of the trial, the participant information sheets, and consent forms, but the consent forms and information sheets will not be available printed in other languages. It will be explained to the potential participant 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 but attempts will be made to avoid this occurrence. 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.

Inclusion criteria:

- All – Adults aged 21 and over with a GP given diagnosis of gout, confirmed following telephone interview to ensure that participants fulfil ACR criteria for gout.
- Nurse intervention and standard care groups (RCT) – at least one acute attack of gout in the previous year.

Exclusion criteria

- Inability to give informed consent
- GPs will be asked not to contact people with terminal or mental illness

Expected duration of participant participation

Study participants will be participating in the trial for 2 years.

Removal of participants from therapy or assessments

This study involves comparison between a nurse-led "best practice" care and ongoing standard care. Participants will be withdrawn from the study if they lose the capacity to consent. Participants may also leave the study in the following circumstances:

1] if they move from the area during the 2 year period or wish to change their GP practice
2] if they withdraw their consent to remain under observation within the study

The participants will be made aware that this will not affect their future care. Participants will be made aware (via the information sheet and consent form) that should they withdraw the data collected to date cannot be erased and may still be used in the final analysis.

Informed consent

All participants in the RCT will provide written informed consent. Participants invited into the RCT will receive a letter of invitation together with an information sheet explaining that the trial will compare two methods of delivering gout care - one primarily led by a nurse and one primarily led by their GP (i.e. ongoing standard care). The research nurse will be able to answer any immediate questions they may have prior to booking an appointment to see the patient at their GP surgery or in their home. At the nurse visit participants will have the opportunity to ask any further questions prior to giving their full informed signed consent. Randomisation will occur at this stage.

Informed consent will be collected from each participant before they undergo 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.

Should there be any subsequent amendment to the final protocol, which 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.

Future contact

Participants will be asked if they are willing for their contact details to be stored on a secure database in Academic Rheumatology, to enable them to be informed of future studies undertaken by the department for which they might be suitable. Participant data will be kept up-to-date in accordance with Data Protection Act, 1998. The consent form includes an optional clause asking participants to confirm whether they are happy for their personal details to be retained for this purpose - if not their contact details will be destroyed at the end of this study after it is no longer necessary to contact them.

TRIAL / STUDY TREATMENT AND REGIMEN

The total study duration will be 3 years (8 month recruitment period, 2 years participation, 4 months analysis and writing up).

All appointments with our research nurses will be at the participants' local GP practice or in the participants' own home.
The study regimen is summarised in the table below (see also appendix1):

	RCT – nurse intervention	RCT – control/ standard care arm
Enquiry: age, sex, gout history, drug history, family history, comorbidities	X	X
Individualised advice on management of acute attack (selecting from ice packs, oral colchicine, oral NSAID plus PPI, corticosteroid).	X	X
Provision of Arthritis UK patient booklet.	X	X
Tophi assessment (sites), if present	X	X
A clear verbal explanation of gout	X	
Individualised explanation of relevant risk factors	X	
Individualised advice on ways to reduce uric acid levels by lifestyle modification, if appropriate	X	
Advice on ULT	X	
Height and weight (BMI)	X	X
Baseline/recruitment questionnaire (incl. SF36 & GAQ)	X	X
Serum uric acid, GFR and creatinine	X	X
Diary of acute attacks	X	X
Record of visits to GPs re gout management		X
SF36 'Quality of life' forms during acute attacks	X	X
12 month SUA	X	X
12 month GFR & creatinine	X	X
12 month questionnaire (incl. SF36 & GAQ)	X	X
12 month weight	X	X

24 month bloods	X	X
24 month questionnaire (inl. SF36, GAQ, joint pain, stiffness & function, gout attack triggers)	X	X
24 month blood pressure	X	X
24 month weight	X	X

A] NURSE INTERVENTION:

The recommended core treatment elements of the current EULAR and BSR recommendations form the basis of the nurse-led intervention (7, 8). These key elements have been incorporated into a management package suitable for implementation in community-based clinical practice. This package was developed during phase 1 of the study which included qualitative interviews of patients exploring illness perceptions and possible barriers to care. The nurse led package of care will be individualised according to the characteristics and needs of the participant and will include elements of the following:

(1) *a clear verbal explanation of gout backed up by written information (Arthritis Research UK patient booklet).* The explanation will 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 SUA levels rise above the critical "saturation point" for crystal formation
- in people with persistently raised SUA crystals slowly accumulate without causing 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 an acute attack of gout
- "shed" crystals are largely dissolved by the inflammation so the attack settles
- over many years acute attacks may increase in frequency and spread to involve other joints
- in addition to acute attacks, continuing deposition may eventually result in hard, slowly expanding lumps of crystals ("tophi") that can cause pressure damage to joint cartilage and bone and even appear as palpable lumps under the skin
- in some people tophi may result in irreversible joint damage (i.e. osteoarthritis) and cause regular chronic pain on using the joints
- reduction and maintenance of SUA levels below the saturation point (1) stops production of new crystals and (2) 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 uric acid above the saturation point* (basically too much production, or insufficient elimination of uric acid) including:

- *hereditary factors* that result in some people having relatively inefficient renal excretion of urate
- a *high body mass* - the majority (2/3) of uric acid being made by the body's cells by breaking down purines into uric acid, releasing energy for the cells
- a *diet* containing plenty of foods that are high in purines (1/3 of uric acid comes from the diet)
- *drugs* (such as diuretics) that reduce the kidney's ability to excrete uric acid
- *chronic renal impairment* associated with ageing or kidney disease.

(3) *individualised advice on management of an acute attack* (selecting from ice packs, oral colchicine, oral NSAID plus PPI, corticosteroid)

(4) *individualised advice* on ways to reduce uric acid levels by *lifestyle modification*, if this is appropriate (e.g reducing weight if overweight or obese, reduction in excessive beer intake, dietary alteration)

(5) *advice on ULT (in line with current recommended guidelines)*, including initiation of new ULT, with an upward titration regimen (with approximately one month between each incremental increase in ULT) and allopurinol the first-line drug to consider (febuxostat, sulphinpyrazone, benzbromarone also considered as appropriate). Prescriptions for ULT will be signed by Prof Doherty and issued through Nottingham City Hospital pharmacy.

The nurse will follow up the patient at variable time intervals as appropriate to the needs of the patient. It is envisaged that visits will be most frequent (e.g. monthly) in the first 6 months when ULT is being initiated and titrated upwards; subsequently visits may reduce to 3, 6 or 9 monthly depending on difficulty of gout management. Telephone contact to review blood test results and to agree any required action can substitute for visits, and home visits for blood tests and advice are permitted if more convenient (e.g. elderly patients). If home visits are undertaken this will be done in accordance with the University of Nottingham fieldwork guidelines. If the nurse requires any advice concerning treatment strategy (e.g. in patients with serious or multiple co-morbidity, taking multiple drug treatments, or experiencing side-effects) this will be offered by Academic Rheumatology (Prof Doherty or, in his absence, another designated Rheumatologist – Dr Frances Rees, Dr Adrian Jones or Dr Philip Courtney). All contacts with the patient (practice visit, home visit, telephone call) and for doctor advice will be logged (date, duration) for subsequent cost effectiveness analysis. Participants will be given a diary to keep during the 2 year study period in which they will record the date and duration of acute attacks of gout.

Assessment will involve:

Enquiry: age, sex, gout history (onset, acute attacks/frequency/sites affected/chronic symptoms), drug history (allopurinol/start date/dose, diuretics/duration; other drugs), family history comorbidities (most detailed first visit), completion of a QOL questionnaire (generic - SF36; and disease-specific - the gout assessment questionnaire (GAQ)) at the end of year one and again at the end of year 2. The questionnaires will take approximately 20 minutes to complete. Participants' blood pressure will also be checked at the end of year 2.

Examination: tophi (sites); height, weight (BMI).

Investgations: serum uric acid, GFR, creatinine.

If tophi are present, the maximum diameter of the longest tophus will be measured using a Vernier calliper and the total number and site of tophi will be recorded.

All investigations will only be undertaken to assist clinical assessment. Individuals participating in the study will receive a package of care based on current recommended guidelines.

Blood samples will be collected by the research nurses and taken to the Nottingham City Hospital laboratory for analysis. The samples will be destroyed following the NUH Trust's standard operating procedures.

All results will be discussed with the patients. Any abnormal findings, unrelated to the diagnosis of gout, will be discussed with the patient and their GP informed to enable appropriate action.

B] Control/Standard Care arm

Participants randomised to this group will have one consultation appointment with the research nurse. At this appointment they will be assessed by the nurse (identical enquiry, examination and investigations as above) and be provided with the Arthritis Research UK gout information booklet and a diary to prospectively document their acute attacks (frequency, duration, medical advice sought, medications taken, absence from work). The discussion will focus on the management of acute attacks and not on long-term management. In addition, they will be asked to provide a blood sample to check their SUA level at baseline, 12 months and 24 months, and complete a QOL questionnaire at 12 months (a new diary will be given at this point) and 24 months. This standard care group of participants will remain under the care of their general practitioner.

Collection of additional blood sample (optional)

All participants will also be invited to give a 10ml sample of blood for use in future gout research. This will include 1] genetic research to help identify genes that associate with gout development and severity and 2] study of metabolic changes (particularly biomarkers that associate with cardiovascular risk) that accompany a change in serum uric acid over time. The samples for genetic testing will be taken at baseline and those for metabolic biomarker research will be taken at baseline and one and two years. These time points allow the additional blood to be taken at the time venepuncture will be undertaken for the main study and therefore will not require an additional venepuncture. It will be explained to patients that participation in this additional genetic and metabolic research is optional and is not required as part of the main Arthritis Research UK Gout Treatment Trial and is covered in a separate optional clause on the consent form.

HUMAN TISSUE

Gout Treatment Trial blood samples will be collected by the research nurses during the appointments undertaken at the GPs surgeries and transported, by the research nurse, to the Nottingham City Hospital laboratory for analysis. Samples will not be retained for future research purposes and will be destroyed by the Nottingham City Hospital laboratory, following the Nottingham University Hospital Trust's standard operating procedures.

If the participant agrees to provide an additional sample for future genetic and metabolic biomarker studies related to gout, these samples will be stored in the Clinical Sciences Building, Nottingham City Hospital and stored within the Research Tissue Bank for future

research (DI Prof Jim Lowe- Licence Number 12265) if participants are agreeable and sign the optional clause on the consent form.
Only de-identified samples will be sent to third parties including close collaborating research groups and/or commercial companies who will undertake some of this analysis.

LABORATORY ANALYSES

Bloods collected for the Gout Treatment trial will be transported to the laboratory at the Nottingham City Hospital for analysis. The bloods will be tested for serum uric acid levels, GRF and liver function (if required).

Bloods collected for future genetic and biochemical markers studies will be stored in the Clinical Sciences Building at the Nottingham City Hospital. Whole blood will be sent to a specialist company for DNA extraction and processing. The DNA will be used to identify genes that identify with gout development and severity. Biochemical marker measurements in sera will be carried out using either radioimmunoassay specific equipment for ELISAs and/or magnetic resonance spectroscopy for metabolite detection.

Compliance

This is a complex intervention. However, compliance with respect to the nurse intervention will be judged by attendance for appointments, and by completion of the end of study questionnaire. Compliance to prescribed ULT will be judged by discussion with the participants, by their prescription requirements and by the results of the serial SUA.

Criteria for terminating trial

It is not envisaged that circumstances will arise that require termination of the trial. The nurse intervention reflects recommended best practice which includes prescription of available licensed ULT.

MONITORING STUDY PARTICIPANTS SUITABILITY TO CONTINUE IN THE STUDY

Prior to contacting participants in the RCT standard care arm, at one and two years, the GP surgeries will be provided with a list of participants in these groups and asked to check their records to ensure that patients are still registered with surgery, living at the same address and are suitable to be contacted. If this is not feasible, the Health and Social Care Information Centre or other central UK NHS body will be contacted to confirm the contact address and health status of patients participating in the trial. As regular contact will be maintained with participants in the RCT Nurse Intervention arm it is envisaged that participants/family members will keep the study team informed. If there is any reason to believe that an individual status may have changed, e.g. no reply to correspondence, telephone calls or non-attendance for appointments the GP surgery will again be contacted.

STATISTICS

Methods

The trial statistician (Dr Weiya Zhang) will oversee the data management, evaluation and analyses. The database will be developed in collaboration with the CTU using access and analysed using SPSS. SUA will be analysed at baseline, 12 months and 24 months. Comparison will be undertaken between the nurse led intervention and control at each observational point. There will be no interim analyses for efficacy or safety. Intention to

treat (ITT) analysis will be undertaken to compare treatment effects between groups. Multilevel models will be used for any missing outcome measures. Chi-square test will be used for dichotomous or categorical data and ANOVA test will be used for continuous variables. Adjustment will be made for baseline co-variables as appropriate. Cost per QALY will be estimated from the SF6D and the direct and indirect costs related to gout and its management.

Sample size and justification

Sample size:

512 participants will be recruited for the RCT (this allows a 10% drop out over the 2 year period).

Power calculations:

Information that includes SUA on community-derived patients with gout is sparse. However, detailed information on frequency of attacks, treatment, SUA and quality of life is available for 250 gout patients from 17 practices in Nottingham (5, 11). In this survey: 30% of patients were on ULT; the rate for acute attacks in the previous year was 32% for patients on ULT and 57% for patients on no ULT; mean SUA was 318 µmol/L in those taking ULT compared to 434 µmol/L in those not taking ULT; and 23% of those taking ULT had a SUA >360 µmol/L, compared to 75% of those not on ULT. For quality of life (SF36) overall mean and SD for those on ULT was 16.41 (2.81) compared to 15.67 (3.05) for those not on ULT, giving a pooled SD of 3.09 and a mean difference of 0.7 between groups (the latter is used as a proxy of effect size d).

According to these results, we have estimated the following sample size requirements, to achieve 90% power at 0.05% significance level, for each outcome:

- reduction in frequency of acute attacks in final year - a sample size of 90 is required for each arm
  reduction in SUA below the therapeutic target - a sample size of 70 patients is required for each arm
- quality of life – a sample size of 233 is required for each arm (80% power at 0.05% significance level

Allowing a 10% drop-out rate over the 2 years, this requires a total of **512 patients** (233 plus 23 dropouts in each arm) to provide adequate power for the primary outcome and for 2 of the key secondary outcomes. There are no data on changes in GAQ in response to treatment, but being a disease-specific instrument, we assume that the GAQ will be more sensitive to change than the SF36 and that a total size of 796 will be adequately powered for this outcome.

The total number of GP practices in Nottinghamshire is 170 and the estimated number of registered patients with gout is 10,720 (i.e. an average of 65 patients per GP). A questionnaire will be sent to all patients (unless they have an exclusion criterion) to detect eligible patents. A random sample of those eligible will be selected using the simple random selection after the consent to the trial.

ASSESSMENT OF EFFICACY

Primary Efficacy Endpoint:

Percentage in each group with SUA levels <360µmol/L (the saturation point form sodium urate crystal formation).

Secondary Efficacy Endpoints:

Percentage in each group with reduced number of acute attacks in the second year of the study
Quality of life scores (SF36 and GAQ) at end point compared to baseline in each group and comparison of endpoint QOL scores between the two groups.
Reduction in size and number of tophi.

Assessment of safety

The nurse intervention reflects recommended best practice involving ULTs that are recommended and licensed for this purpose. Participants will report any adverse events to the nurse. If benzbromarone is prescribed recommended checking of blood liver function tests will be undertaken.

Procedures for missing, unused and spurious data

If participants leave the study for any reason or if there are omitted data we will use multilevel models for any missing outcome measures and an intention to treat (ITT) analysis.

Definition of populations analysed

All patients randomised into the study will be analysed using an ITT analysis and LOCF for any missing data.

ADVERSE EVENTS

The nurse intervention which is being tested in this study reflects recommended best practice and utilises ULT that is recommended and licensed for this purpose. Therefore, the occurrence of adverse events as a result of participation within this study is not expected and no adverse event data will be collected.

Self- reported adverse events in participants in the nurse intervention will be recorded and if judged to be due to ULT the drug will be stopped and an alternative ULT considered (i.e. as recommended in current guidelines). Known side effects of ULT (e.g. allopurinol, febuxostat, benzbromarone) will be reported to the MHRA using the Yellow Card system, in line with recommended practice, but will not be classed as adverse events with respect to the intervention and will therefore not be reported to the NRES as such. However, a summary of the side effects reported using the Yellow Card system will be included in the final summary submitted to NRES. Adverse events that are unrelated to the nurse intervention

and ULT will be treated by the participant's general practitioner, as usual, and again not be reported to the REC.

To ensure clinical governance if the nurse is unsure of causality with respect to ULT she can involve the opinion of Professor Doherty (or in his absence Dr Frances Rees, Dr Philip Courtney or Dr Adrian Jones).

Adverse events occurring in the standard care group will be assessed and managed as part of normal care by the general practitioner and will not be reported to the REC.

COST EFFECTIVENESS AND UTILITY

The direct and indirect costs related to gout and its management during the two year study period will be estimated in the nurse led intervention group by recording of the following data:
number of nurse appointments and telephone contacts; duration of each contact; cost of drugs and blood tests; days off work because of acute attacks; any additional health care utilisation during acute attacks. Identical data will be obtained in the standard care group apart from the duration of each GP contact related specifically to gout management – a mean value will be estimated.

Cost utility will be estimated in each group utilising the direct and indirect costs and the SF6D (derived from the SF36). Quality of life during acute attacks will also be obtained in both groups (SF36) and this will be utilised in the cost utility estimations.

ETHICAL AND REGULATORY ASPECTS

Involvement of General Practitioner

Nurse led group (RCT): GPs will be informed if their patients are randomised to the nurse led group and will be kept informed with respect to changes to their patients' gout medications. If the nurse detects any adverse event or comorbidity unrelated to gout and its management the GP will also be directly informed.

Standard care group (RCT): We will not inform the GP that their patient has been randomised to the ongoing standard care group since this may 'contaminate' the GP care

ETHICS COMMITTEE AND REGULATORY APPROVALS

The trial will not be initiated before the protocol, informed consent forms and participant information sheets have received approval / favourable opinion from the Research Ethics Committee (REC), and the respective National Health Service (NHS) Research & Development (R&D) department. 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 / 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 Department of Health Research Governance Framework for Health and Social Care, 2005.

INFORMED CONSENT AND PARTICIPANT INFORMATION

The process for obtaining participant informed consent or assent 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 participant will receive a copy of the signed and dated forms and the original will be retained in the Trial Master File.

The decision regarding participation in the study is entirely voluntary. The investigator or their nominee shall emphasize to them 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 done 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 approval of the amended Informed Consent Form by the REC and use of the amended form (including for ongoing participants).

RECORDS

Case Report Forms

Each participant will be assigned a trial identity code number, for use on CRFs other trial documents and the electronic database. The documents and database will also use their initials (of first and last names separated by a hyphen or a middle name initial when available) and date of birth (dd/mm/yy).

CRFs will be treated as confidential documents and held securely in accordance with regulations. The investigator 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 Recruitment Log), to permit identification of all participants enrolled in the trial, in accordance with regulatory requirements and for follow-up as required.

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.

Source documents

Source documents shall be filed at the investigator's site and will include but are not limited to, consent forms, history and examination findings, questionnaires and laboratory results and a record of initiated or altered treatments. Only trial staff as listed on the Delegation Log shall have access to trial documentation other than the regulatory requirements listed below.

Direct access to source data / documents

The CRF and all source documents, including progress notes and copies of laboratory and medical test results shall made be available at all times for review by the Chief Investigator, Sponsor's designee and inspection by relevant regulatory authorities.

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, 1998. The CRF will only collect the minimum required information for the purposes of the trial. 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). Computer held data including the trial database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one way encryption method).

Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

QUALITY ASSURANCE & AUDIT

INSURANCE AND INDEMNITY

Insurance and indemnity for trial participants and trial staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but trial participants may have recourse through the NHS complaints procedures.

The University of Nottingham has taken out an insurance policy to provide indemnity in the event of a successful litigious claim for proven non-negligent harm.

TRIAL CONDUCT

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

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

Our Senior Research Nurse will observe each research nurse taking consent in a small sample of study participants to ensure consent is being undertaken in line with GCP guidelines and training provided.

The Trial Co-ordinator and CTU representatives will carry out a site systems audit at least yearly and an audit report shall be made to the Trial Steering Committee.

TRIAL DATA

Monitoring of trial data shall include confirmation of informed consent; source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. The Trial Co-ordinator and CTU representative will 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.

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

RECORD RETENTION AND ARCHIVING

In compliance with the ICH/GCP guidelines, regulations and in accordance with the University of Nottingham Research Code of Conduct, 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.

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 Trial Steering Committee and Data Monitoring Committee as appropriate in making this decision.

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 utilising 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.

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

PUBLICATION AND DISSEMINATION POLICY

The study results will be submitted to Arthritis Research UK, regulatory authorities, and peer reviewed journals for publication. In addition, the results will be presented at national and international conferences. Study participants' identity will not be disclosed when publishing the results.

Study participants will also be informed of the results, if requested.

USER AND PUBLIC INVOLVEMENT

We have audited the standard of care of gout in the Nottingham Community and subsequently undertaken qualitative research during Phase I of the Nottingham Gout Treatment Trial to ascertain patients' understanding and views on gout and its treatment. The findings from this qualitative research and the results from Phase 1 have been used to develop the nurse intervention package of care which is being delivered in Phase 2 of this study. The nurse led intervention incorporates recommended best practice published by the British Society for Rheumatology and the European League Against Rheumatism.

STUDY FINANCES

Funding source

This study is funded by Arthritis Research UK.

Participant stipends and payments

Participants will not be paid to participate in the trial.

SIGNATURE PAGES

Signatories to Protocol:

Chief Investigator: (name)_____

Signature:_____

Date: _____

Co- investigator: (name) _____

Signature:_____

Date: _____

Trial Statistician: (name)_____

Signature:_____

Date: _____

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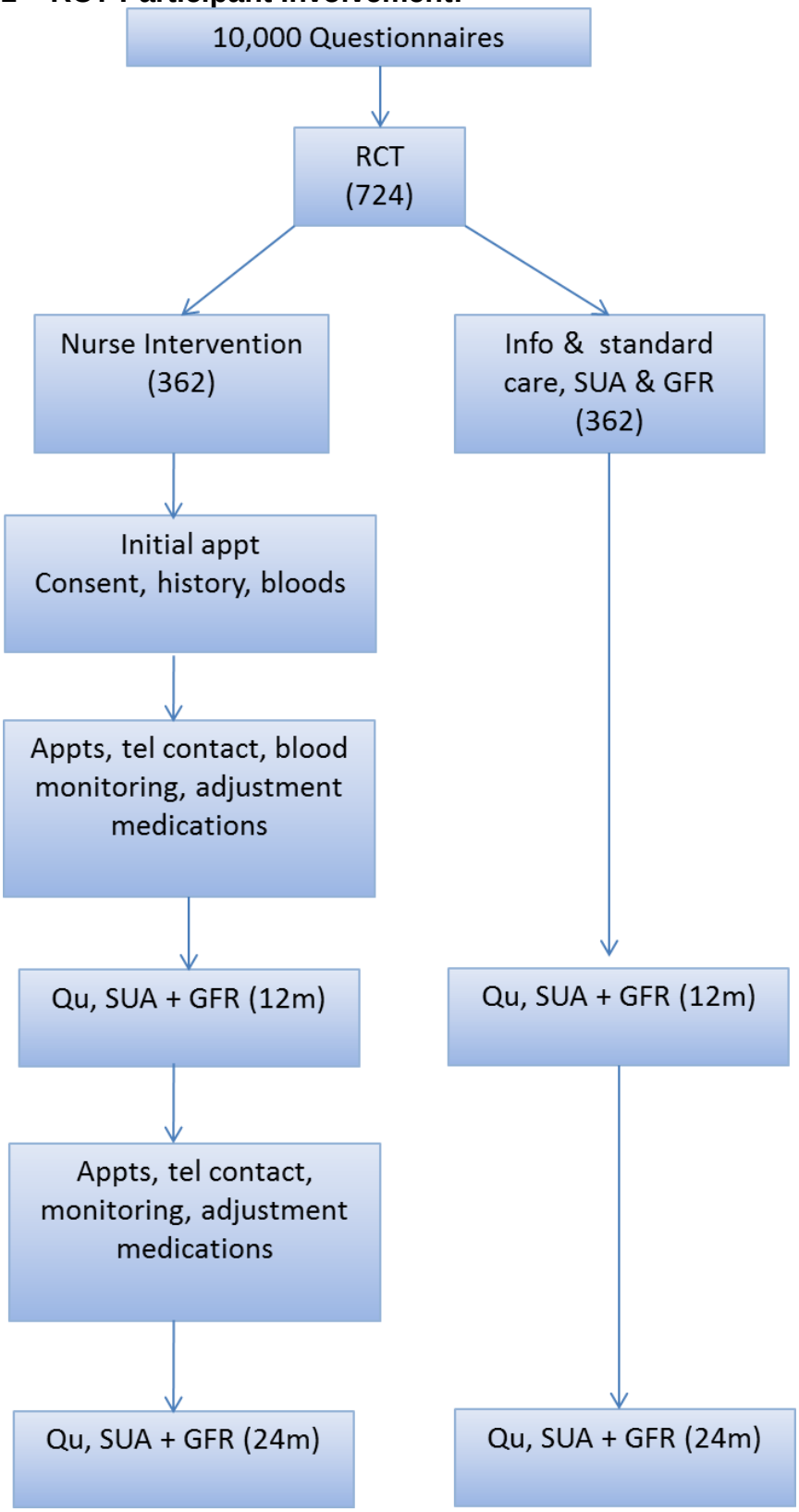
Appendix 1 – RCT Participant Involvement:



Arthritis Research UK Gout Treatment Trial. Phase 2: Two Year Randomised Controlled Trial of a Nurse Led Package of Care

Final Version 4 - 6 February 2013

Short title: Arthritis Research UK Gout Treatment Trial – Phase 2

Trial Registration: www.clinicaltrials.gov
NCT01477346

NRES reference: 12/EM/0044

Trial Sponsor: University of Nottingham

Sponsor reference: 11115

Funding Source: Arthritis Research UK

TRIAL / STUDY PERSONNEL AND CONTACT DETAILS

Sponsor: University of Nottingham

Contact name
Ms Angela Shone
Research Governance Manager
Research Innovation Services
King's Meadow Campus
Lenton Lane
Nottingham NG7 2NR

Chief investigator:
Prof Michael Doherty
Professor of Rheumatology
Academic Rheumatology
Clinical Sciences Building
Nottingham City Hospital
Nottingham NG5 1PB
Phone: 0115 8231756
Fax: 0115 8231757
Email: michael.doherty@nottingham.ac.uk

Co-investigators:
Professor Paul Dieppe
Peninsula College of Medicine and Dentistry
Institute of Clinical Education
University of Exeter
PMS Building
St Lukes Campus
Heavitree Road
Exeter EX1 2LU
EM: paul.dieppe@pms.ac.uk

Co-investigator/Trial Statistician:
Dr Weiya Zhang
Associate Professor and Reader in
Musculoskeletal Medicine
Academic Rheumatology
Clinical Sciences Building
Nottingham City Hospital
Nottingham NG5 1PB
Phone: 0115 8231750
Fax: 0115 8231757
Email weiya.zhang@nottingham.ac.uk

Health Economics Advisor & Statistician:	Dr Matthew Stevenson Reader in Health Technology The University of Sheffield Regent Court, 30 Regent Street Sheffield S1 4DA Phone: 0114-2220691 Tel: 0114 222 0691 Fax: 0114 272 4095 E-mail: m.d.stevenson@sheffield.ac.uk
Statistical Advisor:	Prof Min Yang Professor of Medical Statistics Community Health Sciences Queen's Medical Centre Nottingham NG7 2UH Email: ming.yang@nottingham.ac.uk
Study Coordinator:	Helen Richardson Academic Rheumatology Clinical Sciences Building Nottingham City Hospital Nottingham NG5 1PB Phone: 0115 8231756 Email: helen.richardson@nottingham.ac.uk
CTU Manager:	Diane Whitham Nottingham Clinical Trials Unit Nottingham Health Science Partners C Floor, South Block Queen's Medical Centre Nottingham NG7 2UH Phone: 0115 8844944 Email: diane.whitham@nottingham.ac.uk

SYNOPSIS

Title	Nottingham Gout Treatment Trial. Phase 2: Two Year Randomised Controlled Trial of a Nurse Led Package of Care
Acronym	None
Short title	Nottingham Gout Treatment Trial – Phase 2
Chief Investigator	Professor Michael Doherty
Objectives	To determine in community-based patients with untreated or under treated gout the effectiveness and cost effectiveness of a nurse-led complex intervention that reflects recommended best practice (including urate lowering therapy (ULT) to reduce serum uric acid (SUA) levels to <360 µmol/l).
Trial Configuration	Randomised, parallel group controlled trial comparing nurse led intervention with "standard" (GP led) care over a 2 year period. . Multicentre study within the East Midlands and South Yorkshire (EMSY) Region.
Setting	Primary Care, EMSY Region
Sample size estimate	**RCT:** The sample size was estimated according to both primary and secondary outcomes. To achieve 90% power at 5% significant level (2-tailed), the sample size needed are: • 70 patients for each group for reduction in SUA (primary outcome); • 90 patients for each group for reduction in frequency of acute attacks in the final year, and • 326 patients for each group for quality of life (QOL). Allowing a 10% drop-out rate over the 2 years, this requires a total of **724 patients** (326 plus 36 dropouts in each arm) to provide adequate power for the primary outcome and for the 2 key secondary outcomes.
Number of participants	Nurse intervention (RCT) – 362 Standard care (RCT) – 362
Eligibility criteria	All – Adults aged 21 and over with GP diagnosis gout, confirmed following telephone interview to ensure that participants fulfil ACR criteria for gout.

	Nurse intervention and standard care groups (RCT) – at least one acute attack of gout in the last year.
Description of interventions	• Nurse intervention arm – package of care based on best practice, including full information concerning nature and prognosis of gout, addressing illness perceptions of gout and possible barriers to care, individualised lifestyle modification advice and ULT to reduce SUA to below the saturation point for sodium urate crystal formation (360 µmol/L). Individuals in this group will be followed up regularly according to their clinical need/monitoring requirements. • Standard care/control participants will have a single nurse contact at baseline during which they will be provided with the Arthritis Research UK leaflet on gout and be informed on appropriate management of acute attacks. There will be no discussion on other aspects of gout management – if asked about lifestyle and ULT participants will be asked to question their GP about this. This group will be asked to provide a blood sample at 0, 12 and 24 months and also keep a diary of acute attacks over the next 2 years and complete a questionnaire (including QOL assessment) at 12 and 24 months. •
Duration of study	Total – 3 years Per participant – 2 years Planned recruitment start date 1 January 2013
Randomisation and blinding	Study participants in the RCT will be aware that they have been randomised to either a nurse-led intervention or to continue standard care/GP-led management. Randomisation will be undertaken by the CTU using a web based, computer generated, stratified (by GP practice) random block system and undertaken by the CTU. Following randomisation participants and nurses will obviously both know which group they are in. Although participants will be aware that the study objective is to compare cost effectiveness of nurse versus doctor led management of gout they will not be informed prior to randomisation concerning the recommended best practice strategies which include ULT and treating to target.
Outcome measures	Primary outcome – SUA of <360 µmol/L at study end Secondary outcomes – reduction in number of self-reported acute attacks in year two; improved QOL scores (SF36, Gout Assessment Questionnaire - GAQ); reduction in tophus size and number; cost effectiveness and cost utility based on health utilisation cost and SF6D (derived from SF36).

Statistical methods	Intention to treat (ITT) analysis will be undertaken to compare treatment effects between groups. Multi-level models will be used to handle any missing outcome measures. Chi-square test will be used for dichotomous or categorical data and ANOVA test will be used for continuous variable. Adjustment will be made for baseline co-variables as appropriate using multiple regression models. Cost per quality adjusted life year (QALY) will be estimated.

ABBREVIATIONS

Add to / amend accordingly

ADR	Adverse Drug Reaction
AE	Adverse Event
BSR	British Society for Rheumatology
CI	Chief Investigator overall
CRF	Case Report Form
DAP	Data Analysis Plan
DMC	Data Monitoring Committee
EMSY	East Midlands and South Yorkshire regions
EOT	End of Trial
EULAR	European League Against Rheumatism
GAQ	Gout Assessment Questionnaire
GCP	Good Clinical Practice
GPRD	General Practice Research Database
ICF	Informed Consent Form
ITT	Intention to Treat analysis
NHS	National Health Service
P/GIS	Parent / Guardian Information Sheet
PI	Principal Investigator at a local centre
PIS	Participant Information Sheet
QALY	Quality Adjusted Life Year
QOF	Quality and Outcomes Framework
QOL	Quality of Life
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
R&D	Research and Development department
SAE	Serious Adverse Event
SPC	Summary of Product Characteristics
SUA	Serum Uric Acid
TMG	Trial Management Group
TSC	Trial Steering Committee

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TRIAL / STUDY BACKGROUND INFORMATION AND RATIONALE

Gout is a chronic disabling condition caused by urate crystal deposition. It affects 1-2% of UK adults and is the most common inflammatory arthritis in men and the most common inflammatory arthritis in older women (1, 2). The prevalence increases with age to 7% of men aged >65 and to 3% of women aged >85. Unlike other common forms of arthritis we have a good understanding of gout pathogenesis and have effective strategies and treatments to eliminate the causative agent (i.e. urate crystals) and thus "cure" the disease.

Gout is predominantly managed in primary care. However, the treatment of patients with gout is often suboptimal (3-5). Two recent UK studies, one involving the General Practice Research Database (GPRD) and one an epidemiological study in Nottingham (3, 5), suggest that only one third of patients receive urate lowering therapy (ULT) and that this is inevitably allopurinol. Even when ULT is given it is usually prescribed at a single fixed dose (allopurinol 300 mg daily) that is insufficient for many patients, and without any monitoring of renal function or serum uric acid (SUA) to confirm that the therapeutic target of reducing SUA levels to well below the saturation point for crystal formation (360 µmol/l) has been achieved. The dose of 300mg daily is insufficient for many younger patients with normal renal function, but too much for some older people with renal impairment. Furthermore, very few patients receive information on gout or appropriate advice to modify lifestyle to reduce predisposing risk factors. As a consequence of such management only a minority of patients (<25%) become free of gout attacks, the majority continuing to experience acute attacks and being at risk of progression of their disease and developing irreversible secondary joint damage (6).

To improve current practice, the British Society for Rheumatology (BSR) and the European League Against Rheumatism (EULAR) have developed evidence-based recommendations for management of gout (7, 8). Notwithstanding the absence of randomised controlled trial (RCT) evidence that any intervention reduces the incidence of recurrent gout there is strong consensus on the components of management that will reduce the incidence of recurrent gout (9). Specifically, this is combining patient education and lifestyle advice with appropriate use of ULTs to achieve a target SUA level of ≤360 µmol/l. These elements will form the components of a complex intervention (10).

Whilst these elements have not been shown individually to be effective at reducing recurrent gout, there is good reason, based on knowledge of disease pathogenesis and clinical experience, to believe that such a package has the potential to reduce the incidence of recurrent gout, to reduce the size of tophi (hard palpable lumps of urate crystals which build up under the skin) and to improve quality of life (QOL). However, in phase 1 of the Nottingham Gout Clinical trial we have undertaken a "proof of concept" study in which 106 sub-optimally treated, community-derived patients with gout were managed by Professor Doherty (who saw all patients at their first visit) but subsequently predominantly managed by a trained specialist nurse for one year. At the end of the year the therapeutic target was achieved in 92% of patients. We have also undertaken qualitative work to examine illness perceptions and possible barriers to care in patients with gout and these data have informed the development of the nurse led intervention and the training programme that will be required for the nurses that will deliver it. An RCT is now required to determine the effectiveness of implementing such a strategy and to demonstrate improvement in patient-centred outcomes (reduced frequency of attacks, improved QOL, reduction in size and number of tophi, if present) as a consequence of successful gout management

Despite the existence of evidence based guidelines on management and "cure" of gout it is apparent that it is difficult to alter the behaviour of GPs by education alone and that financial

incentives through a QOF (Quality and Outcomes Framework) are the most effective way of improving the standard of care for a specific condition. Gout would seem ideal for a QOF in that there is a simple measure for standard of care (SUA) and practical national and international guidelines concerning management. The one requirement that is missing is data demonstrating improved QOL as a consequence of successful management. Should we be successful, data obtained from this RCT will be used in a submission to the Department of Health to consider making gout a QOF. Should this happen there will be a significant improvement in the standard of care of the millions of gout sufferers who are currently treated sub-optimally. Furthermore, data from our study could be used to support nurses taking the lead in delivery of gout care, following standard protocols, in the community.

TRIAL / STUDY OBJECTIVES AND PURPOSE

PRIMARY OBJECTIVE:

To determine in community-based patients with untreated or under treated gout the effectiveness and cost effectiveness of a nurse-led complex intervention compared to standard GP led care.

TRIAL / STUDY DESIGN

TRIAL / STUDY CONFIGURATION

This will be a conventional, multicentre, randomised parallel group controlled trial in the EMSY Region comparing, over a 2 year period, the outcomes in patients with gout who receive either (1) a nurse-led package of care reflecting current recommendations or (2) continuing GP led standard care (plus an initial single visit with a nurse to receive an information leaflet and discussion focused just on acute attacks).

The overview of the design of the RCT has been developed according to the MRC framework for complex intervention.

Primary endpoint:

Percentage of patients who hit the therapeutic target at end of year 2 (SUA <360 µmol/L)

Secondary endpoints:

Percentage with reduction of frequency of acute attacks in the second year.
Difference in QOL scores for SF36 and GAQ at end of study.

Percentage with reduction in size of the largest index tophus and reduction in number of tophi.

Safety endpoints

Not applicable

Stopping rules and discontinuation

Not applicable:

This is an adaptive complex intervention and management of participants with gout will continue through the 24 month period unless any participant opts to leave the study. Patients who experience adverse events relating to drug therapy for their gout will have the responsible ULT stopped and an alternative ULT considered. Because of its adaptive nature (i.e. not monotherapy) there is no contingency for early withdrawal from the trial in terms of efficacy or futility of a specific individual treatment.

RANDOMIZATION

Participants will be selected from the information (including reporting of acute attacks in the last year) returned in the initial questionnaire ("the gout survey"). These individuals will be sent a letter of invitation and an information sheet relating to the RCT. Those who reply that they are willing to participate in the study will be contacted by telephone to confirm eligibility, to discuss any queries concerning the study and to make an appointment to see the nurse at their GP surgery. At that visit the nurse will answer any further queries concerning the study and obtain written consent to participate. Random allocation will be undertaken using computer generated random numbers. Immediately following written consent, the nurse will phone into Academic Rheumatology, the administrative team will generate the group allocation via the website. Once allocated the patient will be informed of which group they are in. The study number will be used as the patient ID to de-identify the patient information throughout the study.

Maintenance of randomisation codes and procedures for breaking code:

Not applicable:
The study team will be made aware of whether the individual has been randomised into the nurse Intervention arm or the control arm of the RCT at the outset to enable the appropriate initial consultation and to arrange follow up of those in the nurse-led intervention group.

TRIAL MANAGEMENT

The trial will be coordinated by the research team in Academic Rheumatology, led by Professor Doherty, Chief Investigator. The Project Manager, will manage recruitment and the day to day running of the trial.

There will be a Trial Steering Committee. Membership of the Steering Committee is to be approved by the funders Arthritis Research UK and will include:

- an **independent** Chairperson (not involved directly with the study other than as a member of the Steering Committee)
- two or more other independent expert members (clinical and/or methodological)
- the Chief Investigator
- if possible a lay/consumer representative
- an observer from Arthritis Research UK

The Steering Committee will have an initial meeting to finalise the protocol then will meet again 3 months after the start of the study and then approximately every 6 months. The CI will keep the committee informed of recruitment progress at regular intervals (monthly) throughout the recruitment phase.

The Steering Committee will monitor and supervise the progress of the study and advise on recruitment rate and unforeseen logistical issues to ensure that its objectives are achieved.

DURATION OF THE TRIAL / STUDY AND PARTICIPANT INVOLVEMENT

The total study duration will be 3 years, 8 months recruitment, 2 years participation and 4 months analysis and writing up. Each participant will be in the study for 2 years from the point of entry.

End of the Trial

The study will end following the last visit of the last participant.

SELECTION AND WITHDRAWAL OF PARTICIPANTS

Recruitment

All participants will be recruited from collaborating GP surgeries. Staff at the GP's surgeries will be asked to identify patients with gout from their lists and send them a questionnaire together with covering letters from their GP practice and the CI. The questionnaire will enquire concerning their gout (including any acute attacks in the previous year), current drug treatments, comorbidities, QOL, and willingness to receive information on an additional study relating to management of gout. The questionnaire should take approximately 30 minutes to complete. Patients will be asked to return their questionnaires to Academic Rheumatology and the relevant data will be extracted to enable them to be identified as suitable for the trial. GP surgeries will be asked to send one reminder if a reply is not received within 3 weeks.

Suitable patients who indicated willingness to be informed of a management trial will be sent a letter and information sheet concerning this. Approximately 10 days after posting the information to the patient, the research team in Academic Rheumatology will telephone them to see if they have any questions and whether they have decided whether they wish to participate. If they respond positively a mutually convenient appointment will be arranged, at the patient's GP's surgery. The research nurse will inform the participant or their nominated representative (other individual or other body with appropriate jurisdiction), of all aspects pertaining to participation in the study.

As this study aims to determine, in community-based patients with gout, the effectiveness and cost effectiveness of a nurse-led complex intervention all participants will be seen, by research nurses, at their GP practice.

If needed, the usual translator services will be available to assist with discussion of the trial, the participant information sheets, and consent forms, but the consent forms and information sheets will not be available printed in other languages. It will be explained to the potential participant 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 but attempts will be made to avoid this occurrence. 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.

Inclusion criteria:

- All – Adults aged 21 and over with a GP given diagnosis of gout, confirmed following telephone interview to ensure that participants fulfil ACR criteria for gout.
- Nurse intervention and standard care groups (RCT) – at least one acute attack of gout in the previous year.

Exclusion criteria

- Inability to give informed consent
- GPs will be asked not to contact people with terminal or mental illness

Expected duration of participant participation

Study participants will be participating in the trial for 2 years.

Removal of participants from therapy or assessments

This study involves comparison between a nurse-led "best practice" care and ongoing standard care. Participants will be withdrawn from the study if they lose the capacity to consent. Participants may also leave the study in the following circumstances:

1] if they move from the area during the 2 year period or wish to change their GP practice

2] if they withdraw their consent to remain under observation within the study

The participants will be made aware that this will not affect their future care. Participants will be made aware (via the information sheet and consent form) that should they withdraw the data collected to date cannot be erased and may still be used in the final analysis.

Informed consent

All participants in the RCT will provide written informed consent. Participants who will be invited into the RCT will receive a letter of invitation together with an information sheet explaining that the trial will compare two methods of delivering gout care - one primarily led by

a nurse and one primarily led by their GP (i.e. ongoing standard care). Those who respond positively will receive a telephone call with some further screening questions to confirm their eligibility, to answer any immediate questions they may have and to book an appointment with the nurse. At the nurse visit participants will have the opportunity to ask any further questions prior to giving their full informed signed consent. Randomisation will occur at this stage.

Informed consent will be collected from each participant before they undergo 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.

Should there be any subsequent amendment to the final protocol, which 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.

Future contact

Participants will be asked if they are willing for their contact details to be stored on a secure database in Academic Rheumatology, to enable them to be informed of future studies undertaken by the department for which they might be suitable. Participant data will be kept up-to-date in accordance with Data Protection Act, 1998. The consent form includes an optional clause asking participants to confirm whether they are happy for their personal details to be retained for this purpose - if not their contact details will be destroyed at the end of this study after it is no longer necessary to contact them.

TRIAL / STUDY TREATMENT AND REGIMEN

The total study duration will be 3 years (8 month recruitment period, 2 years participation, 4 months analysis and writing up).

All appointments with our research nurses will be at the participants' local GP practice, unless a home visit is specifically requested.

The study regimen is summarised in the table below (see also appendix1):

	RCT – nurse intervention	RCT – control/ standard care arm
Enquiry: age, sex, gout history, drug history, family history, comorbidities	X	X
Individualised advice on management of acute attack (selecting from ice packs, oral colchicine, oral NSAID plus PPI, corticosteroid).	X	X
Provision of Arthritis UK patient booklet.	X	X
Tophi assessment (sites), if present	X	X
A clear verbal explanation of gout	X	
Individualised explanation of relevant risk factors	X	

Individualised advice on ways to reduce uric acid levels by lifestyle modification, if appropriate	X	
Advice on ULT	X	
Height and weight (BMI)	X	X
Baseline/recruitment questionnaire (incl. SF36 & GAQ)	X	X
Serum uric acid, GFR and creatinine	X	X
Diary of acute attacks	X	X
Record of visits to GPs re gout management		X
SF36 'Quality of life' forms during acute attacks	X	X
12 month SUA	X	X
12 month GFR & creatinine	X	X
12 month questionnaire (incl. SF36 & GAQ)	X	X
12 month weight	X	X
24 month bloods	X	X
24 month questionnaire (incl. SF36 & GAQ)	X	X
24 month weight	X	X

A] NURSE INTERVENTION:

The recommended core treatment elements of the current EULAR and BSR recommendations form the basis of the nurse-led intervention (7, 8). These key elements have been incorporated into a management package suitable for implementation in community-based clinical practice. This package was developed during phase 1 of the study which included qualitative interviews of patients exploring illness perceptions and possible barriers to care. The nurse led package of care will be individualised according to the characteristics and needs of the participant and will include elements of the following:

(1) *a clear verbal explanation of gout backed up by written information (Arthritis Research UK patient booklet).* The explanation will 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 SUA levels rise above the critical "saturation point" for crystal formation
- in people with persistently raised SUA crystals slowly accumulate without causing 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 an acute attack of gout
- "shed" crystals are largely dissolved by the inflammation so the attack settles
- over many years acute attacks may increase in frequency and spread to involve other joints
- in addition to acute attacks, continuing deposition may eventually result in hard, slowly expanding lumps of crystals ("tophi") that can cause pressure damage to joint cartilage and bone and even appear as palpable lumps under the skin
- in some people tophi may result in irreversible joint damage (i.e. osteoarthritis) and cause regular chronic pain on using the joints
- reduction and maintenance of SUA levels below the saturation point (1) stops production of new crystals and (2) 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 uric acid above the saturation point* (basically too much production, or insufficient elimination of uric acid) including:

- *hereditary factors* that result in some people having relatively inefficient renal excretion of urate
- a *high body mass* - the majority (2/3) of uric acid being made by the body's cells by breaking down purines into uric acid, releasing energy for the cells
- a *diet* containing plenty of foods that are high in purines (1/3 of uric acid comes from the diet)
- *drugs* (such as diuretics) that reduce the kidney's ability to excrete uric acid
- *chronic renal impairment* associated with ageing or kidney disease.

(6) *individualised advice on management of an acute attack* (selecting from ice packs, oral colchicine, oral NSAID plus PPI, corticosteroid)

(7) *individualised advice* on ways to reduce uric acid levels by *lifestyle modification*, if this is appropriate (e.g reducing weight if overweight or obese, reduction in excessive beer intake, dietary alteration)

(8) *advice on ULT (in line with current recommended guidelines)*, including initiation of new ULT, with an upward titration regimen (with approximately one month between each incremental increase in ULT) and allopurinol the first-line drug to consider (febuxostat, sulphinpyrazone, benzbromarone also considered as appropriate). Prescriptions for ULT will be signed by Prof Doherty and issued through Nottingham City Hospital pharmacy.

The nurse will follow up the patient at variable time intervals as appropriate to the needs of the patient. It is envisaged that visits will be most frequent (e.g. monthly) in the first 6 months when ULT is being initiated and titrated upwards; subsequently visits may reduce to 3, 6 or 9 monthly depending on difficulty of gout management. Telephone contact to review blood test results and to agree any required action can substitute for visits, and home visits for blood tests and advice are permitted if more convenient (e.g. elderly patients). If home visits are undertaken this will be done in accordance with the University of Nottingham fieldwork guidelines. If the nurse requires any advice concerning treatment strategy (e.g. in patients with serious or multiple co-morbidity, taking multiple drug treatments, or experiencing side-effects) this will be offered by Academic Rheumatology (Prof Doherty or, in his absence, another designated Rheumatologist - Dr Adrian Jones or Dr Philip Courtney). All contacts with the patient (practice visit, home visit, telephone call) and for doctor advice will be logged (date, duration) for subsequent cost effectiveness analysis. Participants will be given a diary to keep during the 2 year study period in which they will record the date and duration of acute attacks of gout.

Asssessment will involve:

Enquiry: age, sex, gout history (onset, acute attacks/frequency/sites affected/chronic symptoms), drug history (allopurinol/start date/dose, diuretics/duration; other drugs), family history comorbidities (most detailed first visit), completion of a QOL questionnaire (generic - SF36; and disease-specific - the gout assessment questionnaire (GAQ)) at the end of year one and again at the end of year 2. The questionnaires will take approximately 20 minutes to complete.

Examination: tophi (sites); height, weight (BMI).

Investigations: serum uric acid, GFR, creatinine.

If tophi are present, the maximum diameter of the longest tophus will be measured using a Vernier calliper and the total number and site of tophi will be recorded.

All investigations will only be undertaken to assist clinical assessment. Individuals participating in the study will receive a package of care based on current recommended guidelines.

Blood samples will be collected by the research nurses and taken to the Nottingham City Hospital laboratory for analysis. The samples will be destroyed following the NUH Trust's standard operating procedures.

All results will be discussed with the patients. Any abnormal findings, unrelated to the diagnosis of gout, will be discussed with the patient and their GP informed to enable appropriate action.

B] Control/Standard Care arm

Participants randomised to this group will have one consultation appointment with the research nurse. At this appointment they will be assessed by the nurse (identical enquiry, examination and investigations as above) and be provided with the Arthritis Research UK gout information booklet and a diary to prospectively document their acute attacks (frequency, duration, medical advice sought, medications taken, absence from work). The discussion will focus on the management of acute attacks and not on long-term management. In addition, they will be asked to provide a blood sample to check their SUA level at baseline, 12 months and 24 months, and complete a QOL questionnaire at 12 months (a new diary will be given at this point) and 24 months. This standard care group of participants will remain under the care of their general practitioner.

Collection of additional blood sample (optional)

All participants will also be invited to give a 10ml sample of blood for use in future gout research. This will include 1] genetic research to help identify genes that associate with gout development and severity and 2] study of metabolic changes (particularly biomarkers that associate with cardiovascular risk) that accompany a change in serum uric acid over time. The samples for genetic testing will be taken at baseline and those for metabolic biomarker research will be taken at baseline and one and two years. These time points allow the additional blood to be taken at the time venepuncture will be undertaken for the main study and therefore will not require an additional venepuncture. It will be explained to patients that participation in this additional genetic and metabolic research is optional and is not required as part of the main Arthritis Research UK Gout Treatment Trial and is covered in a separate optional clause on the consent form.

HUMAN TISSUE

Gout Treatment Trial blood samples will be collected by the research nurses during the appointments undertaken at the GPs surgeries and transported, by the research nurse, to the Nottingham City Hospital laboratory for analysis. Samples will not be retained for future research purposes and will be destroyed by the Nottingham City Hospital laboratory, following the Nottingham University Hospital Trust's standard operating procedures.

If the participant agrees to provide an additional sample for future genetic and metabolic biomarker studies related to gout, these samples will be stored in the Clinical Sciences Building, Nottingham City Hospital and stored within the Research Tissue Bank for future research (DI Prof Jim Lowe- Licence Number 12265) if participants are agreeable and sign the optional clause on the consent form.
Only de-identified samples will be sent to third parties including close collaborating research groups and/or commercial companies who will undertake some of this analysis.

LABORATORY ANALYSES

Bloods collected for the Gout Treatment trial will be transported to the laboratory at the Nottingham City Hospital for analysis. The bloods will be tested for serum uric acid levels, GRF and liver function (if required).

Bloods collected for future genetic and biochemical markers studies will be stored in the Clinical Sciences Building at the Nottingham City Hospital. Whole blood will be sent to a specialist company for DNA extraction and processing. The DNA will be used to identify genes that identify with gout development and severity. Biochemical marker measurements in sera will be carried out using either radioimmunoassay specific equipment for ELISAs and/or magnetic resonance spectroscopy for metabolite detection.

Compliance

This is a complex intervention. However, compliance with respect to the nurse intervention will be judged by attendance for appointments, and by completion of the end of study questionnaire. Compliance to prescribed ULT will be judged by discussion with the participants, by their prescription requirements and by the results of the serial SUA.

Criteria for terminating trial

It is not envisaged that circumstances will arise that require termination of the trial. The nurse intervention reflects recommended best practice which includes prescription of available licensed ULT.

MONITORING STUDY PARTICIPANTS SUITABILITY TO CONTINUE IN THE STUDY

Prior to contacting participants in the RCT standard care arm, at one and two years, the GP surgeries will be provided with a list of participants in these groups and asked to check their records to ensure that patients are still registered with surgery, living at the same address and are suitable to be contacted .

As regular contact will be maintained with participants in the RCT Nurse Intervention arm it is envisaged that participants/family members will keep the study team informed. If there is any reason to believe that an individual status may have changed, e.g. no reply to correspondence, telephone calls or non-attendance for appointments the GP surgery will again be contacted.

STATISTICS

Methods

The trial statistician (Dr Weiya Zhang) will oversee the data management, evaluation and analyses. The database will be developed in collaboration with the CTU using access and analysed using SPSS. SUA will be analysed at baseline, 12 months and 24 months. Comparison will be undertaken between the nurse led intervention and control at each observational point. There will be no interim analyses for efficacy or safety. Intention to treat (ITT) analysis will be undertaken to compare treatment effects between groups. Multilevel models will be used for any missing outcome measures. Chi-square test will be used for dichotomous or categorical data and ANOVA test will be used for continuous variables. Adjustment will be made for baseline co-variables as appropriate. Cost per QALY will be estimated from the SF6D and the direct and indirect costs related to gout and its management.

Sample size and justification

Sample size:

724 participants will be recruited for the RCT (this allows a 10% drop out over the 2 year period).

Power calculations:

Information that includes SUA on community-derived patients with gout is sparse. However, detailed information on frequency of attacks, treatment, SUA and quality of life is available for 250 gout patients from 17 practices in Nottingham (5, 11). In this survey: 30% of patients were on ULT; the rate for acute attacks in the previous year was 32% for patients on ULT and 57% for patients on no ULT; mean SUA was 318 µmol/L in those taking ULT compared to 434 µmol/L in those not taking ULT; and 23% of those taking ULT had a SUA >360 µmol/L, compared to 75% of those not on ULT. For quality of life (SF36) overall mean and SD for those on ULT was 16.41 (2.81) compared to 15.67 (3.05) for those not on ULT, giving a pooled SD of 3.09 and a mean difference of 0.7 between groups (the latter is used as a proxy of effect size d).

According to these results, we have estimated the following sample size requirements, to achieve 90% power at 0.05% significance level, for each outcome:

- reduction in frequency of acute attacks in final year - a sample size of 90 is required for each arm
  reduction in SUA below the therapeutic target - a sample size of 70 patients is required for each arm
- quality of life – a sample size of 326 is required for each arm

Allowing a 10% drop-out rate over the 2 years, this requires a total of **724 patients** (326 plus 36 dropouts in each arm) to provide adequate power for the primary outcome and for 2 of the key secondary outcomes. There are no data on changes in GAQ in response to treatment, but being a disease-specific instrument, we assume that the GAQ will be more sensitive to change than the SF36 and that a total size of 796 will be adequately powered for this outcome.

The total number of GP practices in Nottinghamshire is 170 and the estimated number of registered patients with gout is 10,720 (i.e. an average of 65 patients per GP). A questionnaire will be sent to all patients (unless they have an exclusion criterion) to detect eligible patents. A random sample of those eligible will be selected using the simple random selection after the consent to the trial.

ASSESSMENT OF EFFICACY

Primary Efficacy Endpoint:

Percentage in each group with SUA levels <360µmol/L (the saturation point form sodium urate crystal formation).

Secondary Efficacy Endpoints:

Percentage in each group with reduced number of acute attacks in the second year of the study
Quality of life scores (SF36 and GAQ) at end point compared to baseline in each group and comparison of endpoint QOL scores between the two groups.
Reduction in size and number of tophi.

Assessment of safety

The nurse intervention reflects recommended best practice involving ULTs that are recommended and licensed for this purpose. Participants will report any adverse events to the nurse. If benzbromarone is prescribed recommended checking of blood liver function tests will be undertaken.

Procedures for missing, unused and spurious data

If participants leave the study for any reason or if there are omitted data we will use multilevel models for any missing outcome measures and an intention to treat (ITT) analysis.

Definition of populations analysed

All patients randomised into the study will be analysed using an ITT analysis and LOCF for any missing data.

ADVERSE EVENTS

The nurse intervention which is being tested in this study reflects recommended best practice and utilises ULT that is recommended and licensed for this purpose. Therefore, the occurrence of adverse events as a result of participation within this study is not expected and no adverse event data will be collected.

Self- reported adverse events in participants in the nurse intervention will be recorded and if judged to be due to ULT the drug will be stopped and an alternative ULT considered (i.e. as recommended in current guidelines). Known side effects of ULT (e.g. allopurinol, febuxostat, benzbromarone) will be reported to the MHRA using the Yellow Card system, in line with recommended practice, but will not be classed as adverse events with respect to the intervention and will therefore not be reported to the NRES as such. However, a summary of the side effects reported using the Yellow Card system will be included in the final summary submitted to NRES. Adverse events that are unrelated to the nurse intervention and ULT will be treated by the participant's general practitioner, as usual, and again not be reported to the REC.

To ensure clinical governance if the nurse is unsure of causality with respect to ULT she can involve the opinion of Professor Doherty (or in his absence Dr Philip Courtney or Dr Adrian Jones).

Adverse events occurring in the standard care group will be assessed and managed as part of normal care by the general practitioner and will not be reported to the REC.

COST EFFECTIVENESS AND UTILITY

The direct and indirect costs related to gout and its management during the two year study period will be estimated in the nurse led intervention group by recording of the following data:
number of nurse appointments and telephone contacts; duration of each contact; cost of drugs and blood tests; days off work because of acute attacks; any additional health care utilisation during acute attacks. Identical data will be obtained in the standard care group apart from the duration of each GP contact related specifically to gout management – a mean value will be estimated.

Cost utility will be estimated in each group utilising the direct and indirect costs and the SF6D (derived from the SF36). Quality of life during acute attacks will also be obtained in both groups (SF36) and this will be utilised in the cost utility estimations.

ETHICAL AND REGULATORY ASPECTS

Involvement of General Practitioner

Nurse led group (RCT): GPs will be informed if their patients are randomised to the nurse led group and will be kept informed with respect changes to their patients' gout medications. If the nurse detects any adverse event or comorbidity unrelated to gout and its management the GP will also be directly informed.

Standard care group (RCT): We will not inform the GP that their patient has been randomised to the ongoing standard care group since this may 'contaminate' the GP care and the GPs in that practice will already have agreed for their patients to be approached for the purposes of this study

ETHICS COMMITTEE AND REGULATORY APPROVALS

The trial will not be initiated before the protocol, informed consent forms and participant information sheets have received approval / favourable opinion from the Research Ethics Committee (REC), and the respective National Health Service (NHS) Research & Development (R&D) department. 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 / 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 Department of Health Research Governance Framework for Health and Social Care, 2005.

INFORMED CONSENT AND PARTICIPANT INFORMATION

The process for obtaining participant informed consent or assent 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 participant will receive a copy of the signed and dated forms and the original will be retained in the Trial Master File.

The decision regarding participation in the study is entirely voluntary. The investigator or their nominee shall emphasize to them 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 done 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 approval of the amended Informed Consent Form by the REC and use of the amended form (including for ongoing participants).

RECORDS

Case Report Forms

Each participant will be assigned a trial identity code number, for use on CRFs other trial documents and the electronic database. The documents and database will also use their

initials (of first and last names separated by a hyphen or a middle name initial when available) and date of birth (dd/mm/yy).

CRFs will be treated as confidential documents and held securely in accordance with regulations. The investigator 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 Recruitment Log), to permit identification of all participants enrolled in the trial, in accordance with regulatory requirements and for follow-up as required.

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.

Source documents

Source documents shall be filed at the investigator's site and will include but are not limited to, consent forms, history and examination findings, questionnaires and laboratory results and a record of initiated or altered treatments. Only trial staff as listed on the Delegation Log shall have access to trial documentation other than the regulatory requirements listed below.

Direct access to source data / documents

The CRF and all source documents, including progress notes and copies of laboratory and medical test results shall made be available at all times for review by the Chief Investigator, Sponsor's designee and inspection by relevant regulatory authorities.

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, 1998. The CRF will only collect the minimum required information for the purposes of the trial. 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). Computer held data including the trial database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one way encryption method).

Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

QUALITY ASSURANCE & AUDIT

INSURANCE AND INDEMNITY

Insurance and indemnity for trial participants and trial staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of

HSG (96)48. There are no special compensation arrangements, but trial participants may have recourse through the NHS complaints procedures.

The University of Nottingham has taken out an insurance policy to provide indemnity in the event of a successful litigious claim for proven non-negligent harm.

TRIAL CONDUCT

Trial conduct will be subject to systems audit of the Trial Master File for inclusion of essential documents; permissions to conduct the trial; Trial Delegation Log; CVs of trial staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, correct randomisation, timeliness of visits) and adverse event recording and reporting.

Our Senior Research Nurse will observe each research nurse taking consent in a small sample of study participants to ensure consent is being undertaken in line with GCP guidelines and training provided.

The Trial Co-ordinator and CTU representatives will carry out a site systems audit at least yearly and an audit report shall be made to the Trial Steering Committee.

TRIAL DATA

Monitoring of trial data shall include confirmation of informed consent; source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. The Trial Co-ordinator and CTU representative will 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.

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

RECORD RETENTION AND ARCHIVING

In compliance with the ICH/GCP guidelines, regulations and in accordance with the University of Nottingham Research Code of Conduct, 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.

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 Trial Steering Committee and Data Monitoring Committee as appropriate in making this decision.

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 utilising 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.

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

PUBLICATION AND DISSEMINATION POLICY

The study results will be submitted to Arthritis Research UK, regulatory authorities, and peer reviewed journals for publication. In addition, the results will be presented at national and international conferences. Study participants' identity will not be disclosed when publishing the results.

Study participants will also be informed of the results, if requested.

USER AND PUBLIC INVOLVEMENT

We have audited the standard of care of gout in the Nottingham Community and subsequently undertaken qualitative research during Phase I of the Nottingham Gout Treatment Trial to ascertain patients' understanding and views on gout and its treatment. The findings from this qualitative research and the results from Phase 1 have been used to develop the nurse intervention package of care which is being delivered in Phase 2 of this study. The nurse led intervention incorporates recommended best practice published by the British Society for Rheumatology and the European League Against Rheumatism.

STUDY FINANCES

Funding source

This study is funded by Arthritis Research UK.

Participant stipends and payments

Participants will not be paid to participate in the trial.

SIGNATURE PAGES

Signatories to Protocol:

Chief Investigator: (name)_____

Signature:_____

Date: _____

Co- investigator: (name) _____

Signature:_____

Date: _____

Trial Statistician: (name)_____

Signature:_____

Date: _____

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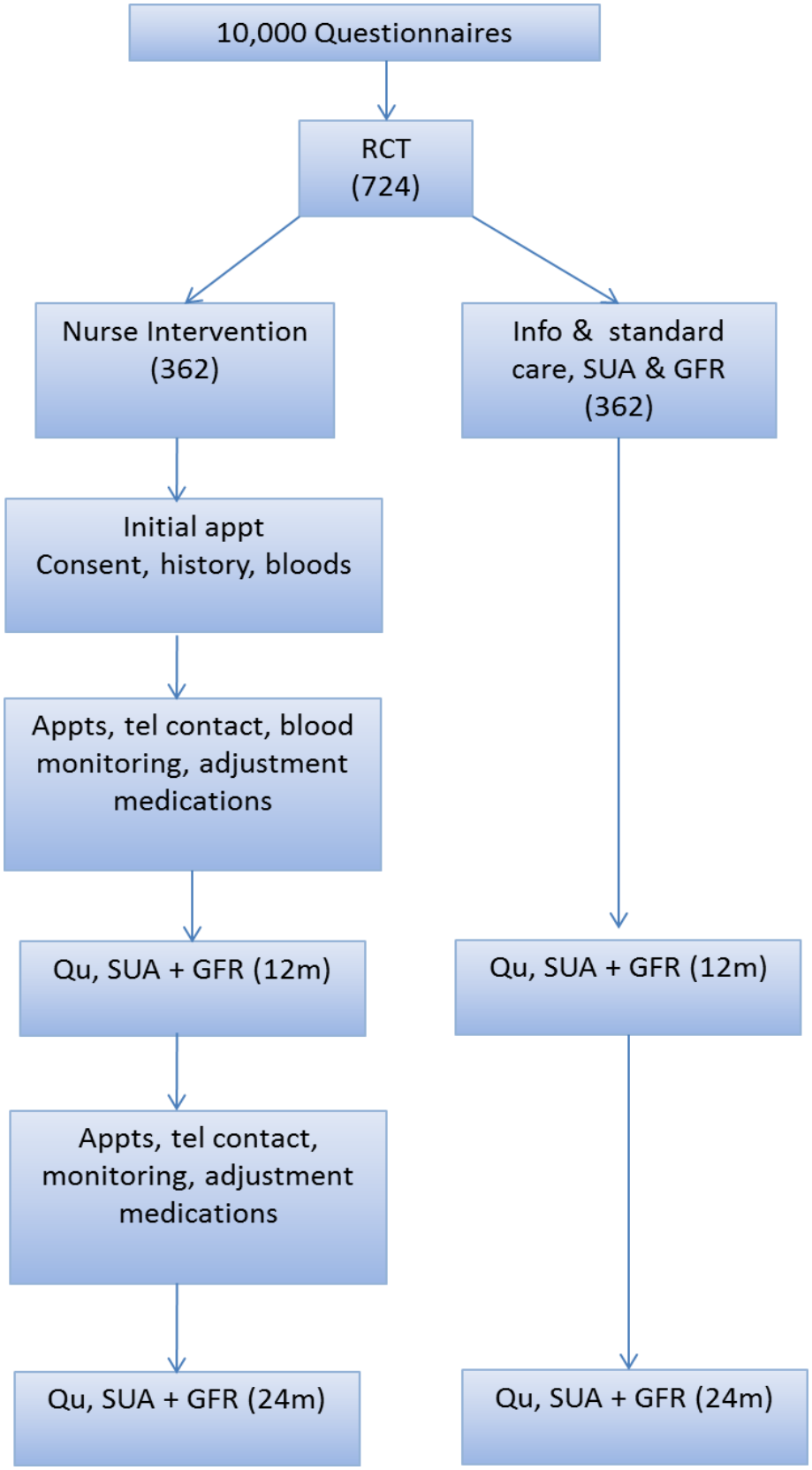
Appendix 1 – RCT Participant Involvement:



A community based randomised controlled trial comparing nurse-led intervention with standard care

-Analysis plan

Synopsis of the design: A 2 year community based randomised controlled trial will be undertaken in Nottingham to investigate clinical effectiveness and cost-effectiveness of a nurse-led quality of care intervention versus standard of care control. A questionnaire survey will be undertaken in the GP practices in Nottinghamshire to obtain 724 patients with gout according to the American College of Rheumatology (ACR) criteria and at least one acute attack in the past year. They will be randomly allocated to the intervention and the control group using stratified (according to the participated GP practices), block (fixed block of 4 for random allocation to keep the balance between the groups) randomisation method. Participants will be examined at baseline, 12 months and 24 months for outcomes such as serum uric acid (SUA), number of acute attacks in the previous year and quality of life (QoL) (SF36).

Principles of analysis: Intention to treat (ITT) analysis will be conducted. Descriptive analysis on raw differences between groups at baseline, 12 months and 24 months will be undertaken. Multi-level regression model (MLM) will be used for the overall comparison of the treatment effect between groups with repeated measures and missing data. We shall include all data from 3 time points in the same model, with repeated measures as level 1 units and individuals as level 2 units. The treatment group and time points will be considered as covariates in the model together with covariates at baseline for the adjustment purpose. Continuous data (eg, SUA, QoL score, etc) will be analysed using MLM linear regression, whereas dichotomous and categorical data will be analysed using MLM logistic or multinomial models. Comparison will be made between the intervention and the control in the RCT, as well as between the control in the RCT and the observational group.

Outcome measures:

1. Primary outcome: % patients hitting the therapeutic target (SUA≤ 360 µmmol/l) is the primary outcome of the trial. We will examine
    - % patients reaching the target at baseline, 12 months and 24 months within each group
    - % patients reaching the target at baseline, 12 months and 24 months between groups
    - Mean SUA at baseline, 12 months and 24 months within each group
    - Mean SUA at baseline, 12 months and 24 months between groups
    - Mean change of SUA from baseline to 12 months and 24 months within each group
    - Mean change of SUA from baseline to 12 months and 24 months between groups

    We will also calculate the number needed to treat (NNT) for % patients reaching the therapeutic target SUA less than 360 µmol/l, as appropriate.

2. Secondary outcomes
    - Number of acute attacks in preceding year, year 1 and year 2 within each group and between groups
    - Number of patients with tophi at baseline, 12 months and 24 months with each group and between groups
    - Mean QoL scores (overall, different domain scores of SF36 and the Gout Asssessment Questionnaire (GAQ) including the Gout Impact Scale (GIS) of the GAQ. at 0, 12 and 24 months within each group and between groups
    - Mean change of QoL scores from baseline to 12 months and 24 months within each group and between groups

Covariates and baseline predictors: age, gender, body mass index, disease duration, tophi, associated comorbidity etc.

Task allocation and timetable: The Nottingham CTU will undertake randomisation, development of the database for RCT and the web-based data entry platform. CTU will also conduct data monitoring and quality control for the RCT data. Academic Rheumatology will recruit patients, enter the data through a web-based data entry platform for the RCT data and develop an independent database for the observational group. Both datasets are not open for any interim analysis between baseline and 24 months to keep the randomisation. Analysis will start after 24 months when the data has been fully completed, quality checked over and closed. Analysis for clinical effectiveness (efficacy and side effects) will be completed in 3 months after the closing date of the data. Analysis for cost-effectiveness will be completed in 12 months, as it requires acquisition of additional data for cost. In brief:

- Recruitment – 8 months
- RCT and observation – 24 months
- Results for clinical effectiveness – 3 months
- Results for cost-effectiveness – 12 months

Economic Analyses Plan.

Two economic analyses are planned: the first being an economic analysis alongside the RCT and the second modelling the costs and benefits over a longer time horizon. The base case in both models would use an NHS perspective, with a societal perspective (that include indirect costs such as lost productivity) being undertaken in a sensitivity analysis.

Economic analysis alongside the RCT

This analysis would simply use the costs recorded in each arm of the trial and the utility of the patients, as estimated through the SF36 and SF6-D. Costs will relate to both the interventions and the consequences of the interventions, with both direct NHS costs and indirect costs recorded. Utility will be comprised of two parts, the underlying quality of life associated with patients with gout and decrements in utility associated with a flare. Utility will be combined with quantity of life to form quality-adjusted life years (QALYs).

The incremental costs associated with the nurse-led intervention will be divided by the incremental QALY gain to form a cost per QALY ratio that can be compared with current NICE thresholds. (http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf)

Modelling the costs and benefits over a longer time horizon.

It may be the case that there are larger costs associated with the initial period of the nurse-led intervention and that these becoming markedly reduced over time. Contrastingly the benefits associated with a patient managing their disease more appropriately may remain constant. As such, limiting an economic analysis to the initial 2 year period may provide an over-estimate of the true cost per QALY ratio. In order that alternative cost per QALY ratios can be calculated a mathematical model would be constructed that can model a longer time horizon. This model would be consistent with NICE's reference case.
(http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf)

If appropriate from the analysis of the RCT data, subgroup analyses would be undertaken in order to assess differential cost per QALYs across different patient types.